CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office of Drug Evaluation-I: Decisional Memo

Date	July 7, 2015
From	Ellis F. Unger, MD, Director Office of Drug Evaluation-I, Office of New Drugs, CDER
Subject	Office Director Decisional Memo
New Drug Application (NDA) #	207620
Applicant Name	Novartis Pharmaceuticals Corporation
Date of Submission	December 17, 2014
PDUFA Goal Date	August 17, 2015
Proprietary Name/ Established (USAN) Name	Entresto sacubitril and valsartan
Dosage Forms/ Strengths	24 mg sacubitril and 26 mg valsartan; film-coated tablets 49 mg sacubitril and 51 mg valsartan; film-coated tablets 97 mg sacubitril and 103 mg valsartan; film-coated tablets
Indication originally sought by applicant (see page 29 for final)	(b) (4)
Action:	Approval

Material Reviewed/Consulted - Action Package, including:	
Project Manager	Alexis Childers, RAC
Medical Officer Clinical Review	Kimberly Smith, MD (Efficacy), Tzu-Yun McDowell, PhD (Safety)
Clinical Pharmacology/Pharmacometrics	Luning Zhuang PhD, Sreedharan Sabarinath, PhD
Statistical Review	John Lawrence, PhD; James Hung, PhD
Pharmacology Toxicology	William Link, PhD, Al De Felice, PhD
Executive Cancer Assessment Committee	Paul Brown, PhD (acting chair)
Office of New Drug Quality Assessment	Wendy Wilson-Lee, PhD (technical lead), Anamitro Banerjee, PhD (drug substance), Sherita McLamore-Hines, PhD (drug product), Bogdan Kurtyka, PhD (process), Zhong Li, PhD (facility)
Office of Scientific Investigations	Sharon K. Gershon, PharmD
Division of Pediatric and Maternal Health	Miriam Dinatale, DO
Biopharmaceutics Review	Salaheldin Hamed, PhD
Carcinogenicity Study	Mohammad Rahman, PhD; Karl Lin, PhD
Division of Medication Error Prevention and Analysis	Janine Stewart, PharmD; Alice Tu, PharmD
Risk Management Review	Danny Gonzales, PharmD, MS, Kim Lehrfeld, PharmD
Cross-Discipline Team Leader	Aliza Thompson, MD
Director, Division of Cardiovascular and Renal Products	Norman Stockbridge, MD, PhD

1. Introduction

Novartis is seeking approval of LCZ696 for the proposed indication: (b) (4)

With a number of changes to the label, including changes to the indication statement (see Summary/Conclusions), the review team endorses approval, and I agree with their recommendation.

2. Background

Description:

LCZ696 is a co-crystal, a type of sodium salt complex, consisting of valsartan and sacubitril anions, sodium cations, and water. These 4 individual components are present in a 2:2:6:5 molar ratio, and are not ionically bound. The drug product contains the LCZ696 co-crystal as the active ingredient. The active moieties in the LCZ696 co-crystal are sacubitril and valsartan.

The description of the chemical nature of the active ingredient was an important issue that had to be negotiated with the applicant. The Office of Pharmaceutical Quality (OPQ) initially recommended use of the term "co-crystal" to describe the tablet's active ingredient in Section 11 of labeling, whereas the applicant had proposed the term (b) (4)

In an addendum to the Quality review, OPQ noted that both descriptions correctly represent the chemical nature of the active ingredient and are scientifically valid. The structural X-ray diffraction data submitted demonstrate that the active ingredient meets the criteria delineated in FDA Guidance Regulatory Classification of Pharmaceutical Co-Crystals (April, 2013) for a co-crystal, based on orthogonal spectroscopic characterization data, evidence of dissociation *in vivo*, and the non-ionic interactions between the individual components. The active ingredient can also be considered a complex, however, based on the IUPAC Gold Book definition: a molecular entity formed by loose association involving two or more molecular entities (ionic or neutral); bonding is normally non-covalent.

Although the applicant's preferred description of the active ingredient, (b) (4) is correct, OPQ noted that the term suggests (b) (4), which could cause confusion. Thus, OPQ is recommending use of the term "complex" be used to refer to the active ingredient in Section 11 of labeling, and the applicant has agreed.

Valsartan is a previously approved molecular entity, an angiotensin II receptor blocker (ARB), which is widely marketed for hypertension and heart failure as Diovan and generics. Sacubitril is a neprilysin inhibitor, a first-in-class new molecular entity (NME), although there is some experience with this class of agents, as discussed later in this memo.

Although the active ingredient in the tablet is a co-crystal, it dissociates *in vivo* to the active moieties valsartan and sacubitril, and so it has been consistently viewed as a combination product from a regulatory perspective.

Disease Background:

Over 5 million people in the US have heart failure, about half of whom have reduced left ventricular ejection fraction or systolic heart failure. (Many patients with heart failure have preserved left ventricular systolic function, so-called "diastolic heart failure," for which there are no approved treatments.) According to the 2013 American College of Cardiology Foundation/American Heart Association "Guideline for the Management of Heart Failure," the lifetime risk of developing heart failure is 20% for the U.S. population ≥ 40 years of age, with over 650,000 new cases diagnosed annually (*J Am Coll Cardiol* 2013;e147-239). The incidence of heart failure increases with age: from ~2 per 100 individuals at age 65 to 69 to over 8 per 100 individuals at age 85 and over. As life expectancy increases in the US, the prevalence is anticipated to rise. Moreover, despite improvements in the pharmacologic and non-pharmacologic management of heart failure, 5-year survival rates are still only ~50%.

There is an excellent summary of current therapy for heart failure in the Clinical Review, page 14.

For the regulatory history, refer to the clinical review and the cross-discipline team leader review.

3. Product Quality

OPQ recommends approval from a drug product perspective.

As noted above, the active ingredient in LCZ696 is a co-crystal comprised of two active moieties – sacubitril and valsartan anions – with 1:1 stoichiometry. The other components are sodium cations and water. (b) (4) The co-crystal quickly dissociate *in vivo* to release sacubitril and valsartan.

Although designated as regulatory drug substances, it was agreed that the applicant's quality systems and standards control sacubitril (b) (4) and valsartan (b) (4) to produce the co-crystal. (b) (4) specifications for sacubitril (b) (4) and valsartan (b) (4) include appropriate tests and acceptance criteria to ensure the identity, purity, strength, quality, and bioavailability of these compounds.

A 24-month drug product expiration date has been granted when stored at room temperature and protected from moisture in the intended container closure. The drug product is packaged in bottles and unit dose blister packages.

Based on firm inspectional history and data reviewed during the pre-approval inspections, OPQ found the manufacturing facilities to be acceptable.

Following discussions regarding the expression of strength in the carton and container labels, OPQ agreed on a compromise to allow use of a "/" between the sacubitril and valsartan in the established name, and found the carton and container labels acceptable.

Post-Marketing Commitment:

It was determined during the review that the dissolution data submitted for the clinical and the registration batches of the (b) (4) mg strength did not support the dissolution acceptance criterion proposed by the applicant (Q = (b) (4) % at (b) (4) minutes). (b) (4)

OPQ recommended that the applicant optimize the dissolution method and acceptance criterion, which would require a post-marketing commitment. It was noted that the control strategy for the current product (e.g., operating closely to the normal operating ranges for the clinical trial batch) would ensure the quality of the drug product.

In the absence of an adequate *in vitro* to *in vivo* relation and proper exposure-response data, FDA recommended establishment of a release specification at Q = (b) (4) % to ensure complete release of the drug substance.

There will be a post-marketing commitment with the following goals: 1) Development of a new dissolution method for all the strengths with demonstrated discriminating ability, (b) (4) and 2) Setting of the final dissolution acceptance criterion for Entresto (sacubitril/valsartan) Tablets, 97/103, 49/51, and 24/26 mg using the new method and the overall multipoint dissolution profile data from a minimum of 12 commercial batches/strength, manufactured under the same conditions as those used for the manufactured of the batches used in pivotal clinical trials.

The FDA would be open to the possibility of a (b) (4) OPQ reiterated that a justification would need to be provided, supported by data, before agreeing to (b) (4) for the drug product.

The applicant has agreed to this post-marketing commitment, and agreed to submit a development report by February 1, 2016, and the final report by July 1, 2016.

4. Nonclinical Pharmacology/Toxicology:

Salient findings in mice, rats, rabbits, and cynomolgus monkeys included renal juxtaglomerular hypertrophy/hyperplasia, renal tubular changes; decreased hemoglobin/hematocrit and reticulocytes; decreased heart weights (without histopathological findings); reversible focal gastric mucosal erosion, and emesis and diarrhea without histologic correlates. According to Dr. Link, these findings do not raise concerns for human use because they reflect adaptive responses and/or exaggerated pharmacodynamic responses to high doses.

Genotoxicity assays of LCZ696, sacubitril and LBQ657, sacubitril's active metabolite, were negative.

