CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207620Orig1s000

OTHER REVIEW(S)

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Overview

NDA: 207620
Drug: Entrsto (sacubitril/valsartan) 24/26 mg; 49/51 mg; 97/103 mg Tablets
Class: a combination of sacubitril, a neprilysisn inhibitor, and valsartan, an angiotensin receptor neprilysin inhibitor
Applicant: Novartis Pharmaceuticals Corp.
Proposed Indication:

- The treatment of heart failure (NYHA class II–IV) [redacted] (b) (4)
- [redacted] (b) (4)

Final indication:

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.

Date of submission: 17 December 2015
PDUFA date: 17 August 2015
Action date: 7 July 2015

❖ **REVIEW TEAM**

- Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Products
  - Cross Discipline Team Leader (CDTL)
    - Aliza Thompson
  - Medical Reviewer
    - Kimberly Smith (Efficacy), Tzu-Yun McDowell (Safety)
  - Pharmacology & Toxicology
    - William Link
  - Regulatory Health Project Manager
    - Alexis Childers
- Office of Pharmaceutical Quality (OPQ)
  - – CMC & Biopharmaceutics
    - Wendy Wilson (Application Technical Lead)
    - Anamitro Banerjee (Drug Substance), Sherita McLamore-Hines (Drug Product)
    - Salaheldin Hamed (Biopharmaceutics)
    - Robert Mello (Microbiology)
- Office of Clinical Pharmacology
    - Sreedharan Sabarinath (Clinical Pharmacology)
    - Luning Zhuang (Pharmacometrics)

- Office of Biostatistics, Division of Biometrics I
    - John Lawrence
- Office of Surveillance and Epidemiology
    - – DMEPA
        - Janine Stewart
    - DRISK
        - Somya Dunn

❖ BACKGROUND

LCZ696, developed by Novartis is a novel combination of sacubitril and valsartan for the treatment of heart failure (NYHA class II-IV) (b) (4). The Phase 3 trial, CLCZ696B2314 (PARADIGM-HF) was a randomized, double-blind pivotal outcome study comparing the efficacy and safety of LCZ696 to enalapril in patients with heart failure and reduced ejection fraction (HFrEF). In March 2014, the Data Monitoring Committee recommended early closure of the trial because of compelling efficacy after the third interim analysis.

In addition to the Phase 3 trial, there are two supportive phase 2 studies in patients with heart failure, CLZ696B2214 (PARAMOUNT) and CLCZ696B2228 (TITRATION). Safety data is provided from completed studies in patients with hypertension as well.

The applicant submitted a SPA in June 2009 for the phase 3 trial. The Division issued a No Agreement letter on 16 July 2009. There were subsequent discussions with the applicant but a new SPA was never submitted. The applicant opened the IND with the phase 3 trial.

The NDA had fast track designation with a rolling review. The NDA was given a priority review with a PDUFA date of 17 August 2015. An early action is being taken.

The proposed doses are 24/26 mg; 49/51 mg; 97/103 mg (sacubitril/valsartan) tablets for the treatment of heart failure.

The review of the application in general met all of the 21st century review guidelines through primary reviews. The CDTL, Division Director and Signatory memos were all accelerated as an early action was taken.

User Fee

The user fee for this application was paid in full on 22 September 2014. User Fee ID 3014514.

Pediatric Review Committee (PeRC)

The applicant submitted a waiver request in Pediatrics. The PeRC meeting to discuss this application was held on 24 June 2015. The committee agreed to grant a full waiver in pediatric patients because studies are impossible or highly impractical as there are too few patients with disease/condition to study. The causes and mechanisms of heart failure in children and adults are different.

Advisory Committee

There was no Advisory Committee meeting for this NDA because this drug does not raise significant safety or efficacy issues.

Trade name

The applicant originally submitted the proposed name Entresto to IND 104628 on 19 June 2014. The name was approved on 17 November 2014. Novartis submitted the same name request on 15 January 2015 to the NDA. The name was still considered acceptable. Novartis was asked to resubmit the name

request due to a change in strength presentation. The request was submitted on 24 April 2015 and found acceptable on 11 June 2015. A grant letter was issued on 19 June 2015.

Facilities Inspection
The Office of Compliance provided an overall recommendation of acceptability for the manufacturing sites on 30 June 2015.

Division of Scientific Investigations: Four foreign clinical investigator inspections were conducted in support of NDA 207620, for audit of Study CLCZ696B2314 (PARADIGM-HF). A site inspection also occurred at Novartis New Jersey. No regulatory violations were found during 3 of the inspections. Minor regulatory violations were found during the inspections of 2 of the sites: one for failure to follow the investigational plan and one for failure to prepare or maintain accurate records. These issues did not significantly impact the quality or the integrity of the data submitted in support of this NDA.

❖ REGULATORY TIMELINE

- Top-Line Results Meeting: 22 September 2014 (minutes dated 22 October 2014)
- Pre-NDA Meeting: 25 June 2014 (minutes dated 14 July 2014)
- CMC Pre-NDA : 14 August 2014 (minutes dated 18 September 2014)
- NDA Received Date: 17 December 2014
- Filing Day 60: 15 February 2015
- Filing/74 Day Letter: 12 February 2015
- Mid-cycle Communication Meeting: 19 March 2015 (minutes dated 7 April 2015)
- Late-Cycle Meeting: 3 June 2015 (minutes dated 24 June 2015)
- Advisory Committee: N/A
- PDUFA Date: 17 August 2015

❖ REVIEWS

Below are the conclusions reached by the Entresto team members, organized by role or discipline.

ODE I Memorandum (dated 7 July 2015)
Dr. Unger provided a thorough synopsis of each disciplines review, (see full memo for details). He states that the following factors make the theoretical risk of cognitive impairment acceptable: if the risk exists, it could take a long time to develop, life expectancy of heart failure patients is short, there are proven effects on meaningful outcomes, and the risk is based on mechanistic theory without supportive data.

He explains that although all-cause mortality was statistically significantly lower in the LCZ696 arm, it was driven entirely by cardiovascular mortality (b) (4)

(b) (4) (b) (4) (b) (4)

He agrees with the angioedema PMR.

Dr. Unger does not agree with Dr. Marciniak's cancer assessment.

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

data from the Phase 3 trial and literature, the potential PMR study would lay the question to rest. Though Dr. Unger certainly shared the Division's concerns, (FDAAA) states that post-marketing 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 Dr. Unger reached the conclusion that the company's proposed CNS study will be appropriate as a post-marketing requirement.

Overall, Dr. Unger agrees with the review team's recommendation for approval.

Divisional Memorandum (dated 22 June 2015)
Dr. Stockbridge's memo recommends approval. The memo provides a brief overview of the program and results. He finds available pharm/tox data regarding reassuring in regards to the potential for Entresto to cause cognitive decline. He concurs with the reviewers' assessment regarding KCCQ and symptom assessment in that the effect is smaller than what is generally regarded as clinically relevant (b) (4) . He does not agree with the reviewers' recommendation for a PMR for angioedema. He states the risk is well known and feels our pharmacovigilance tools are better than what Novartis can obtain. He mentions a review conducted by Dr. Marciniak, who was not part of the review team. While Dr. Marciniak feels there are flaws in the case report forms and the validity of the data can be questioned, he states it was not severe enough to reject the trial. Dr. Stockbridge agrees that the data should not be rejected. Dr. Stockbridge does not agree with Dr. Marciniak's assessment regarding cancer findings.