LCZ696 had no effect on fertility in rats. Both sacubitril and valsartan are known to cause fetal toxicity and embryo-fetal lethality in rabbits, and LCZ696 increased embryo lethality in both rats and rabbits. LCZ696 was teratogenic in rabbits at ≥10 mg/kg. As for all drugs that act directly on the renin-angiotensin-aldosterone system, LCZ696 will be contraindicated during pregnancy.

Neprilysin is a major beta amyloid-degrading enzyme in the brain. There is, therefore, a theoretical risk that LCZ696, by inhibiting neprilysin, could cause accumulation of β-amyloid (Aβ) in the brain, leading to cognitive impairment. There was much interest, therefore, in the non-clinical studies designed to examine LCZ696's effect on Aβ.

The applicant assessed the effects of LCZ696 on Aβ concentrations in brain and cerebrospinal fluid (CSF) in young (2.5 to 4 year-old) female cynomolgus monkeys treated with LCZ696, 50 mg/kg/day, for 2 weeks. Treatment was associated with increases in $A\beta_{1-40}$, $A\beta_{1-42}$, and $A\beta_{1-38}$ in cerebrospinal fluid (CSF), without corresponding increases in brain. The Division of Neurology Products (DNP) was consulted, in part to review this study. DNP noted that sufficient levels of LBQ657 reached the central nervous system (CNS) to inhibit neprilysin, but that other Aβ clearance mechanisms, including transport into the CSF, compensated, such that there was no apparent net increase in brain Aβ at steady state.

DNP also had two major criticisms of the study. First, DNP stated that the LCZ696 dose used should have been higher. The applicant deemed the LCZ696 dose tested to be "clinically relevant," based on similar concentrations of LBQ657 achieved in the CSF of monkeys and healthy volunteers given the maximum recommended human dose (MRHD) – a comparison of exposures based on C_{max}. Based on $AUC_{0-24\ hr}$, however, DNP noted that exposure in monkeys was approximately half the exposure in humans. DNP would have preferred testing of higher doses, to provide CNS exposures several-fold higher than those expected at the MRHD. Second, DNP expressed the view that effects observed in young monkeys may not be predictive of effects in elderly humans, because cynomolgus monkeys do not typically develop measurable cerebral amyloid pathology until they are much older.

Study 0670621 was a 39-week toxicology study where 12 young (2 to 4 year-old) cynomolgus monkeys received LCZ696 300 mg/kg/day (AUC exposure ~2X the MRHD), and there was no $A\beta_{42}$ immunostaining in the brain (tissues with known Aβ positivity were included to establish assay sensitivity). DNP also questioned the informativeness of this study, however, because of the young age of the monkeys. DNP suggested a study in aged monkeys, to quantify levels of soluble and insoluble Aβ in brain homogenates, and to assess immunoreactive Aβ.

Carcinogenicity:

Two-year carcinogenicity studies of sacubitril were performed in rats and mice, and there were no effects on tumor incidence or survival. The Executive Carcinogenicity Assessment Committee found the studies acceptable.

5. Clinical Pharmacology

The Clinical Pharmacology team recommends approval, with a lower starting dose in patients with severe renal function impairment and moderate hepatic impairment. The applicant has accepted these recommendations.

Mechanism of action: LBQ657, the active metabolite of sacubitril, inhibits neprilysin, which causes proteolytic degradation and inactivation of natriuretic peptides, including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-Type natriuretic peptide (CNP). These peptides activate membrane-bound guanylyl cyclase-coupled receptors and increase concentrations of cyclic guanosine monophosphate (cGMP). With inhibition of the inactivation of these proteins, LBQ657 is thought to promote vasodilation, natriuresis and diuresis, increase renal blood flow and glomerular filtration, inhibit renin and aldosterone release, and reduce sympathetic activity. By blocking the binding of angiotensin II to the AT1 receptor, valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II, cardiac stimulation, and renal reabsorption of sodium.

Pharmacokinetics:

- Upon oral administration, LCZ696 dissociates into sacubitril and valsartan; both moieties are rapidly absorbed without significant food effects.
- Sacubitril is a pro-drug that undergoes metabolism via esterases to form LBQ657, which inhibits neprilysin. LBQ567 is not further metabolized. Valsartan does not undergo significant metabolism.
- Absolute bioavailability of sacubitril from LCZ696 is $\geq$ 60%. The bioavailability of valsartan from LCZ696 is at least 50% higher than valsartan when valsartan is administered alone. For example, valsartan from 400 mg LCZ696 (containing ~ 203 mg valsartan) is approximately equivalent to 320 mg of the marketed valsartan formulation.
- Sacubitril and valsartan are highly protein-bound (97% and 94%, respectively).
- There is no significant CYP isozyme involvement in the metabolism of sacubitril or valsartan.
- Approximately 52-68% of sacubitril is excreted in urine (as LBQ657) and 37-48% recovered in feces. Approximately 83% of valsartan is excreted in feces and about 13% in urine.
- In healthy subjects, the average elimination half-lives of sacubitril, LBQ657, and valsartan are 1.4, 11.5 and 9.9 hours, respectively.
- Age, sex, race, and weight have little effect on exposure.
- Renal impairment: Steady state exposure of LBQ657 increases by about 2-fold in patients with all degrees of renal impairment (mild to severe), whereas effects on valsartan exposure were minimal. No study was conducted in patients on dialysis, but LBQ657 and valsartan are highly protein-bound and unlikely to be removed by dialysis. Note: out of caution, the recommended starting dose will be halved in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2).
- Hepatic impairment: In patients with mild hepatic impairment, exposures of sacubitril, LBQ657 and valsartan are increased only slightly relative to healthy subjects. In patients with moderate hepatic impairment, exposures of sacubitril, LBQ657, and valsartan were increased by ~245%, 90%, and 109%, respectively, relative to healthy subjects, and the recommended starting dose will be halved in these patients. No studies were conducted in patients with severe hepatic impairment, where use of the drug will not be recommended.

Pharmacodynamics:

Aβ concentrations: In 39 healthy subjects, administration of LCZ696 400 mg once a day for 2 weeks was associated with a 42% increase in CSF $A\beta_{1-38}$ relative to baseline and a 50% increase in plasma $A\beta_{1-40}$. As explained in the clinical review, the clinical significance of these findings is unknown.

QT Effects:

QT effects: No significant QTc prolongation was observed with LCZ696 (400 mg and 1200 mg) in a thorough QT study.

6. Clinical Microbiology

The drug is not an antimicrobial. According to the product quality review, the tests and proposed acceptance criteria for microbial burden are adequate.

7. Clinical/Statistical Efficacy

The evidence of efficacy for LCZ696 is provided by PARADIGM-HF, described in detail below. The results of this study were published recently (McMurray JJ, et al: Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; 371:993).

PARADIGM-HF

Novartis conducted PARADIGM-HF, a single phase 3 outcome trial, in support of the proposed indication. PARADIGM-HF was an international, randomized, double-blind, double-dummy, event-driven, active-control trial comparing LCZ696 with enalapril in adult patients with NYHA class II to IV chronic heart failure and left ventricular ejection fraction (LVEF) ≤ 40% (changed to ≤ 35% per protocol amendment 1), who were able to tolerate both of the test drugs during run-in phases (i.e., the study was enriched for patients who could tolerate the drugs).

Although the population has been described as having "stable" heart failure, the meaning of "stable" is not straightforward here and is somewhat of a misnomer. Patients were to have been on stable doses of a beta-blocker (unless contraindicated or poorly tolerated) and an ACE inhibitor or an ARB for ≥ 4 weeks prior to screening. On the other hand, patients had to have B-type natriuretic peptide (BNP) ≥ 150 pg/mL, or ≥ 100 pg/mL with a hospitalization for heart failure within the last 12 months (an enrichment maneuver).

PARADIGM-HF was essentially an add-on study that tested the concept that LCZ696, a combination of sacubitril and a RAAS inhibitor (valsartan), was superior to a RAAS inhibitor alone (enalapril).

The 1° endpoint was a composite endpoint of time-to-first heart failure hospitalization or cardiovascular (CV) death. Secondary endpoints included:

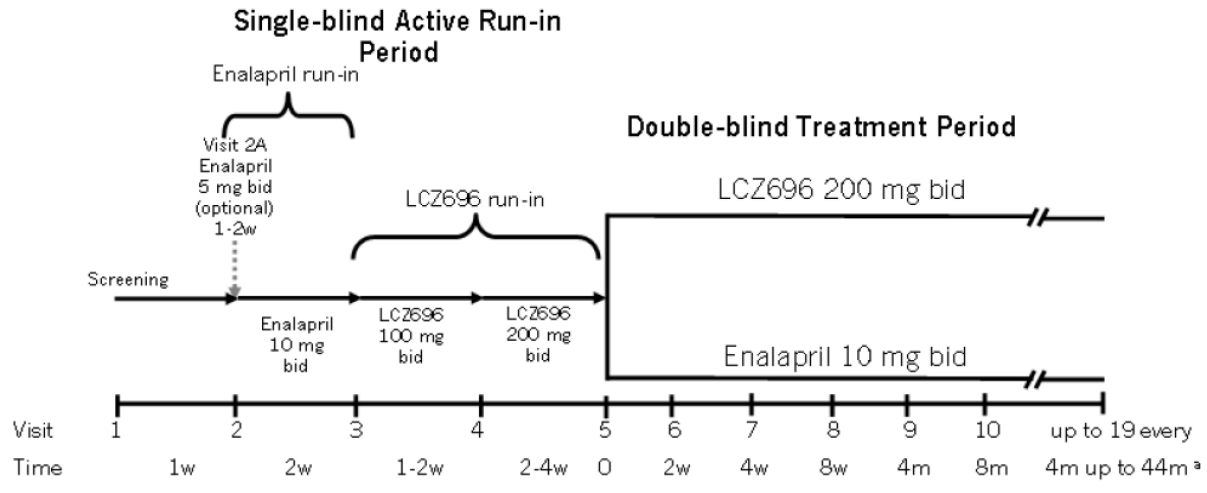
- time to all-cause death;
- change from baseline to Month 8 in the clinical summary score for heart failure symptoms and physical limitations as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ);
- time to new-onset of atrial fibrillation;

- time to first occurrence of: a 50% decline in estimated glomerular filtration rate (eGFR) relative to baseline; a > 30 mL/min/1.73 m^2 decrease in eGFR to a value < 60 mL/min/1.73 m^2; or end-stage renal disease (ESRD).

A Clinical Endpoint Committee adjudicated all reported deaths, unplanned hospitalizations for heart failure and myocardial ischemia, non-fatal myocardial infarctions, non-fatal strokes, resuscitated sudden deaths, new-onset atrial fibrillation, new-onset diabetes mellitus, ESRD, and worsening renal function events that occurred during the run-in and randomized periods.

After discontinuing their ACE inhibitor or ARB, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg BID, followed by LCZ696 100 mg BID, increasing to 200 mg BID. Subjects who completed the sequential run-in periods were randomized 1:1 to LCZ696 200 BID or enalapril 10 mg BID (see Figure 1).

Figure 1: PARADIGM-HF Study Design



Based on various assumptions, 2,410 composite endpoint events were expected to provide 97% power to detect a 15% reduction in the 1° endpoint.

Three (3) interim analyses were planned to assess efficacy: when 1/3, 1/2, and 2/3 of the expected 1° endpoint events were reported. A Haybittle-Peto boundary rule was used to assess superiority and control the overall Type-I error at 0.025 (1-sided). An α of 0.0001 (one-sided) was spent at the first interim analysis; with 0.001 (one-sided) spent at the second and third interim analyses. If the study were stopped at an interim analysis, the 2° endpoints were to be tested using the same α used for the 1° endpoint. The testing of the 4 secondary endpoints was to be done using the Bonferroni-Holm's method. As shown in Figure 1 of Dr. Lawrence's review, the α was initially split between the first two secondary endpoints, with 80% of the α allocated to all-cause mortality and 20% allocated to the KCCQ. If both hypotheses were rejected, the full α was to be allocated to the next secondary endpoint on the testing chain; if only one of the initial hypotheses was rejected, the α allocated to the rejected hypothesis would then be allocated to the next 2° endpoint.

According to the statistical analysis plan, the 1° composite endpoint would be analyzed using a Cox regression model with terms for treatment and region. The 1° efficacy analysis was to include all positively adjudicated events occurring between randomization and March 31, 2014 (the date the trial was terminated early for efficacy). The analysis was to be based on all randomized patients, excluding patients who did not qualify for randomization but were inadvertently randomized and did not receive study drug.

There were no controversies or disagreements with the applicant with respect to the statistical plan or analyses.

Results:

Disposition:
The trial was initiated on December 8, 2009 and terminated for efficacy on March 31, 2014 on the basis of the third planned interim analysis. A total of 10,521 subjects entered the initial run-in period. Of these, 1,102 subjects failed the enalapril run-in period and 982 failed the LCZ696 run-in period (10.5% and 10.4% of subjects entering each run-in period, respectively). In total, approximately 20% of those who entered the initial run-in period were not randomized. About half of these patients discontinued because of an adverse event, most commonly renal dysfunction, hyperkalemia, or hypotension. Importantly, as the review team points out, because of the run-in periods, the randomized population was enriched in terms of tolerating the drug and their willingness to stay in the trial. In "real-world" use, of course, renal dysfunction, hyperkalemia, and hypotension are expected more often than reported in the randomized phase of PARADIGM-HF.

A total of 8,442 subjects were randomized, and all but 10 received study drug. A total of 35 (0.4%) subjects did not complete study follow-up because of withdrawal of consent or loss to follow-up. In the double-blind treatment period, ~17% of subjects prematurely discontinued therapy in the LCZ696 group, compared with ~19% in the enalapril group. The most common reason for treatment discontinuation during the double-blind treatment period was an adverse event (10.4% of subjects randomized to LCZ696 and 12.1% of subjects randomized to enalapril). Vital status was unknown for 20 (0.2%) subjects.

Serious GCP violations were identified at 4 sites that had enrolled a total of 37 subjects. The applicant prospectively chose to exclude all 37 from the efficacy analyses, but included them in the safety analyses. Six (6) subjects were "misrandomized:" IVRS randomization calls were mistakenly placed, in spite of the subjects failing the run-in period. None of the 6 received study medication, and all were prospectively excluded from efficacy analyses.

Table 1: PARADIGM-HF - Subject disposition during the randomized double-blind period

	Enalapril n (%)	LCZ696 n (%)
Randomized	4233 (100)	4209 (100)
Not treated	4 (0.1)	6 (0.1)
Primary efficacy population (full analysis set)	4212 (99.5)	4187 (99.5)
Excluded	21 (0.5)	22 (0.5)
Misrandomized[1]	2 (0.1)	4 (0.1)
Site excluded for GCP violations	19 (0.5)	18 (0.4)
Completed study on treatment	3379 (79.8)	3441 (81.8)
Alive at study termination	2869 (67.8)	3011 (71.5)
Prematurely discontinued study treatment	815 (19.3)	729 (17.3)
Did not complete study	18 (0.4)	17 (0.4)
Withdrew consent	13 (0.3)	15 (0.4)
Vital status unknown	4 (0.1)	9 (0.2)
Lost to follow-up (vital status unknown)	5 (0.1)	2 (0.1)

As expected for an 8,000-patient study, the two treatment arms were balanced with respect to baseline characteristics. Approximately 5% of subjects were enrolled at U.S. sites. Mean age was 64 years, with ~19% of patients over 75. The majority of subjects were Caucasian (66%) and male (78%). Approximately 5% of subjects were black. Most subjects (70%) were NYHA Class II; 24% were Class III and 0.7% were Class IV. Mean ejection fraction was 29%; mean baseline eGFR was 68 mL/min/1.73m^2; and mean systolic blood pressure and heart rate were 122 and 73, respectively. The majority of subjects were taking beta-blockers (94%), mineralocorticoid antagonists (56%), and diuretics (82%). Most patients (71%) had a history of hypertension. Atrial fibrillation was reported in 37% of patients. The cause of heart failure was reported to be ischemic in 60% of patients.

Patients were reasonably representative of a U.S. heart failure population with respect to demographics (race notwithstanding) and disease-specific factors. But patients were not representative with respect to use of implantable cardioverter-defibrillators (ICD) or cardiac resynchronization therapy-defibrillator (CRT-D). Only 15% of the overall study population used these devices; in contrast, device use was reported in 60% of subjects enrolled at U.S. sites. Thus, relative to the U.S. population, patients with ICDs or CRT-D were under-represented in the study. The Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting included ~35,000 patients at 167 US outpatient cardiology practices with reduced LVEF ($\leq$ 35%) and chronic HF or previous myocardial infarction. Based on chart review, use of a CRT with a pacemaker or defibrillator ranged from 37 to 66%; use of ICDs ranged from 50 to 77% (*Circulation* 2010;122:585).

Median duration of exposure was ~2 years in both treatment groups.

Primary endpoint findings:

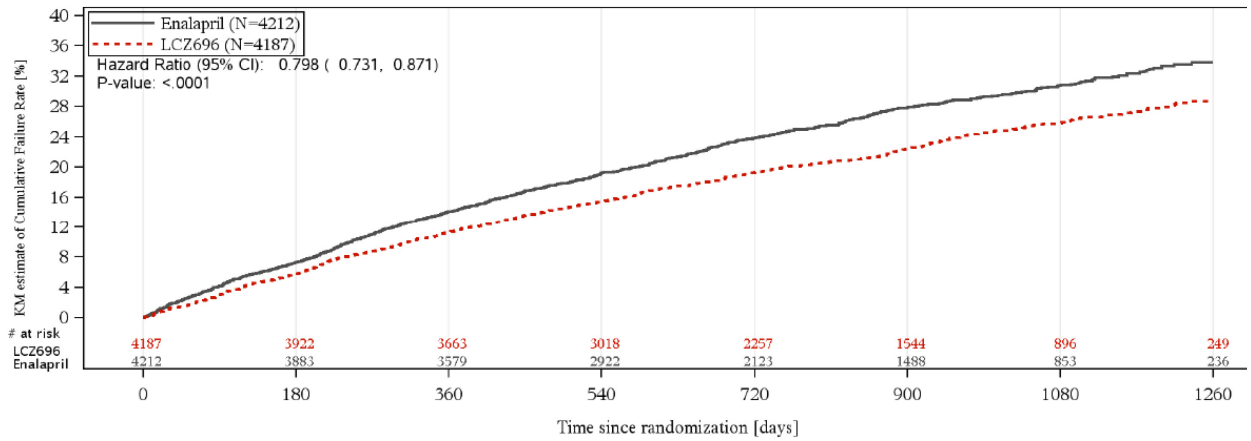
As of the interim analysis cut-off date, there were 914 endpoint events in the LZ696 arm (21.8%) and 1117 events (26.5%) in the enalapril arm (HR = 0.80; 95% confidence interval [CI] 0.73; 0.87, $p < 0.001$). See Table 2 and Figure 2. The treatment effect reflected reductions in both of the endpoint components. Approximately 40% of first events were cardiovascular deaths; ~60% were hospitalizations for worsening heart failure.