Cross-Discipline Team Leader (CDTL) Review (dated 12 June 2015)
Dr. Thompson recommends approval. Her review summarizes each disciplines findings including consult review. She also provided a detailed regulatory history. She notes that Dr. Lawrence did not recommend approval for the combination policy. She did not agree with his assessment stating that the trial provides a mortality benefit; there were no safety signals that would lead one needing to determine the contributions of each component, nor would it be ethical to conduct such a trial; there is a benefit over an active comparator.

Dr. Thompson's review discusses the applicant's (b) (4) as well as the clinical reviewers' assessments. She agrees with the clinical reviewers.

She discusses a theoretical safety concern that inhibition of neprilysin by LCZ696 could accentuate accumulation of beta amyloid in the brain causing an increased risk of Alzheimer's disease. There has been a lot of internal discussion including whether the information should be included in the label. Findings have been included in the label. She notes that at the point of her review, there have been no discussions to discuss next steps. The clinical reviewers did not recommend a PMR and she agreed as the (b) (4) (b) (4) .

Medical (dated 15 May 2015)
Dr.'s Smith and McDowell provided a combined review discussing safety and efficacy. They both recommended approval stating that the benefits outweigh the risks. They state that LCZ696 reduced the risk of the primary composite endpoint based on a time-to-event analysis with patients having fewer first heart failure hospitalizations and cardiovascular deaths as first event compared to enalapril. The most important risks identified in the review were angioedema, hypotension, renal impairment, and hyperkalemia. Although, the over-all incidence was low, the most concerning of the risks is angioedema. The incidence of angioedema was higher in black subjects but only 5% of the test subjects were black in PARADIGM. It is therefore difficult to assess the true risk. A PMR to assess the risk of angioedema in black patients is recommended by the reviewers. A PMR has been created and agreed upon with the sponsor (see action letter for details).

The review also points out that LCZ696 is a fixed-dose combination. Per the regulations, each component must contribute to the effect. With the design of PARADIGM, one could not establish the individual contributions of each component. The reviewers used other available data to make an assessment, including the VAL-HeFT trial. Based on the assessment and the fact that no studies have directly compared valsartan to enalapril, they feel that both therapies are at least equivalent therapies, and sacubitril alone contributed to the treatment effect. They believe the risks they identified can be managed through clinical monitoring and dose titration.

Dr. Marciniak, who was not part of the review team, also wrote a review regarding flaws in case report forms that can bring into question the validity of the data. He did not feel that is was severe enough to reject trial data. He also pointed out concerns regarding cancer.

Biostatistics Review (dated 20 May 2015)
Dr. Lawrence's review stated that the combination should not be approved. Due to limitations in the study design, he states that it is not possible to know whether both components contribute to the effects. If the drug is approved, he feels that this should be clearly stated in the label.

He suggests that sacubitril should be approved as a monotherapy for reducing CV mortality only. He explains that it is unknown whether valsartan alone could explain the heart failure hospitalization benefit. Dr. Lawrence's review also notes that:

- One-sided p-values were used sometimes in the report (b) (4). The label should show 2-sided p-values.
- Primary endpoint and all-cause mortality endpoints had significant p-values.

Clinical Pharmacology Review (dated 15 May 2015 & 26 June 2015)
Dr.'s Sabarinath (clinical pharmacology) and Zhuang (pharmacometrics) provided a combined review. They find the information submitted to the NDA to be supportive of approval with the following dose recommendations: Use a lower starting dose of 50 mg BID in patients with (1) severe renal function impairment or (2) moderate hepatic impairment.

The most noteworthy findings were (for a complete list, see review):

- On oral administration, LCZ696 dissociates into sacubitril and valsartan and these moieties are absorbed rapidly.
- Sacubitril undergoes metabolism via esterases to form the active moiety LBQ657, which inhibits neprilysin.
- Absolute bioavailability of sacubitril from LCZ696 is at least 60 %. The bioavailability of valsartan from LCZ696 is at least 50 % higher than valsartan administered alone. Valsartan from 400 mg LCZ696 (containing ~ 203 mg valsartan) is equivalent to 320 mg valsartan marketed formulation.
- The LCZ696 analytes have high plasma protein binding (97 % for sacubitril and LBQ657 and 94 % for valsartan)
- Drug interaction potential for LCZ696 as a victim drug is low.
- Approximately 52-68 % of sacubitril is excreted in urine (as LBQ657) and 37-48 % was recovered in feces in a mass balance study. Approximately 83 % of valsartan was excreted in feces and about 13 % in urine.
- The average elimination half-life is about 1.4 h, 11.5 h and 9.9 h respectively for sacubitril, LBQ657 and valsartan in healthy subjects.

They also provided an addendum to compare the mean daily dose of enalapril to that in the SOLVD-Treatment (SOLVD-T) study. They determined that based on limited information from publications for SOLVD-T, it can be concluded that the daily dose of enalapril in PARADIGM-HF is numerically higher.

They also documented revised estimates for apparent volume of distribution of sacubitril and valsartan in the addendum and label.

Pharmacology & Toxicology Review (dated 15 May 2015)
Dr. Link's review states that the LCZ696 was tested in a several different species including mice, rats, rabbits, marmosets and cynomolgus monkeys. Target organs were kidney, red blood cells, heart and GI tract. He didn't consider any of the findings detrimental to the safe use of LCZ.

The genotoxicity studies included in vivo and in vitro bacterial and mammalian systems.

The carcinogenicity studies were evaluated with Executive CAC concurrence. There was no effect on fertility in rats. LCZ696 did show teratogenicity in rabbits and increased embryo lethality in rats and rabbits.LCZ696 is contraindicated during pregnancy.

Dr. Link's review mentions the theoretical risk associated with NEP inhibition as it relates to effects on β-amyloid (Aβ) metabolism, and the potential accumulation of Aβ in the brain. Elevated levels of β-amyloid were present in the CSF and plasma but not brain in monkeys. He states the relevance to humans is not clear.

Dr. Link stated the preclinical program was thorough and well conducted. He agrees with the applicant's interpretations of the data and recommends approval.

Tertiary Pharmacology Review (2 July 2015)
Dr. Brown summarized the pharmacologists review and agrees with the primary reviewers assessments.

Office of Pharmaceutical Quality Review (dated 15 May 2015, 30 June 2015)
An integrated summary was written for product quality. Approval is recommended from a quality perspective. LCZ696 is a (b) (4) comprised of two active ingredients, sacubitril and valsartan. OPQ prefers the term (b) (4) to describe the active moiety; whereas the applicant preferred (b) (4) . It was agreed during labeling negotiations that the active moiety will be called complex.