Table 2: PARADIGM-HF - 1° Efficacy Endpoint; Events at Any Time

	LCZ696	Enalapril	Hazard ratio
	N=4187	N=4212	
	n(%)	n(%)	(95% CI, p-value)
Primary composite endpoint	914 (21.8)	1117 (26.5)	0.80 (0.73, 0.87)
cardiovascular death	377 (9.0)	459 (10.9)	
heart failure hospitalization	537 (12.8)	658 (15.6)	<0.0001
Subjects with events at any time**			
cardiovascular death	558 (13.3)	693 (16.5)	0.80 (0.71, 0.89)
heart failure hospitalization	537 (12.8)	658 (15.6)	0.79 (0.71, 0.89)

*Analysis of time-to-first component; **Analyses of events at any time were not prospectively planned endpoints.

Figure 2: PARADIGM-HF, Kaplan-Meier for 1° Efficacy Endpoint



Subgroup Analyses on the 1° Endpoint:

The results for the primary composite endpoint were consistent across a number of subgroups of interest. Some subgroup analyses were planned by the applicant; additional analyses were requested and/or conducted by the review team. Results were consistent (in fact, the point

estimate of the hazard ratio was <1) for all[1] of the following subgroups: age ≤65 Y/N; age ≥75 Y/N, sex, weight quartiles, race, region, US alone, NYHA functional class, eGFR ≥60 Y/N, diabetes Y/N, baseline systolic blood pressure (roughly quartiles), ejection fraction (roughly quartiles), history of atrial fibrillation Y/N, history of hypertension Y/N, prior use of ACE inhibitor or ARB Y/N, use of aldosterone antagonists Y/N, cause of heart failure (ischemic Y/N), and use of ICD or CRT-D. For some 434 patients enrolled in the U.S., where use of ICDs or CRT-D was common (~60% of patients), the 95% confidence interval of the hazard ratio excluded 1, providing some reassurance that the overall results are applicable to U.S. patients.

Secondary Efficacy Endpoints:

All-Cause Mortality:

The trial was successful on its 1° endpoint; therefore, all-cause mortality was tested with the prospectively planned α (80% of the α used to test the 1° endpoint). All-cause mortality was statistically significantly lower in the LCZ696 arm (HR of 0.84 [0.76, 0.93]; $p < 0.001$)). It is important to note, however, that the finding for all-cause mortality was driven entirely by cardiovascular mortality (some 80% of deaths were deemed to be cardiovascular in nature; there were few non-cardiovascular deaths, and there were numerically more in the LCZ696 group). Thus, the review team has concluded that statements to the effect that LCZ696 improves survival should be accompanied by a notation that the effect was driven by a decrease in cardiovascular death. I would go further, and say that the concept of a decrease in all-cause mortality is actually misleading, even though the study technically "won" on this endpoint. There is no reasonable expectation that LCZ696 would decrease deaths that are unrelated to the cardiovascular system; indeed, there were numerically more cardiovascular deaths in the LCZ696 group. (b) (4) Our interest in all-cause mortality is to evaluate the unlikely possibility that a therapy has unanticipated, deleterious effects beyond the cardiovascular system. (b) (4) display the all-cause mortality results in Section 14. The indication statement will state that LCZ696 reduces cardiovascular mortality (b) (4)

KCCQ Clinical Summary Score:

The change in the KCCQ Clinical Summary Score from randomization to Month 8 was tested with its prospectively planned α (20% of the α used to test the 1° endpoint). At month 8, there was less of a decline in the Clinical Summary Score in the LCZ696 treatment group compared to the enalapril group; however, the treatment effect was small. The least square mean of the difference was only 1.6 (95% CI [0.6, 2.7]) in subjects with a mean baseline score of ~76. Moreover, although the *p*-value for this analysis was quite low, it exceeded the allocated α, so that the study was technically not a "win" on this endpoint.

Furthermore, as the reviews note, subjects who died were assigned a score of zero for all subsequent visits. Given the disparity in numbers of deaths between groups, deaths were

[1] The hazard ratio was >1 for the small number patients who were NYHA Functional Class I (about 5 % of patients in the trial), but the drug is not indicated for these patients.

responsible for more than one-third of the treatment difference in KCCQ, providing additional reason to doubt the clinical significance of the effect on KCCQ.

As discussed in the Clinical Review, the applicant also conducted responder analyses based on the number of subjects with ≥ 5-point deterioration or improvement in the clinical summary score from baseline to Month 8, because a 5-point change is thought to represent a clinically meaningful change in score according to the applicant. Fewer LCZ696 subjects deteriorated by ≥ 5 points on the clinical summary score compared with enalapril subjects; however, there was no difference in the number of subjects with a ≥ 5 point improvement. A cumulative distribution plot of the change in Clinical Summary Score did not suggest a subpopulation with a marked treatment response.

(b) (4)

Finally, as stated in the regulatory history provided in Dr. Thompson's review, (b) (4)

New Onset Atrial Fibrillation and Progression of Renal Disease:

For the remaining secondary endpoints, new onset atrial fibrillation and the renal composite endpoint, there were no treatment effects. Atrial fibrillation was reported as an adverse event in 6.0 vs. 5.6% of patients in the LCZ696 and enalapril groups, respectively.

8. Safety

The clinical review provided a meticulous, in-depth description and analysis of safety. The safety database from PARADIGM-HF includes 4,203 subjects who received at least 1 dose of LCZ696 during the double-blind period of the study, a number that far exceeds ICH E1 recommendations. The noteworthy issues are well-characterized by the review team and summarized below: angioedema, hypotension and related adverse events, renal impairment, hyperkalemia, cognitive impairment, and gynecomastia.

General Tolerability

The label will note that "…subjects 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. During the enalapril run-in period, 1,102 patients (10.5%) 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, 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."

As summarized in the clinical pharmacology review, 58% of patients were able to maintain their target dose throughout the study duration, and 42% had at least one dose reduction. Approximately 80% of the dose reductions were for adverse events, most commonly hypotension, renal dysfunction, and hyperkalemia.

Fetal Toxicity

LCZ696 is teratogenic and causes fetal harm in non-clinical studies. Drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy are well known to increase fetal and neonatal morbidity and death. There will be a warning in the label similar to that in other RAAS inhibitors.

Angioedema

Angioedema was a safety topic of interest in part because of the experience with omapatrilat, a combination ACE inhibitor and neprilysin inhibitor. In the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial, a multicenter, double-blind, 24-week trial in 25,302 patients with hypertension, the incidence and severity of angioedema was worse with omapatrilat than enalapril (2.2% of patients with angioedema on omapatrilat vs. 0.7% on enalapril; risk ratio = 3.2 (source: FDA advisory committee briefing book for omapatrilat tablets NDA 21-188, Cardiovascular and Renal Drugs Advisory Committee Meeting; July 19, 2002, downloaded on June 19, 2015 at http://www.fda.gov/ohrms/dockets/ac/02/briefing/3877B2_01_BristolMeyersSquibb.pdf). Moreover, of the omapatrilat cases, a third occurred on the first day of exposure compared with practically none in the enalapril group. Importantly, the risk was 3-fold higher in black subjects than Caucasians. Among Blacks, the incidence was 5.5% and 1.6% on omapatrilat and enalapril, respectively.

In the LCZ696 development program, potential angioedema adverse events were adjudicated by a blinded adjudication committee. In PARADIGM-HF, there were 54 confirmed cases of angioedema: 15 (0.1%) in the enalapril run-in, 10 (0.1%) in the LCZ696 run-in, and 29 in the double-blind treatment period (19 [0.5%] in the LCZ696 group and 10 [0.2%] in the enalapril group). Thus, although the incidence of angioedema was low, it was some 2.5-fold higher with LCZ696 than enalapril.

The review team shows K-M plots for each of the run-in periods and the double-blind period. They show that angioedema tended to occur earlier rather than later, but many cases were delayed: 2 cases were reported after 2 years on LCZ696. The K-M curves could be interpreted as showing that angioedema is an early event; however, they are also consistent with the concept that risk decreases as susceptible patients who develop angioedema are progressively removed from the study. A few patients required hospitalization but none required mechanical airway protection or died from airway compromise.

Because black patients are more susceptible to angioedema with ACE inhibitors, Dr. McDowell examined the incidence of angioedema by race, and specifically at U.S. sites. Approximately 5% of subjects in the study were black. For the 213 black subjects randomized to LCZ696, 5

(2.4%) had a confirmed case of angioedema. In the U.S., however, there were 3 cases of confirmed angioedema in the LCZ696 group among only 54 patients (5.6%) vs. 0 of 57 in the enalapril group. Because of the small numbers of black subjects enrolled in the trial, there is considerable uncertainty about the risk of serious events of angioedema in this population. The review team has recommended a post-marketing requirement (PMR) to evaluate the risk of serious angioedema events in black patients treated with LCZ696 in the United States, and I agree with their recommendation.

The Division consulted the Division of Epidemiology II (DEPI). They recommended (b) (4), because a number of factors can confound the level of risk determined post-marketing.

During implementation of the PMR, DEPI intends to conduct active monitoring (safety surveillance) of angioedema events in the post-marketing period. Active monitoring activities will include, but not be limited to, examining observational data to try to determine the incidence of angioedema events in association with sacubitril/valsartan use in the general population, in Blacks specifically (if possible), and in newly exposed patients. DEPI plans to use other medications indicated for heart failure as comparators. DEPI will consider observational data sources including Sentinel and CMS data for these efforts.

The review team believes that the risk of angioedema can be managed with labeling. Specifically, the label includes a contraindication in patients with hypersensitivity to either sacubitril or valsartan and those with a history of angioedema related to previous ACEs or ARBs. Based on the experience with omapatrilat, concomitant use with an ACE inhibitor or within 36 hours of switching to or from an ACE inhibitor is also contraindicated. Finally, the label contains a Warning related to the risk of angioedema, which notes: (b) (4) Based on the available data, I agree that the labeling should be adequate to mitigate this risk.

Of note, the applicant proposed a (b) (4)

Hypotension

Hypotension was a safety topic of interest based on the recognized class effect of RAAS agents. Hypotension was one of the more common AEs leading to run-in failure in PARADIGM-HF. The incidence of hypotension-related adverse events (including dizziness, syncope, presyncope, etc.) was 3.2% in the enalapril run-in period (1.5% discontinued from the study) and 5.1% in the LCZ696 run-in period (1.8% discontinued from the study).

In the double-blind period of PARADIGM-HF, ~24% of patients in the LCZ696 group had a hypotension-related adverse event, vs. ~19% in the enalapril group. The respective percentages for serious adverse events were 3.5% and 2.8%.

About half of the time, the drug was dose-reduced, interrupted, or discontinued (12.2% in the LCZ696 group; 8.4% in the enalapril group; from Clinical Review, Table 65, copied below), and about half the time, no actions were taken. It is notable, however, that <1% of these adverse events led to permanent discontinuation.

Consistent with the excess hypotension with LCZ696, there was more orthostasis in the LCZ696 group (2.1% vs. 1.1%) and more falls (1.9% vs. 1.3%), but the numbers of patients with fractures were similar in the 2 groups.

Table 3: Actions taken for hypotension-related events during the double-blind period in PARADIGM-HF (Clinical Review, Table 65)

	Enalapril N =4,229 n (%)	LCZ696 N=4,203 n (%)
Hypotension-related AE[a]	786 (18.6%)	1027 (24.4%)
- No action taken	384 (9.1%)	504 (12.0%)
- Study dose adjusted/temporary interruption	327 (7.7%)	475 (11.3%)
- Study drug permanently discontinued	29 (0.7%)	36 (0.9%)
- Concomitant medication taken[b]	128 (3.0%)	175 (4.2%)
- Non-drug therapy given	23 (0.5%)	38 (0.9%)
- Hospitalization/prolonged hospitalization	121 (2.9%)	104 (2.5%)

Similar to the analyses for angioedema, the reviewer's time-to-event analyses show that hypotension tends to occur early (half of the events during the first 6 months), but not exclusively so. Again, it is possible that susceptible patients were having dose adjustments or treatment discontinuations, such that the number of patients at risk was depleted with time.

Dr. McDowell performed subgroup analyses for hypotension-related AEs. In both treatment groups, patients at higher risk of hypotension events included those ≥ 65 years old, those with lower baseline eGFR, and those with lower baseline systolic BP; however, the relative risk for all subgroups was consistent with that of the overall population.

Renal Impairment

Renal impairment was a topic of interest based on the class effect of RAAS agents. Renal impairment was the most common adverse event leading to study withdrawal during the run-in in PARADIGM-HF. During the enalapril and LCZ696 run-in periods, 1.7% and 1.8% of patients, respectively, discontinued from the study because of renal dysfunction.

During the double-blind period of PARADIGM-HF, 16.2% of patients had renal impairment adverse events in the LCZ696 group, vs. 17.6% in the enalapril group. For serious adverse events, the respective frequencies were 3.8% and 4.4%.

When analyzed on the basis of changes in creatinine or eGFR, results in the two groups during the double-blind treatment period were similar. The clinical reviewer's time-to-event analysis of

renal impairment adverse events shows that the incidence is fairly constant over time (Figure 17, clinical review).

Subgroup analyses for renal impairment events do not identify any subgroup where there is a meaningful difference in relative risk, but the overall risk is highest in patients with baseline eGFR < 60mL/min, in US patients, and in patients with lower systolic BP.

Hyperkalemia

Hyperkalemia was a safety topic of interest based on known class effects. Hyperkalemia was reported in 2.8% of patients during both of the run-in periods. Hyperkalemia was one of the major reasons patients discontinued from the study during the run-in periods: during the enalapril and LCZ696 run-in periods, 1.7% and 1.3% of patients, respectively, discontinued from the study because of hyperkalemia.

The incidence of hyperkalemia was numerically lower (and, as reported by the review team, nominally statistically significantly lower) in the LCZ696 group (11.9%) compared to the enalapril group (14.3%). It is certainly *possible* that LCZ696 causes less hyperkalemia than enalapril, (b) (4)

(b) (4)

When hyperkalemia occurred, no actions were taken with respect to study medication some 60% of the time, but there were dose adjustments, interruptions, or discontinuations in ~30% of cases (Clinical Review, Table 75). Specifically, 3.9% of subjects in the LCZ696 treatment group had a dose adjustment, interruption, or discontinuation of study medication for hyperkalemia during the double-blind period, vs. 4.6% in the enalapril group.

In summary, hyperkalemia is a safety concern for both drugs, (b) (4)

Cognitive Impairment

As discussed above, neprilysin degrades Aβ in the brain, and there is a theoretical risk that LCZ696 could increase cerebral accumulation of Aβ, causing cognitive dysfunction and/or an increased risk of Alzheimer's disease.

Dr. McDowell performed comprehensive analyses of adverse events suggestive of dementia or cognitive dysfunction in PARADIGM-HF and found no signal (see clinical review, Table 77; reprinted below as Table 4). The incidence of potential dementia-related adverse events (as defined using the broad standard MedDRA query [SMQ]) was similar in the two treatment groups in the double-blind period: 2% in both groups for adverse events; 0.5% in both groups for serious adverse events.

Table 4: PARADIGM-HF: Potential dementia-related AEs during the double-blind period (Reprinted: Table 77 of the Clinical Review)

	AE		SAE	
SMQ/Preferred term	Enalapril N=4,229	LCZ696 N=4,203	Enalapril N=4,229	LCZ696 N=4,203
Dementia broad SMQ	**83 (2.0%)**	**86 (2.0%)**	**20 (0.5%)**	**21 (0.5%)**
Confusional state	18 (0.4%)	12 (0.3%)	8 (0.2%)	6 (0.1%)
Somnolence	9 (0.2%)	11 (0.3%)	0 (0.0%)	0 (0.0%)
Delirium	8 (0.2%)	10 (0.2%)	4 (0.1%)	2 (0.0%)
Amnesia	7 (0.2%)	10 (0.2%)	1(0.0%)	0 (0.0%)
Dementia	10 (0.2%)	6 (0.1%)	0 (0.0%)	0 (0.0%)
Memory impairment	6 (0.1%)	6 (0.1%)	0 (0.0%)	0 (0.0%)
Agitation	3 (0.1%)	7 (0.2%)	0 (0.0%)	0 (0.0%)
Aphasia	4 (0.1%)	5 (0.1%)	0 (0.0%)	2(0.0%)
Disorientation	4 (0.1%)	5 (0.1%)	2 (0.0%)	0 (0.0%)
Cognitive disorder	5 (0.1%)	4 (0.1%)	0 (0.0%)	0 (0.0%)
Hallucination	5 (0.1%)	3 (0.1%)	2 (0.0%)	0 (0.0%)
Mental status changes	1 (0.0%)	5 (0.1%)	0 (0.0%)	4 (0.1%)
Restlessness	2 (0.0%)	3 (0.1%)	0 (0.0%)	0 (0.0%)
Mental disorder	1 (0.0%)	3 (0.1%)	1(0.0%)	2 (0.0%)
Dementia Alzheimer's type	2 (0.0%)	2 (0.0%)	0 (0.0%)	1 (0.0%)
Initial insomnia	2 (0.0%)	2 (0.0%)	0 (0.0%)	0 (0.0%)
Cerebral atrophy	0 (0.0%)	4 (0.1%)	0 (0.0%)	1(0.0%)
Psychotic disorder	2 (0.0%)	1 (0.0%)	2 (0.0%)	0 (0.0%)
Vascular dementia	1 (0.0%)	2 (0.0%)	0 (0.0%)	0 (0.0%)
Senile dementia	2 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mental impairment	2 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mood altered	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Amnestic disorder	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
Feeling abnormal	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Affect lability	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hippocampal sclerosis	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
Presenile dementia	0 (0.0%)	1 (0.0%)	0 (0.0%)	1 (0.0%)