There were several discussions throughout the review regarding expression of strength. Novartis originally wanted a single strength expressed for each dose level. OPQ stated that each component needed to be shown. While the review team and the applicant agreed that the dose strengths can be separated by a "/", OPQ feels that "and" is more appropriate. Ultimately, they agreed with using "and".

A 24 month expiry has been assigned when stored at room temperature.

From a Biopharmaceutics perspective it was determined that the dissolution data submitted for clinical and registration batches did not support the dissolution acceptance criteria proposed by the applicant. A post-marketing commitment was agreed upon regarding dissolution (see full review and action letter for details).

Regarding drug substance, the applicant did not propose any BCS Classification. It was determined that the BCS classification is BCS IV.

From a microbiology perspective, the tests and proposed acceptance criteria for microbial burden are adequate.

CONSULTS

Office of Surveillance and Epidemiology Reviews

DMEPA (1 Jun 2015), (16 Jun 2015)
Dr. Stewart reviewed that carton and container labels and labeling insert using a Failure Mode and Effects Analysis. The risk assessment performed on the PI and container labels identified deficiencies that may lead to medication errors and areas for improvement.

Full details on recommendations can be found in the review. Comments regarding the container labels were sent to the applicant via email. The applicant revised the container labels per DMEPA's recommendations. DMEPA found them acceptable. Final agreed upon cartons were submitted June 11, 2015.

DRISK (22 May 2015)
Dr. Dunn evaluated the need for a risk evaluation and mitigation strategy (REMS). She concludes that no risk mitigations measures other than professional labeling and a PPI are needed as no safety concerns have been identified. Of note, the applicant originally (b) (4) .

DEPI (5 June 2015)
Dr. Eworuke reviewed the applicant's proposed post marketing study plan. She concludes that that the applicant's approach to evaluating the risk of angioedema is reasonable and provided recommendations to the Division and applicant. See full review.

Office of Medical Policy Initiatives, Division of Medical Policy Programs (4 June 2015)
Ms. Dowdy did a combined review with Dr. Patel evaluating the 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 (8 June 2015)
Dr. Patel provided comments on the draft prescribing information and carton container. See full review for details

Division of Pediatric and Maternal Health (26 May 2015)
Dr. Dinatale provided comments regarding the applicant's submission of PLLR. They provided comments on draft prescribing information. See full review for details.

Labeling
Labeling discussions occurred with the applicant. The final agreed upon labeling will be attached to the approval letter.

CONCLUSION

The review team recommended approval.

An approval letter was drafted and signed by Dr. Unger on 7 July 2015.

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

/s/

ALISON L BLAUS
07/08/2015
Signing on behalf of Alexis Childers

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA # 207-620
Product Name: Entresto™ (sacubitril/valsartan) Tablets, 97/103, 49/51, and 24/26 mg

PMR/PMC Description:
1) Optimization of the dissolution method for Entresto™ (sacubitril/valsartan) Tablets, and
2) Setting of the final acceptance criterion for the dissolution test, based on data from a minimum of 12 commercial batches per strength (using the optimized dissolution method).

PMR/PMC Schedule Milestones:

Dissolution Method Development Report Submission:	February 2016
Study/Trial Completion:	NA
Final Report Submission:	July 2016
Other:	NA

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

During the review cycle it was determined that the dissolution acceptance criterion proposed by the Applicant (b) (4) *(Q =* (b) (4) *% at* (b) (4) *minutes) was not supported by the dissolution data submitted for the clinical and the registration batches. The FDA recommended Q =* (b) (4) *% at* (b) (4) *minutes;* (b) (4) *The FDA recommended that the Applicant further optimize the dissolution method* (b) (4) *Therefore, a PMC is necessary to allow for the optimization of the dissolution method and acceptance criterion, which would require time beyond the remaining review clock time. It is noted that the control strategy for the current product (e.g., operating closely to the normal operating ranges for the clinical trial batch) ensures the quality of the drug product.*

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The currently proposed dissolution method (b) (4) *The currently proposed acceptance criterion (Q =* (b) (4) *% at* (b) (4) *minutes)* (b) (4) *. In the absence of an adequate in vitro to in vivo relation and proper exposure response data, a release specification at Q =* (b) (4) *% should be established to ensure complete release of the drug substance. The goals of the in vitro dissolution study under the PMC are: 1) to optimize the dissolution method parameters to* (b) (4) *and 2) to set an adequate dissolution acceptance criterion for the drug product using the full dissolution profile data collected from an adequate number of commercial batches (i.e., n=12 batches/each strength).*

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This Post-Marketing Commitment should be fulfilled within 12 months from action date for:
1) *Development of a new dissolution method for all the strengths with demonstrated discriminating ability,* (b) (4) ,

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 per strength, manufactured under the same conditions as those used for the manufactured of the batches used in pivotal clinical trials. The FDA will be open to providing feedback during the method's development process as needed.*

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

_____

Agreed upon:

- ☒ Quality study without a safety endpoint (e.g., development of a discriminating dissolution method)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

- ☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Do the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(Signature line for BLAs)

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

/s/

Lori A WACHTER
07/07/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 207620
Product Name: Sacubitril/valsartan (Entresto®)

PMR/PMC Description: Conduct a randomized controlled study to evaluate the effects of Entresto compared to valsartan on cognitive function and PET imaging in patients with chronic heart failure with preserved ejection fraction.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	April 2016
Trial Completion:	October 2021
Final Report Submission:	March 2022

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☒ Theoretical concern
   ☐ Other

   Neprilysin (NEP) is a major beta amyloid (β-amyloid) degrading enzyme in the brain and sacubatril is a NEP inhibitor. Hence, there is a theoretical risk that NEP inhibition by Entresto could lead to accumulation of β-amyloid in the brain, causing cognitive dysfunction and/or increasing the risk of Alzheimer's disease.
   In non-clinical studies, sacubitril/valsartan increased β-amyloid levels in the CSF, without corresponding increases in the brain. In a study in healthy subjects, sacubitril/valsartan is associated with increases in CSF β-amyloid 1-38 and plasma β-amyloid 1-40 concentrations, though the clinical significance of these findings is unclear. Analyses of adverse event data from the phase 3 trial-PARADIGM-HF did not reveal an obvious signal. The incidence of potential dementia-related adverse events 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.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Review Issue: There is a theoretical risk that NEP inhibition by Entresto could lead to accumulation of β-amyloid in the brain, causing cognitive dysfunction and/or increasing the risk of Alzheimer's disease.

The primary objective of the study is to evaluate the effects of Entresto compared to valsartan on cognitive function (b) (4) in patients with heart failure with preserved ejection fraction.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Type of Study: A (b) (4), multicenter, randomized, double-blind, active-controlled (valsartan) study (N=~(b) (4) enrolled and (b) (4) completers).
Cognitive function will be assessed using a comprehensive cognitive assessment battery (b) (4) will be assessed with PET scans (b) (4).

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☒ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☒ There is a significant question about the public health risks of an approved drug
☒ There is not enough existing information to assess these risks
☒ Information cannot be gained through a different kind of investigation
☒ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☒ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

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/s/

Lori A WACHTER
07/07/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 207620
Product Name: Sacubitril/valsartan (Entresto®)

PMR/PMC Description: Conduct an epidemiologic study using claims or electronic health records data to evaluate the incidence of angioedema in black Entresto patients compared to a control. A target sample size, supported by sample size calculation, should be included in the protocol.