These data are somewhat reassuring, but they have limitations. Given the likely timeframe for progression of Aβ-related cognitive dysfunction, the trial was too short to detect longer-term toxicity. Moreover, dementia and cognitive function were not prospectively assessed or identified as adverse events of special interest; dementia-related events were simply captured through standard adverse event collection. Assessment of more sensitive metrics of cognition might detect more subtle abnormalities.

Despite these limitations, I believe that if sacubitril had caused obvious CNS toxicity over the duration of the study, we would have observed a difference in adverse events in this controlled study, given that a large number of patients were exposed to sacubitril (4,200) over a median of 2 years, and the study was enriched for patients at higher risk of cognitive dysfunction (median age was 64 years, with 19% of patients [~800] older than 75). If CNS toxicity were subtle, however, the study could have missed it.

Gynecomastia

The frequencies of gynecomastia as an adverse event were 1.2% and 0.6% in the LCZ696 and enalapril groups, respectively (relative risk = 2). This signal is not easy to interpret.

Gynecomastia is a known side effect of spironolactone, a concomitant medication that was used in half of the patients in PARADIGM-HF. The vast majority of subjects with adverse events of gynecomastia in both treatment groups were taking spironolactone (42 of 50 [84%] in the LCZ696 group; 22 of 24 [92%] in the enalapril group).

Of note, however, the incidence of gynecomastia was very low in subjects treated with LCZ696 in other studies (1 of 149 in patients with diastolic heart failure and 1 of 2004 in patients with hypertension), and there were no findings suggesting a risk of gynecomastia in non-clinical studies.

Thus, I agree with the review team: considering the totality of evidence, the observed numerical imbalance in gynecomastia in PARADIGM-HF is most likely a chance finding.

9. Advisory Committee Meeting

We chose not to convene the Cardiovascular and Renal Drugs Advisory Committee to evaluate this NDA. Although one of the drugs is a new molecular entity with a novel mechanism of action, the applicant provided a conventionally-designed study with typical endpoints. The study was well executed, the clinical benefit was clear, both in terms of the effect size and the statistical persuasiveness, and there were no risks of sufficient magnitude to make one seriously question whether the benefit outweighed the risk. We also considered the likelihood that convening our Advisory Committee could delay approval, and we endeavored to complete our reviews expeditiously to permit as rapid an action as practicable. We believe our decision not to hold an advisory committee meeting to review this application was reasonable and appropriate.

10. Pediatrics

The applicant requested a waiver for all pediatric age groups, and the review team believes one should be granted. As noted by the review team, the etiology of heart failure differs in children and adults, and studies would be impossible or highly impracticable. PeRC reviewed and granted the waiver request on June 24, 2015.

11. Other Relevant Regulatory Issues

Site Inspections:

The Office of Scientific Investigation (OSI) inspected 4 foreign clinical sites in PARADIGM-HF, as well as the applicant. No regulatory violations were found during inspections at 2 sites, and minor regulatory violations were found at 2 sites (failure to follow the investigational plan; failure to prepare and maintain accurate records). OSI considered the violations unlikely to affect the quality or the integrity of the data, and deemed all 4 sites acceptable for support of the NDA. No regulatory violations were observed during the inspection of the applicant.

Financial Disclosures:

Is noted by Dr. Thompson and others, the applicant has adequately disclosed financial arrangements with clinical investigators in PARADIGM-HF, and there are no concerns about the integrity of the data.

Name Review:

The Division of Medication Error Prevention and Analysis concluded that the proposed proprietary name, “Entresto,” is acceptable from both a promotional and safety perspective.

Combination Policy:

LCZ696 is a fixed-combination drug that includes two active ingredients, valsartan and sacubitril, combined at a fixed dosage in a single dosage form. According to regulations at 21 CFR 300.50, both active ingredients must contribute to the effect of the combination – to enhance effectiveness or safety. Typically, individual contributions are demonstrated through a factorial study (AB vs. A vs. B), where AB is shown to have a larger effect than either A or B alone (i.e., AB > A and AB > B). Such studies can be conducted with or without a placebo group, depending on whether it is necessary to determine the overall treatment effect. Drs. McDowell and Smith addressed the salient points of the combination rule on pp. 43-44 of their clinical review.

Although the use of valsartan as the active comparator in PARADIGM-HF has obvious logic and would have been reasonable, both ARBs and ACE inhibitors have claims for the treatment of heart failure, and the claims for ACE inhibitors have stronger support. As discussed with Novartis at the April, 2009, pre-IND meeting, ACE inhibitors are generally recognized as the standard of care and treatment of choice for heart failure, with ARBs reserved for patients who cannot tolerate ACE inhibitors. The Division agreed that either valsartan or enalapril would be a reasonable choice for the comparator.

PARADIGM-HF can be construed, therefore, as a study of sacubitril plus a RAAS inhibitor vs. a RAAS inhibitor, in essence, AB vs. B. The primary hypothesis was designed to test whether sacubitril, added on to proven therapies, reduced cardiovascular mortality and heart failure hospitalizations. *This was a classic “add-on” study; what sets it apart from other trials in heart failure is the unusual feature that one of the standard therapies was part of a fixed-combination product.*

PARADIGM-HF shows superiority for LCZ696, which establishes sacubitril’s independent contribution to the efficacy of the fixed combination. Although a number of trials, outlined by Drs. McDowell and Smith, show that valsartan is also effective in this patient population, *the unknown here is whether valsartan adds to the efficacy of sacubitril in this patient population, i.e., whether valsartan is contributing to the efficacy of the fixed combination.* Whereas PARADIGM-HF tested AB vs. B, there is no test of AB vs. A, i.e., LCZ696 vs. sacubitril.

The applicant contends that treatment with sacubitril alone could lead to increases in angiotensin II, which is detrimental in heart failure, such that sacubitril should not be administered without concomitant blockade of the renin-angiotensin-aldosterone system. This argument was not well substantiated by the applicant; in fact, the non-clinical data did not suggest that sacubitril would be harmful if used alone. There is, however, a far more compelling reason for not conducting a study to compare LCZ696 to sacubitril alone. In such a study, those in the sacubitril group would not receive an ARB or ACE inhibitor, and therefore would be denied a proven life-saving therapy. It seems clear that a study of this design would be unethical. Comparing a fixed-combination drug to its individual active ingredients is always a

problem if both active ingredients have established beneficial effects on mortality or important morbidity endpoints. In this case, comparing LCZ696 to enalapril was not a problem because all patients received the established life-saving therapies (valsartan or enalapril), and sacubitril had not yet been shown to be effective.

Dr. Lawrence, the primary statistical reviewer, questions whether LCZ696 should be approved at all, arguing that we should obtain evidence that both components contribute to the overall treatment effect. The remainder of the review team disagrees. Though we might wish for a study to examine whether valsartan contributes to the efficacy of sacubitril in this patient population, the ethical considerations described above make this study impossible to conduct.

As troublesome as this may seem, given the combination rule, this is a common scenario that arises whenever we evaluate a drug of a new class studied on top of established therapies with important benefits. For example, the efficacy of carvedilol and metoprolol were characterized in patients with heart failure when used in addition to ACE inhibitors and diuretics. It is not known whether ACE inhibitors or diuretics provide additive benefit when used with beta-blockers. Similarly, spironolactone and hydralazine/isosorbide dinitrate were added to extant heart failure therapies, but the contributions of these background therapies to the combination of therapies have not been documented. Though we might like to obtain data to answer these questions, the trials would be unethical, e.g., a study of carvedilol plus an ACE inhibitor vs. carvedilol alone. Withholding an ACE inhibitor from a group of patients with heart failure, where the drug is known to prolong survival in this population, would not be ethical.

Cancer Risk:

As noted by Dr. Stockbridge, Dr. Thomas Marciniak, formerly a team leader in the Division of Cardiovascular and Renal Products, had a longstanding interest in the potential of various medications to cause cancer, including angiotensin receptor blockers (ARBs). In 2010, he raised concerns sparked by a 5-trial meta-analysis by Sipahi I, *et al* (*The Lancet Oncology* 2010;11: 627-36) that suggested a modest risk of cancer associated with ARBs. Ultimately, FDA conducted a 31-trial meta-analysis and concluded that treatment with ARBs does not increase the risk of cancer (http://www.fda.gov/Drugs/DrugSafety/ucm257516.htm; downloaded 6/30/2015).

For this NDA, Dr. Marciniak filed an unsolicited 114-page review, focused largely on cancer. He noted that "For the evaluation of malignancies in PARADIGM I used the methodology I had developed for evaluating malignancies in ARB trials. I have included the pre-specified plan describing that methodology as Attachment 1."

Overall, he found essentially equal numbers of solid tumors in the two treatment groups in PARADIGM-HF (122 in LCZ696; 118 in enalapril), but he expressed concern about a difference in the numbers of lung cancers (27 in LCZ696; 22 in enalapril, relative risk = 1.2), consistent with his longstanding concern about ARBs and lung cancer. He wrote: "The statistically insignificant lung cancer imbalance in PARADIGM in isolation would not be concerning. However, the point estimate of the increased risk of lung cancer with LCZ696 (about 20% by logistic or Cox regression) is similar to that seen with ARBs."

As Dr. Stockbridge notes, he minimized the importance of the very favorable relative risk for non-melanomatous skin cancer (11 in LCZ696; 29 in enalapril, relative risk = 0.38), because

such cancers are “variably reported,” and he noted he has “seen many similar imbalances of skin cancers in other trials that were not confirmed in other trials of the same drug.”

With respect to lung cancer, I will go a bit farther. Whereas Dr. Marciniak used his own “pre-specified plan” for assessing adverse events related to cancer, I believe that such methodologies, beyond simple counting of adverse events related to cancer, are fraught with difficulty, subject to interpretation, and potentially misleading. For cardiovascular outcome trials, there is little or no emphasis on assessing patients’ past medical histories related to cancer, i.e., whether there was a past history of cancer, and if so, whether the cancer was thought to be cured, in remission, or active. My preference, therefore, is simply to count the adverse events related to various cancers, recognizing the inherent limitations and uncertainties of the method – the extent to which cancer adverse events are reported, and whether cancers are newly diagnosed, recurrent, or stable.

From the 42,427 adverse events recorded in PARADIGM-HF, I found 50 adverse events related to lung cancer: there were 25 in both groups (See Table 5). In short, I cannot corroborate the minor difference reported by Dr. Marciniak (27 lung cancers with LCZ696; 22 with enalapril).

Table 5: PARADIGM - Adverse Events Related to Lung Cancer

	LCZ696	Enalapril
ADENOSQUAMOUS CELL LUNG CANCER		1
BRONCHIAL CARCINOMA	2	5
BRONCHIOLOALVEOLAR CARCINOMA		1
LUNG ADENOCARCINOMA	5	1
LUNG CANCER METASTATIC	2	
LUNG CARCINOMA CELL TYPE UNSPECIFIED STAGE IV		2
LUNG NEOPLASM MALIGNANT	11	13
NON-SMALL CELL LUNG CANCER	2	
SMALL CELL LUNG CANCER	1	2
SQUAMOUS CELL CARCINOMA OF LUNG	2	
Total	**25**	**25**

As previously noted by the Division and disseminated in a Drug Safety Communication, there is no evidence that ARBs cause cancer.

12. Labeling

Some of the major labeling issues are described below:

1 INDICATIONS AND USAGE

(b) (4)

(b) (4)

3 DOSAGE FORMS AND STRENGTHS

There was considerable discussion on finding an appropriate way to express the various strengths. The applicant had originally proposed (b) (4) we agreed on Entresto 24/26 mg, (sacubitril 24 mg and valsartan 26 mg), 49/51 mg, and 97/103 mg.

6 ADVERSE REACTIONS

Because LCZ696 was compared to an active drug, listing adverse drug reactions in the table can be problematic. For example, although there is reasonable evidence that LCZ696 causes hyperkalemia, it caused numerically less hyperkalemia than enalapril. Ultimately, we selected adverse events that seemed causally related to LCZ696 for listing in the adverse reaction table.

14 CLINICAL STUDIES

The applicant wanted data on (b) (4) to be included in labeling. As the review team pointed out, however, an (b) (4) Thus, we will limit the description of (b) (4)

The applicant also wanted labeling to state that LCZ696 was shown to be superior to enalapril. Essentially PARADIGM-HF was an add-on study: a study of sacubitril with a RAAS inhibitor vs. a RAAS inhibitor alone (enalapril). The superiority shown in PARADIGM-HF reflects the effect of sacubitril (vs. nothing) on a background of a RAAS inhibitor, beta-blockers, diuretics, and mineralocorticoid receptor antagonists, not superiority of LCZ696 over enalapril. Thus, Section 14 will state: "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…."

For the 1° endpoint of PARADIGM-HF, (b) (4)

Ultimately the statisticians prevailed in their arguments that: 1) *p*-values are asymptotic and less reliable in the 'tails' of the distribution; 2) PARADIGM-HF was a group-sequential trial that was stopped early, but the *p*-value was not adjusted for this; 3) $p<0.0001$ is a fair approximation; 4) 0.0001 is little different from zero; 5) $p<0.0001$ conveys all the information that any reader needs to know; and 6) $p<0.0001$ is not likely to be misinterpreted.

13. Decision/Action/Risk-Benefit Assessment

Benefit-Harm

Benefits and harms must be considered in their proper context, and the situation for LCZ696 is somewhat complex. LCZ696 is a combination product consisting of sacubitril (a neprilysin inhibitor) and a RAAS inhibitor, and this combination product was compared to a RAAS inhibitor alone. Thus, the benefits and harms demonstrated in PARADIGM-HF represent those of sacubitril relative to nothing, administered on top of a RAAS inhibitor.

In patients with chronic heart failure (NYHA Functional Class II to IV) and left ventricular systolic dysfunction, there were 2.8% fewer heart failure hospitalizations (as first events) and 3.1% fewer cardiovascular deaths (including those that occurred after a hospitalization) over a median follow-up of 2 years. When adjusted for exposure, these translate into reductions of 1.6% and 1.5% per year, respectively (see Table 6, below, copied from Table 4 of the FDA Statistical Review). Thus, one would need to treat 63 patients for 1 year to keep 1 patient free of heart failure hospitalizations (number needed to treat [NNT] = 63); one would need to treat 67 patients for a year to prevent 1 cardiovascular death (NNT = 67).

Table 6: PARADIGM-HF - 1° Endpoint, Exposure-adjusted Incidence Rates/100 Patient-years (EAIR)

Response variable	LCZ696 n/N (%)	Enalapril n/N (%)	LCZ696 n/T (EAIR)(1) (95% CI)	Enalapril n/T (EAIR)(1) (95% CI)	HR (95% CI)
Primary Composite	914/4187 (21.83)	1117/4212 (26.52)	914/87.22 (10.48) (9.81,11.18)	1117/84.93 (13.15) (12.39,13.95)	0.80 (0.73,0.87)
CV death	558/4187 (13.33)	693/4212 (16.45)	558/93.08 (5.99) (5.51,6.51)	693/92.35 (7.50) (6.96,8.08)	0.80 (0.71,0.89)
1st HF Hospitalization	537/4187 (12.83)	658/4212 (15.62)	537/87.22 (6.16) (5.65,6.70)	658/84.93 (7.75) (7.17,8.36)	0.79 (0.71,0.89)

Although the numbers needed to treat and absolute effect sizes may not seem impressive, these reductions in hospitalizations and cardiovascular death are in addition to those provided by RAAS inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and diuretics, which together have cut the morbidity and mortality of heart failure substantially. Devices (CRT, ICD) are in wide use in the U.S., and also importantly decrease the morbidity and mortality of heart failure.

I will also point out that many patients with heart failure will simply take this drug indefinitely. There will be no way to tell whether, in an individual patient, the drug is helping to avoid hospitalization or prolong life. Typical of many cardiovascular drugs, there are no symptoms, signs, or laboratory tests that can be used to assess a patient's responsiveness to the drug.

Principal known potential harms (i.e., risks) include fetal toxicity, angioedema, hypotension, renal impairment, and hyperkalemia. None represents a barrier to approval.

Angioedema: Overall, about 0.7% of patients had angioedema in ~2 years, or about 0.4% per year. Angioedema tends to occur early, but not exclusively so. There is advice in a Warning in the label intended to mitigate risk by warning to avoid use in patients with predisposing factors

(essentially those with a history of angioedema), and to provide appropriate therapy and vigilance with respect to airway protection. The higher risk in Blacks is also noted. Because this advice was also followed in PARADIGM-HF, there is no expectation that the risk will be lower in actual practice than it was in the trial. Of note, there were no cases of angioedema with serious consequences in ~4000 patients in PARADIGM-HF. We have to presume, however, that with millions of patients exposed, there will be serious outcomes, including, very rarely, death. I find it reassuring that we have millions of patient-years of experience with a number of ACE inhibitors, all of which cause angioedema. In spite of this risk, we deem ACE inhibitors to be adequately safe for the long-term treatment of essentially healthy adults with hypertension. The risk with LCZ696 is likely to be of the same order of magnitude as the risk with ACE inhibitors, and is certainly small in compared to the benefit of LCZ696 in the heart failure population.