PMR/PMC Schedule Milestones:		
	Draft Study Protocol Submission	December 2015
	Final Study Protocol	July 2016
	Interim Study Report #1	July 2017
	Interim Study Report #2	July 2018
	Final Report Submission	July 2019

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☒ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

   In the pivotal trial, PARADIGM-HF, the incidence of angioedema was 0.5% in the sacubitril/valsartan arm as compared to 0.2% in the enalapril arm in the double-blind treatment period. When stratified by race, the incidence was 2.4% in black subjects in the sacubitril/valsartan arm as compared to 0.5% in black subjects in the enalapril arm. Among black subjects in the U.S., three out of 54 patients (5.6%) developed angioedema in the LCZ696 arm as compared to zero out of 57 patients treated with enalapril. Given that only 5% of PARADIGM-HF subjects were black, there is substantial uncertainty in these risk estimates. The findings are nonetheless concerning as a large proportion of heart failure patients in the U.S. are black and blacks are known to be more susceptible to angioedema induced by ACE inhibitors and neprilysin inhibitors. Hence, we believe that a postmarking observational study is needed to better characterize the risk of serious angioedema in black patients treated with sacubitril/valsartan. The study should have a reasonable representation of U.S. patients so that we have confidence that the reported risk reflects the experience in U.S. patients and the risk in the setting of U.S. practice of care.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Review Issue: There is substantial uncertainty about the risk of serious angioedema in black heart failure patients treated with sacubitril/valsartan. The primary objective of the study is to assess the incidence of serious angioedema in black heart failure patients exposed to sacubitril/valsartan relative to active comparator(s).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Type of Study: Pharmacoepidemiologic study using claims or electronic health records data Population: Black patients with heart failure

Required

☒ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

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☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
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☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☒ There is a significant question about the public health risks of an approved drug
☒ There is not enough existing information to assess these risks
☒ Information cannot be gained through a different kind of investigation
☒ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☒ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

Lori A WACHTER
07/07/2015

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:	June 16, 2015
Requesting Office or Division:	Division of Cardiovascular & Renal Products (DCRP)
Application Type and Number:	NDA 207620
Product Name and Strength:	Entresto (sacubitril/valsartan) Tablets 24 mg/26 mg, 49 mg/51 mg, 97 mg/103 mg
Submission Date:	June 11, 2015
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation
OSE RCM #:	2015-233-1
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

The Division of Cardiovascular & Renal Products (DCRP) requested that we review the revised container labeling and carton labels (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSIONS

The revised container labeling and carton labels are acceptable from a medication error perspective.

[1] Stewart J. Label and Labeling Review for Entresto (NDA 207620). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JUN 01. 40 p. OSE RCM No.: 2015-233.

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/s/

CHI-MING TU on behalf of JANINE A STEWART
06/16/2015

CHI-MING TU
06/16/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: June 8, 2015

To: Alexis T. Childers, RAC
Senior Regulatory Health Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Zarna Patel, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **Sacubitril/Valsartan Tablets**
NDA: 207620
Comments on draft product labeling

OPDP has reviewed the proposed Package Insert (PI) submitted for consult on January 16, 2015, for Sacubitril/Valsartan Tablets. OPDP's comments are provided directly on the attached copy of the proposed labeling emailed to us on May 22, 2015.

OPDP has also reviewed the Carton and Container Labeling submitted by the sponsor on May 15, 2015 and has the following comments pertaining specifically to the proposed Carton and Container Labeling for a proposed starter kit (entresto-49-51-28s starterkitcarton-115203):

- (b) (4)

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

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/s/

ZARNA PATEL
06/08/2015

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 5, 2015

TO: Aliza Thompson, Team Leader
Kimberly Smith, Medical Officer Clinical
Tzu-Yun McDowell, Medical Officer Safety
Alexis Childers, Regulatory Health Project Manager
Division of Cardio-Renal Drug Products

FROM: Sharon K. Gershon, Pharm. D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 207620

APPLICANT: Novartis Pharmaceuticals Inc.

DRUG: Entresto™ (sacubitril/valsartan) LCZ696

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Treatment of heart failure (New York Heart Association class II-IV) (b) (4) .

PROTOCOL: Study CLCZ696B2314 (PARADIGM-HF): A Phase III, multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure and reduced ejection fraction.

CONSULTATION REQUEST DATE:	February 2, 2015
INSPECTION SUMMARY GOAL DATE:	May 15, 2015 (extended to June 8, 2015)
DIVISION ACTION GOAL DATE:	August 15, 2015
PDUFA DATE:	August 17, 2015

I. BACKGROUND:

Novartis Pharmaceuticals Inc. submits NDA 207620, for drug LCZ696 for the treatment of heart failure ((New York Heart Association) NYHA class II-IV) (b) (4) . The clinical evidence which supports the efficacy and safety of this submission is Study CLCZ696B2314 (PARADIGM-HF): A Phase III, multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure and reduced ejection fraction.

A total of 8442 subjects were randomized (4209 subjects to LCZ696 and 4233 subjects to enalapril) at 984 sites in 47 countries worldwide.

LCZ696 (sacubitril/valsartan) is a new therapy, administered orally for the treatment of heart failure. LCZ696 dissociates into the pro-drug sacubitril (known as AHU377, a new chemical entity), which is further metabolized to the neprilysin inhibitor LBQ657, and valsartan. LCZ696 has a novel mechanism of action of an angiotensin receptor neprilysin inhibitor (ARNI) and simultaneously inhibits neprilysin (neutral endopeptidase 24.11; NEP) via LBQ657, and blocks the angiotensin II type-1 (AT1) receptor via valsartan. These complementary actions on the cardiovascular system are beneficial in heart failure patients.

The primary objective of this study was to test if LCZ696 is superior to enalapril in delaying time to first occurrence of the composite endpoint, which was defined as either cardiovascular (CV) death or heart failure (HF) hospitalization, in patients with chronic heart failure (CHF) (NYHA class II – IV) and reduced ejection fraction (left ventricular ejection fraction [LVEF] ≤ 40%, changed to ≤ 35% by Protocol Amendment 1).

The secondary objectives were:

- to test whether LCZ696 is superior to enalapril in delaying the time to all-cause mortality;to test whether LCZ696, compared to enalapril, improves the clinical summary score for HfF symptoms and physical limitations, as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ), at 8 months;

- to test whether LCZ696 is superior to enalapril in delaying time to new onset atrial fibrillation (per Protocol Amendment 3); and
- to test whether LCZ696 is superior to enalapril in delaying the time to first occurrence of either
  (1) a 50% decline in estimated glomerular filtration rate (eGFR) relative to baseline,
  (2) >30 mL/min/1.73 m2 decline in eGFR relative to baseline to a value below 60 mL/min/1.73 m2, or
  (3) reaching end stage renal disease (ESRD).

Patients entered an active run-in period ranging from 5 to 10 weeks before entering the double-blind period. This study was event-driven and patients remained in the study (regardless of whether they were receiving study medications) until the projected number of patients with primary events (2410 events) had been reached or early termination of the study by the DMC when pre-specified efficacy or futility criteria were met. The primary composite endpoint consisted of the following components:

- CV death;
- HF hospitalization

There were four secondary variables:

- Time from randomization to all-cause death;
- Change from baseline (CFB) (compared withrandomization visit) in the clinical summary score for HF symptoms and physical limitations (as assessed by KCCQ) at 8 months;
- Time from randomization to new onset of atrial fibrillation;
- Time from randomization to first occurrence of either (1) a 50% decline in eGFR relative to baseline, (2) >30 mL/min/1.73 m2 decline in eGFR relative to baseline to a value below60 mL/min/1.73 m2, or (3) reaching ESRD

.

Reasons for Site Selection: Sites chosen for inspection had high enrollment and high favorable efficacy results for the active drug arm.

II. Results

Name of CI/ Site #	Protocol #, # of Subjects Enrolled	Inspection Dates	Final Classification
Rakesh Aggarwal India Site 665	LCZ696B2314 46 subjects	April 6 – 9, 2015	NAI

Roberto Botelho Brazil Site 98	LCZ696B2314 61 subjects	April 27 - May 8, 2015	VAI
Weimin Li China Site 217	LCZ696B2314 51 subjects	May 11-17, 2015	VAI
Angelina Staneva Bulgaria Site 117	LCZ696B2314 70 subjects	May 18 – 22, 2015	NAI
Novartis Pharmaceuticals, Inc. New Jersey Sponsor Inspection	LCZ696B2314	April 14-28, 2015	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **Rakesh Aggarwal (Site 665)**
   478-L, Model Town
   Ludhiana, Punjab 141002
   India

   a. What was inspected: Dr. Aggaral is not listed in the CDER COMIS database. This was the first FDA inspection of the Principal Investigator.

   The site screened 86 subjects and enrolled 46 subjects. A total of 26 subjects completed the study. There were no drop-outs or subjects loss to follow-up in the study.

   A total of 44 Serious Adverse Events (SAEs) were reported including nineteen deaths. The inspection reviewed records for thirty subjects, with about one-quarter of the source documents cross-referenced with electronic CRF records to ensure accuracy of reporting to the sponsor.

   Source documents were reviewed to ensure subjects met inclusion and exclusion criteria and were compliant with the protocol for required visits, required tests and medication compliance. Test results for required visits were reviewed to ensure subjects consistently met the requirements of the study.

   SAEs were reviewed to assure proper and timely reporting. Death was considered an SAE. This site had 19 deaths. Each SAE event was reviewed. The inspection reviewed monitoring logs and visit follow-up letters. Drug accountability logs and records were reviewed.

b. General observations/commentary: The inspection reviewed subject records for thirty subjects, and reported no discrepancies between source records, eCRF data and data listings. The protocol requirements were met in terms of scheduled visits and tests. For the SAEs reviewed, one isolated instance was found where the site did not report the SAE within 24 hours.

In the review of monitoring visit follow-up letters, the inspection observed that although protocol deviations had occurred, the site did not report any protocol deviations to the sponsor. The Novartis representative present during the inspection stated that the deviations were minor and did not require reporting. No issues were found during the review of drug accountability records.

c. Assessment of data integrity: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. **Roberto Botelho (Site 98)**
Rua Rafael Marino Neto 600
EuroLatino Medical Research
Uberlândia, MG,
Brazil

a. **What was inspected:** Dr. Botelho has [redacted] (b) (4) no FDA prior inspections. This site was selected for inspection because of high enrollment and high favorable efficacy results in the active arm.

The site screened 128 subjects, and enrolled 62 subjects. There were 66 screen failures and eighteen subjects discontinued prematurely from the study.

The FDA field investigator reviewed the following: IRB review and approval of the protocol and informed consent versions, IRB approval of the Kansas City Cardiomyopathy Questionnaire (KCCQ), sponsor monitoring, protocol adherence during the study, reported protocol deviations, reporting of adverse events (AEs) and serious adverse events (SAEs), concomitant medications, corroboration of study endpoints and other data with data listings for twenty-two subjects, site training, and drug accountability records.

b. **General observations/commentary:** There were no adverse findings in the review of drug accountability records and no unexplained discrepancies. Reporting of the SAEs appeared to be complete. Protocol deviations were appropriately reported to the sponsor and IRB.

A one-item FDA 483, Inspectional Observations, was issued at the conclusion of the inspection for failure to ensure that an investigation was conducted in accordance with the investigational plan. Specifically:

1) One subject experienced an AE of abdominal cramping and diarrhea on November 27, 2012, which was documented in the source record, but not listed in the eCRF and data submitted to the sponsor.

2) Eight of twenty-two subject records reviewed had at least one concomitant medication documented in the source records but not listed in the eCRF/data submitted to the Sponsor. For example, Subject 00029 was randomized on 8/22/2011, and source records identified the concomitant medication of carvedilol on 8/13/2012 and 12/10/2012 that was not listed in the eCRF data submitted to the sponsor.

OSI Reviewer Comments: *Review division may consider including the unreported concomitant medication in the safety and efficacy analysis.*

In his response letter dated May 21, 2015, Dr. Botelho acknowledged the observations and promised to implement corrective action and training.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

Note: The final EIR for Dr. Botelhol was not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

3. **Weimin Li (Site 217)**
No.199, Dazhi Street East,
Nangang District, Harbin,
Heilongjiang, China

a. **What was inspected:** Dr. Li has (b) (4) no prior inspections. This site was chosen to inspect because of high enrollment and high effect size in favor of study drug. This was the initial FDA inspection of Dr. Li. (b) (4)

The site screened 89 subjects – seven subjects were rescreened once, two subjects were rescreened twice, 51 subjects met eligibility criteria after completing the run-in period and participated in the double-blind portion of the study.

The inspection reviewed the following: all subjects where the site had reported a potential primary endpoint event; adverse events for 32 of 51 subjects that participated in the double-blind portion of the study including SAEs and primary endpoint events; concomitant medications for 25 of the 51 subjects who participated in the double blind period; scores at randomization and the eight month visit for 25 subjects for the KCCQ (secondary endpoint); laboratory data for the

estimated glomerular filtration rate (GFR). The FDA field investigator reviewed test article accountability records.

b. **General observations/commentary:** The FDA field investigator confirmed that all screened subjects signed the informed consent document on the date of screening, and confirmed that later versions of the ICD were signed appropriately for forty subjects.

The site did not keep an explicit record of inclusion and exclusion criteria. The source notes included statements that the eligibility criteria had been evaluated, and Dr. Li stated that she referred to a copy of the inclusion and exclusion criteria when screening subjects. The FDA field investigator did not observe any subjects who did not appear to meet the eligibility criteria.

For the renal failure secondary endpoint, there were no discrepancies observed between the data listings and the reported laboratory values from the central laboratory. There were no discrepancies between the data listings and source records in reported deaths or atrial fibrillation endpoints.