Hypotension: Treatment with LCZ696, as compared to enalapril, was associated with a higher incidence of hypotension, and orthostatic hypotension in particular. There was also an excess in falls (1.9% with LCZ696 vs 1.3% with enalapril; relative risk = 1.5). Neither syncope nor fractures were greater in the LCZ696 group than in the comparator group. In general, the hypotension was manageable. Hypotension is generally not considered to be clinically significant unless it causes end-organ hypoperfusion – basically cerebral or renal dysfunction. Cerebral hypoperfusion is likely to be sensed by patients, and should cause them to seek medical attention. Similarly, important postural hypotension is likely to be sensed by patients and should cause them to seek medical attention. Conversely, renal hypoperfusion can be silent, but if important, would affect creatinine and/or blood urea nitrogen (see below).

Renal Impairment and Hyperkalemia: Analyses of adverse event and laboratory data did not show an increased risk of hyperkalemia or renal impairment in the LCZ696 group compared to the enalapril group. Nevertheless, the drug has the potential to cause both, and the label will suggest monitoring of patients.

Cognitive Dysfunction: As explained above, sacubitril inhibits neprilysin – a protease that cleaves several peptide hormones, including natriuretic peptides and vasoactive peptides. Neprilysin is also one of the major enzymes that break down Aβ peptide in the CNS. The Aβ peptide has been a major focus of Alzheimer's disease (AD) research, because accumulation of misfolded Aβ peptide has been implicated as the cause of AD; accordingly, lysis/prevention of accumulation of Aβ peptide has been a therapeutic target. It is theoretically possible, therefore, that inhibition of neprilysin could increase levels of Aβ in the brain and CSF, leading to cognitive dysfunction and/or the development of AD.

The salient non-clinical and clinical data were reviewed by the Division and considered by consultants from DNP in light of what is known – and what is not known – about AD.

Although some investigators have demonstrated Aβ peptide brain accumulation in animal models of neprilysin deficiency, DNP notes there is no evidence that neprilysin deficiency is causal in the pathogenesis of human AD. Findings have not been consistent with respect to polymorphisms in neprilysin genes and the risk of AD. Also, as noted by DNP, alternative clearance pathways and enzymes participate in the breakdown of Aβ. It seems likely that there is redundancy in the system, such that alternate pathways can compensate for decreases in neprilysin activity.

DNP makes the point that one of the applicant's studies showed that only a small fraction of LCZ696 (0.3%) crosses the blood brain barrier; however, I will note that changes in CSF Aβ in non-clinical and clinical studies prove a pharmacodynamic effect. Thus, it is clear that the drug (or its active metabolite[s]) is somehow able to exert a CNS effect.

Even if LCZ696 were to lead to accumulation of Aβ in the brain, DNP stresses that it is not known whether it would increase the risk of AD. In recent years it has become apparent that disturbances in amyloid regulation are but one of a number of complex pathophysiologic changes that occur in AD. And despite much effort, drugs targeted to reduce Aβ peptide in the brain have not proven effective.

Cardiovascular disease can also contribute significantly to the onset of dementia in patients with AD. Given that patients with heart failure often have some degree of cognitive impairment, the applicant points out, and DNP agrees, that it is theoretically possible that LCZ696 could have a salutary effect in these patients.

With respect to the clinical data, PARAGON-HF was a controlled trial that exposed a relatively large numbers of patients – older patients who are vulnerable to cognitive dysfunction – for a median duration of 2 years. (b) (4)

Thus, the unanswered questions are whether sacubitril causes subtle CNS toxicity in the short term, or more severe toxicity in the longer-term. These are salient questions, given that approximately 50% of patients with heart failure will survive longer than 5 years. If there were a longer-term risk of cognitive dysfunction, use of the drug would still be rational for most patients; nevertheless, patients and providers would need to be apprised of the frequency and severity of the risk.

It would not be feasible, however, to obtain long-term data in patients with heart failure and reduced systolic function to address this question. In light of LCZ696's life-prolonging effect in such patients, randomizing to placebo would be unethical. An alternative consideration would be to attempt to contact patients who were in PARADIGM-HF and collect longer-term follow-up data on them; however, the likelihood of locating and enrolling such patients would be influenced by their overall health status. Thus, patient selection would be biased, and interpretation would be difficult at best.

The applicant is pursuing further development of LCZ696 in a population with heart failure and preserved ejection fraction, and will be conducting a large study to try to establish efficacy in this patient population. In addition, they are planning a (b) (4)-patient, multinational, randomized, double-blind, active-controlled study to evaluate the effects of LCZ696 compared to valsartan on cognitive function, to be assessed with a comprehensive neurocognitive battery. The study would compare patients randomized to LCZ696 (i.e., sacubitril plus valsartan) to valsartan alone. Study details have not been finalized, (b) (4)

heart failure with preserved ejection fraction and the study would be (b) (4) (b) (4) A subset of patients would undergo positron emission tomography (PET) imaging to assess (b) (4) Cognitive function would also be assessed by (b) (4)

DNP believes the study would be reasonable to undertake to assess further the potential effect of LCZ696 on cognition and amyloid pathology. The study could provide worthwhile information, but a few points are worth noting:

(b) (4)

The Division is generally not in favor of ordering a post-marketing requirement to assess longer-term cognitive effects. The Division has major concerns around publicizing this potential risk – a purely theoretical issue – because publicity will discourage patients from using the drug. Moreover, they question whether this theoretical concern meets the threshold for a PMR, and whether, in light of the above, the proposed study will lay the question to rest.

Though I certainly share the Division's concerns, the medical community deserves to know whether there is a longer-term risk of cognitive dysfunction – to the extent it can be investigated.

Section 505(o)(3)(A) of the Food and Drug Administration Amendments Act of

2007 (FDAAA) states that postmarketing studies and clinical trials may be required to identify an unexpected serious risk when available data indicates the potential for a serious risk.

Based on its mechanism of action, sacubitril poses a potential risk for serious CNS toxicity, and I have reached the conclusion that the company's proposed CNS study will be appropriate as a post-marketing requirement, with appropriate time lines to be determined.

In communicating this to the public, it will be important to stress that the risk is purely theoretical at this point, based on mechanistic theory. The clinical data from PARADIGM-HF, though imperfect, do not suggest a risk.

Post-marketing Agreements

The applicant has agreed to 2 post-marketing requirements:

1. To conduct a multicenter, randomized, double-blind, active-controlled trial to evaluate the effects of Entresto compared to valsartan on cognitive function as assessed by comprehensive neurocognitive battery and PET imaging in patients with chronic heart failure with preserved ejection fraction.

2. To conduct an epidemiologic study using claims or electronic health records data to evaluate the incidence of angioedema in Black patients treated with Entresto compared to a control drug.

In addition, the applicant has agreed to a post-marketing commitment to develop a new dissolution method and set final dissolution acceptance criteria, as described on page 4.

The time lines and specific expectations are delineated in the approval letter.

Summary/Conclusions

LCZ696, a combination neprilysin inhibitor and angiotensin-II receptor blocker, represents a first-in-class drug for heart failure. Its effectiveness is well established from PARADIGM-HF, an 8,000-subject randomized, double-blind, active-controlled trial. LCZ696's benefit is in reducing the need for heart failure hospitalization by ~1.6 per 100 patient-years, and in reducing cardiovascular death by 1.5 per 100 patient-years.

The treatment effect of LCZ696 was evident when added to adequate background medical therapy (a RAAS inhibitor, beta-blockers, aldosterone antagonists, and diuretics). Although these absolute reductions in heart failure hospitalizations and cardiovascular death seem modest, they must be considered in the context of the enormity of the public health problem. Heart failure is the *leading cause* of hospitalization and re-hospitalization in the US. Thus, even small treatment effects can have considerable impact on the public health because of the size of the patient population and burden of hospitalization.

The risks are manageable, as noted above. Some of the side effects cause symptoms that would lead patients to seek medical attention (angioedema; hypotension), others would be detected through routine monitoring (hyperkalemia and renal dysfunction). Patients with

important hypotension, hyperkalemia, or renal dysfunction can simply stop the drug, and for the most part, all of the untoward effects are reversible.

The typical patient in PARADIGM-HF was a 64 year-old Caucasian European male who had not received CRT or an ICD. Important information missing in this NDA includes a more precise estimate of the risk of angioedema in Blacks, information that will be obtained through a post-marketing requirement. Although women were somewhat under-represented in the development program, PARADIGM-HF provides ample evidence of efficacy in women, with ~900 subjects in each treatment group. Elderly patients were well represented in PARADIGM-HF.

Having negotiated the labeling with the applicant, LCZ696 will be approved with agreed upon labeling and the following indication statement:

> "ENTRESTO is indicated 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. ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB."

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
07/07/2015