The site did not report any protocol deviations. At the close of the inspection, the FDA field investigator issued a Form FDA 483, Inspectional Observation for failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation. Specifically, data listing/records of AEs submitted to the sponsor did not include all AEs documented in source records and observed during the conduct of the study.

a) Study records for Subject #47 documented a hospitalization for transient ischemic attack with onset date of (b) (6). The data listings included two abnormal blood chemistry results as adverse events during that hospitalization, but do not include the hospitalization for TIA.

Reviewer Comments: OSI defers to the review division for determining if this isolated event should have been reported as an AE or considered a primary endpoint event.

b) Hospital records for Subject #29 included bronchitis during hospitalization from (b) (6) to (b) (6). The data listings included the SAE of myocardial infarction during this timeframe, but do not include the AE bronchitis.

c) Subject #73 reported palpitations from April 7 to 12, 2013 during a visit to the study site on April 19, 2013. This AE was not included in the data listings of AEs for this subject.

d) Subject #77 reported edema with an onset of August 8, 2012 during a visit to the site on August 15, 2012. This adverse event was not included in the data listings of AEs for this subject.

OSI Reviewer Comments: *Given that under reported adverse events are few, they are unlikely to have an impact on data reliability. The review division may wish to include the unreported AEs in the safety analysis.*

c. **Assessment of data integrity:** Although the above deficiencies were observed, they are unlikely to importantly impact the efficacy analysis for this NDA. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

Note: The final EIR for Dr. Weimin Li was not available at the time this clinical inspection summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

4. **Angelina Staneva (Site 117)**
79, Skobelev Blvd.
Sofia, NA 1606
Bulgaria

a. **What was inspected:** Dr. Staneva has (b) (4) no prior FDA inspections. This site was chosen to inspect because of high enrollment and high favorable effect size in the active arm.

The site screened 147 subjects and enrolled 70 subjects. A total of 48 subjects completed the study at the site.

General observations/commentary: No FDA 483 was issued at the conclusion of the inspection. The study team was changed in the site in the middle of the study due to the initial PI, Professor Raez and Sub-investigator Dr. (b) (4) leaving the facility in November 2012. Dr. Staneva was then appointed as the PI and the Ethics Committee was notified. During Professor Raez's and Dr. (b) (4) tenure, the inspection found that drug accountability records were disorganized and there were a few isolated instances where concomitant medications that were recorded in the source documents were not transferred to the CRFs. After Dr. Staneva took over the study, the records were much better in detail, completeness, and organization. The FDA inspectors also noted that the monitor changed at about the same time that the previous study team left, and the new monitor was much more diligent in reviewing records, communicating between the site and the sponsor, and keeping track of drug accountability. The primary and secondary endpoints were reported accurately, and there did not appear to be under-reporting of adverse events.

c. Assessment of data integrity: The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

Note: The final EIR for Dr. Staneva was not available at the time this clinical inspection

summary was written. The observations noted are based on email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

5. Novartis Pharmaceutical, Corp.
Edison, New Jersey

a. What was inspected: This inspection was conducted according to Compliance Program 7348.811. A prior Sponsor inspection of Novartis was conducted in July – August 2014 and covered NDA 205353. That inspection was classified as VAI for failure to report an adverse event to the FDA within 15 days, and failure to conduct monitoring visits according to the monitoring plan schedule. There were no monitoring visit reports for three visits performed by the CRA of Site 561.

The current inspection focused on the following clinical investigator sites, conducted as concurrent BIMO inspections:

- Site 665, Rakesh Aggarwal, India, 46 subjects
- Site 98, Roberto Botelho, Brazil, 61 subjects
- Site 217, Weimin LI, China, 51 subjects
- Site 117, Angelina Staneva, Bulgaria, 70 subjects

The inspector reviewed 100% of monitoring logs and Monitoring Visit Reports (MVR) for study Sites 098, 117, 217, and 665. During Study CLCZ696B2314, Novartis was responsible for providing monitoring of all study sites up until February 2012, when this function was transferred over to (b) (4) to improve efficiency. The inspectior reviewed the Transfer of Obligation between Novartis and (b) (4) which appeared to be adequate. Central monitoring was added during the study which consisted of review of eCRF data for high enrolling sites in Argentina, Bulgaria, China, Hungary, Germany, Italy, and India.

The inspection reviewed several SOPs, especially those pertaining to quality assurance, study monitoring, and protocol deviation reporting.

The inspection reviewed the Master Service Agreements, Study Specific Contracts and Consultant Contracts for the following consultants:

- Data Monitoring Committee (DMC): the inspection noted that in March 2014, the DMC stopped the study after the 3rd interim analysis due to the statistically significant benefits of LCZ696 over Enalapril. Topics discussed during the biannual meetings were documented in Meeting Minutes and Open and Closed Reports. The inspection reviewed member Contracts and CVs, several Meeting Minutes, Open Reports, and Closed Reports; no deficiencies were noted.
- Angioedema Adjudication Committee: to provide analysis of reported angioedema events from sites during the study;

- Endpoint Adjudication Committee: who were responsible for classification of all death events and evaluation of whether non-fatal events met the pre-specified endpoint criteria.

The inspection reviewed the site specific Trial Inventory Logs and the patient specific LCZ696B2314 Drug Assignment and Accountability Logs, the Oracle eCRF Study Medication Pages, the Clinical Trial Drug Transmittal Sheets, Clinical Product Return Forms, and Study Drug Destruction Letters for Study Sites 098, 117, 217, and 665.

b. General observations/commentary: No deficiencies were noted during review of SOPs and Trial Master Agreements and Study Contracts. All records appeared to be adequate except for the following issues: several subjects were noncompliant with study drug administration which was noted in the MVRs; MVRs for Sites 217 and 665 were signed off by the CRA and reviewed/approved by management several months after the visit occurred.

During the study the following sites were closed for protocol noncompliance:

- Site 0030- serious GCP findings during monitoring visits and insufficient staff to conduct the clinical trial
- Site 0096- serious GCP deviations discovered during site audit (data integrity was compromised)
- Site 1009- serious GCP findings during monitoring visits
- Site 2321- inconsistencies with the informed consent forms

No deficiencies were noted regarding study drug destruction.

Once the study was completed, the Oracle database records were verified, approved, locked, and frozen, and a Clinical Study Report (CSR) was drafted with all pertinent study data tables and listings. All hardcopy medical records and patient files remained at the study sites. Novartis provided all sites with a CD-ROM containing site specific study data and eCRFs, queries and responses, and audit trails of data changes that were made throughout the study. Novartis also internally archives copies of the above data in their CREDI system (Clinical Research Electronic Documentation and Information system). During the inspection the Sponsor was only able to provide eCRFs and the attached discrepancies/queries from the Oracle Clinical database in PDF format on a CD-ROM for review. Novartis also provided the AE/SAE data listing, protocol deviation listings, and fatalities listings for Sites 098, 117, 217, and 665.

c.Assessment of data integrity: No significant deficiencies were observed during the inspection of Novartis, and no FDA 483 was issued. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four foreign and a Sponsor inspection were conducted in support of NDA 207620, for audit of Protocol Study CLCZ696B2314 (PARADIGM-HF). No regulatory violations were found during the inspections of Dr. Aggarwal (India), and Dr. Staneva (Bulgaria). These inspections were classified as NAI. Minor regulatory violations were found during the inspection of Dr. Botelho (Brazil) with a one-item FDA 483 issued for failure to follow the investigational plan. Minor regulatory violations were also observed during the inspection of Dr. Li (China) with a one observational FDA 483 issued for failure to prepare and maintain accurate records. These issues are unlikely to significantly impact the quality or the integrity of the data submitted in support of this NDA. No regulatory violations were observed during the sponsor inspection (Novartis). OSI recommends the data be accepted.

Note: The final EIRs for Drs. Botelho, Li, and Staneva were not available at the time this Clinical Inspection Summary was written. The observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

{See appended electronic signature page}

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/s/

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06/08/2015

SUSAN D THOMPSON
06/08/2015

KASSA AYALEW
06/08/2015

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:	June 4, 2015
To:	Norman Stockbridge, MD, PhD Director **Division of Cardiovascular and Renal Products (DCRP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Britt Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN 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):	TRADE NAME (sacubitril/valsartan)
Dosage Form and Route:	Tablets, film-coated, for oral use
Application Type/Number:	NDA 207620
Applicant:	Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On December 17, 2014, Novartis Pharmaceuticals Corporation submitted for the Agency's review an original New Drug Application (NDA) 207620 for TRADE NAME (sacubitril/valsartan) Tablets with the proposed indication for the treatment of heart failure (NYHA class II-IV) (b) (4).

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 Cardiovascular and Renal Products (DCRP) on January 16, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRADE NAME (sacubitril/valsartan) Tablets.

2 MATERIAL REVIEWED

- Draft TRADE NAME (sacubitril/valsartan) Tablets PPI received on December 17, 2014 and received by DMPP and OPDP on May 22, 2015.
- Draft TRADE NAME (sacubitril/valsartan) Tablets Prescribing Information (PI) received on December 17, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 22, 2015.

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. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- 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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/s/

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06/04/2015

ZARNA PATEL
06/04/2015

MARCIA B WILLIAMS
06/04/2015

LASHAWN M GRIFFITHS
06/04/2015

LABEL AND LABELING REVIEW

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)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 1, 2015
Requesting Office or Division:	Division of Cardiovascular & Renal Products (DCRP)
Application Type and Number:	NDA 207620
Product Name and Strength:	Entresto (sacubitril/valsartan) Tablets 24 mg/26 mg, 49 mg/51 mg, 97 mg/103 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation
Submission Date:	May 4, 2015 May 15, 2015
OSE RCM #:	2015-233
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of this new drug application (NDA) review for Entresto (sacubitril/valsartan) Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg, this review evaluates the proposed container label, carton labeling, and Prescribing Information for areas of vulnerability that can lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B-N/A
Previous DMEPA Reviews	C- N/A
Human Factors Study	D- N/A
ISMP Newsletters	E-N/A
Other	F-N/A
Container Label, Carton Labeling	G
Full Prescribing Information	H

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA performed a risk assessment of the proposed Prescribing Information, the container labels and carton labeling to identify deficiencies that may lead to medication errors and areas for improvement. We note product information on the container labels and carton labeling can be revised to promote the safe use of the product. We also note the use of sequential NDC numbers for the different strengths of Entresto, which may lead to wrong product and wrong strength errors.

Thus, we provide our recommendations to mitigate confusion and promote the safe use of this product in Section 4.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase clarity, readability, and the prominence of important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

Based on this review, we have made revisions to the Prescribing Information (See Appendix H).

4.2 RECOMMENDATIONS FOR NOVARTIS PHARAMCEUTICALS CORPORATION

We recommend the following be implemented prior to approval of this NDA:

A. General Comments

1. As currently presented, the product codes for Entresto 24 mg/26 mg bottle (0078-**659**-XX), Entresto 49 mg/51 mg bottle (0078-(b) (4)-XX), and Entresto 97 mg/103 mg bottle (0078-(b) (4)-XX) (b) (4). (b) (4)
2. Consider revising the order of product information on the container labels and carton labeling. The customary order of information is the proprietary name, followed underneath by the full established name, followed underneath by the strength (see example below)[2]. Retain the color block to help to differentiate the strengths to prevent selection errors.

   Entresto
   (sacubitril /valsartan) tablets
   24 mg/26 mg
3. Revise the statement on the side panels of container labels and carton labeling, (b) (4) to read, "Usual Dose: See prescribing information".
4. Consider including a picture of Entresto tablet, such as the image on starter kit cartons, on all carton labeling. Additionally, ensure that the picture of Entresto tablet accurately reflects the actual tablet and its color as described in the proposed Prescribing Information Section 16.

[1] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. (lines 521-544) Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[2] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. (lines 344-349) Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

B. Professional Sample Container Label

1. Relocate the net quantity statement away from the product strength. From post-marketing experience, the risk of numerical confusion between strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.
2. Minimize the Novartis logo on the Principal Display Panels (PDP). As currently presented, it competes for prominence with important product information such as the proprietary name, established name, and strength.

C. Professional Sample Carton Label

1. Remove the statement [redacted] (b) (4)

D. 28-count Professional Sample Starter Kit Carton Labeling

1. Revise the net quantity statement [redacted] (b) (4) to read '2 bottles of 14 tablets (14-day starter supply)' to accurately describe the package configuration.
2. Increase the prominence of the 'Physician Sample. Not for Sale.' statement.

E. Commercial Container Label

1. Minimize the Novartis logo on the Principal Display Panels (PDP). As currently presented, it competes for prominence with important product information such as the proprietary name, established name, and strength.

F. Hospital Unit Dose Blister Label

1. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product barcode to each individual blister label as required per 21CFR 201.25(c)(1)(ii).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Entresto that Novartis Pharmaceuticals Corporation submitted on May 4, 2015.

Table 2. Relevant Product Information for Entresto	
Initial Approval Date	N/A
Active Ingredient	sacubitril/valsartan
Indication	For the treatment of heart failure (NYHA II-IV) (b) (4)
Route of Administration	Oral
Dosage Form	Film-coated tablets
Strength	24 mg/26 mg, 49 mg/51 mg, 97 mg/103 mg
Dose and Frequency	The target dose of Entresto is 200 mg twice daily. The recommended starting dose for patients not currently taking an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocking (ARB) agent is 50 mg twice daily, and should be considered for patients previously taking low doses of these agents. The dose of Entresto should be doubled every 2 to 4 weeks, as tolerated, to the target dose of 200 mg twice daily.
How Supplied	14-count professional sample 60-count trade bottle 180-count trade bottle 100-count Hospital Unit Dose (HUD) blister packages
Storage	Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from moisture. Store in original container.
Container Closure	14-count Professional Sample- White, round high density polyethylene bottles with plastic, (b) (4) closure with an aluminum induction seal. 60 and 180-count trade bottle- White, square high-density polyethylene bottles with aluminum induction seal and (b) (4) screw cap closure. HUD Blister Package- (b) (4) blister packs backed with a heat sealable (b) (4) aluminum foil.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[3] along with postmarket medication error data, we reviewed the following Entresto labels and labeling submitted by Novartis Pharmaceuticals Corporation on May 4, 2015 and May 15, 2015.

- Prescribing Information submitted May 4, 2015.
- Submitted May 15, 2015:
    - Professional Sample Container Label
    - Professional Sample Carton Labeling
    - Professional Sample Starter Kit Carton Labeling
    - Commercial Container label
    - Hospital Unit-Dose Blister labels
    - Unit-Dose Carton Labeling

34 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[3] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JANINE A STEWART
06/01/2015

CHI-MING TU
06/01/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: May 26, 2015

From: Miriam Dinatale, D.O., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Acting Division Director
Division of Pediatric and Maternal Health

To: Division of Cardiovascular and Renal Products (DCRP)

Drug: LCZ696 (sacubitril/valsartan) tablets

NDA: 207620

Applicant: Novartis Pharmaceutical Corp

Drug Class: angiotensin receptor neprilysin inhibitor

Proposed Indication: Treatment of heart failure (NYHA class II-IV) (b) (4)

Subject: Pregnancy and Lactation Labeling

Submission Date: May 26, 2015

Consult Date: April 6, 2015

Materials Reviewed:

- DPMH consult request dated April 6, 2015, DARRTS Reference ID 3726193
- Sponsor's submitted background package for NDA 207620, LCZ696 (sacubitril/valsartan) tablet

Consult Question:

DCRP requests DPMH assistance with reviewing the PLLR format of labeling that was provided by the sponsor and providing edits and comments.

INTRODUCTION

On September 30, 2014, Novartis Pharmaceutical Corp submitted 505 (b)(1) New Drug Application (NDA) for LCZ696 (sacubitril/valsartan), which is an angiotensin receptor neprilysin inhibitor. LCZ696 has the proposed indication of treatment of heart failure (NYHA class II-IV) (b) (4). On June 23, 2014, the FDA granted LCZ696 Fast Track designation and agreed to an NDA rolling submission schedule.

The Division of Pediatric and Maternal Health (DPMH) was consulted by the Division of Cardiovascular and Renal Products (DCRP) on April 6, 2015, to review the Pregnancy and Lactation subsections of labeling to ensure compliance with the Pregnancy and Lactation Labeling Rule formatting requirements and to provide comments to be included in the labeling that will be sent to the applicant.

BACKGROUND

LCZ696 (sacubitril/valsartan) Mechanism of Action

Following oral administration, LCZ696, dissociates into valsartan and the pro-drug sacubitril, which is further metabolized to LBQ657 (the neprilysin inhibitory moiety). LCZ696 has the mechanism of action of an angiotensin receptor neprilysin inhibitor (ARNI), simultaneously inhibits neprilysin (neutral endopeptidase, NEP) via LBQ657, and blocks the angiotensin II type-1 (AT1) receptor via valsartan. This results in complementary effects on the cardiovascular system that are beneficial in heart failure patients.[1]

Cardiovascular Disease and Pregnancy

Cardiovascular Disease (CVD) complicates 1-4% of pregnancies, with congenital heart disease being the most common preexisting condition and hypertension being the most common acquired condition. Women with heart failure of any etiology with an ejection (EF) <40% or NYHA class III-IV symptoms should be counseled to avoid pregnancy. Hypertrophic cardiomyopathy (HCM), which can cause heart failure, is associated with an increased maternal morbidity and mortality. Tachycardia and a decrease in systemic vascular resistance, which can occur during pregnancy, can exacerbate outflow tract obstruction in patients with HCM.[2]

[1] Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review, December 17, 2014, DARRTS Reference ID 3708368.

[2] Naderi, Sahar and Raymond, Russell. Pregnancy and Heart Disease. Cleveland Clinic Center for Continuing Education. Accessed 4/21/2015.

Pregnancy and Nursing Mothers Labeling

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[3] also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule[4] format to include information about the risks and benefits of using these products during pregnancy and lactation.

The PLLR will take effect on June 30, 2015; however, at this time applicants may voluntarily convert labeling to PLLR format.

DISCUSSION

Sacubitril/valsartan and Nonclinical findings

Animal reproduction studies have been conducted with sacubitril/valsartan and have demonstrated increased fetal lethality in rats (≤0.14 and 1.5-fold the MRHD for LBQ 657 and Valsartan, respectively) and rabbits (0.06-fold and 4-fold the MRHD for LBQ 657 and Valsartan, respectively) given the drug during organogenesis. Sacubitril/valsartan was also found to be teratogenic based on the presence of fetal hydrocephaly, associated with maternally toxic doses, which was observed in rabbits at a sacubitril/valsartan dose of ≥10 mg/kg/day. The adverse fetal effects of sacubitril/valsartan are attributed to the angiotensin receptor antagonist activity (the reader is referred to the nonclinical review by William Link, PhD, for further details).

Sacubitril and Pregnancy

The applicant did not conduct studies with sacubitril alone in pregnant women. A search of literature for available published human pregnancy data for sacubitril was performed to update the Pregnancy subsection of labeling for this application, and no studies were found.

Valsartan and Pregnancy

A search of literature for available published human pregnancy data for valsartan, angiotensin II (AT-II) receptor blockers and angiotensin converting-enzyme inhibitors (ACE-I) was performed to update the Pregnancy subsection of labeling for this application. A review of TERIS [5] demonstrates that fetal and neonatal morbidity (hypotension,

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http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/cardiology/pregnancy-and-heart-disease/Default htm

[3] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

[4] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

[5] TERIS is the TERatology Information Service located at University of Washington. It is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women. Review date 07/14. Accessed 5/15/ 15.

hyperkalemia, oliguria, neonatal skull hypoplasia, anuria, renal failure) and death have been reported in several dozen cases of pregnant women who received drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy. There are also reports of spontaneous abortions, oligohydramnios and newborn renal dysfunction that have been reported with valsartan use in pregnant women. The occurrence of oligohydramnios is possibly due to decreased fetal renal function and has been associated with fetal limb contractures, craniofacial deformities, and hypoplastic lung development.

Current valsartan labeling[6] notes that if pregnancy occurs during use, valsartan should be discontinued as soon as possible. In rare cases, when discontinuation of the drug is not an option, the mother should have serial ultrasounds to assess the intra-amniotic environment. If oligohydramnios is noted, valsartan should be stopped unless it is considered life-saving for the mother. Therefore, infants with a history of exposure to AT II receptor antagonists should be monitored for hypotension, oliguria, and hyperkalemia.

Sacubitril/valsartan and Pregnancy
The applicant did not conduct studies with sacubitril/valsartan in pregnant women. However, there were four cases of pregnancy during clinical trials with sacubitril/valsartan. See appendix B for narratives of patients with pregnancy and/or spontaneous abortion.

- One pregnancy resulted in a normal, full-term female infant, delivered via Cesarean section. The mother was enrolled in the study on July 17, 2012 (Day 1), had a positive pregnancy test at approximately five weeks gestation (day 198 of the study) and received treatment until approximately 27 weeks gestation (day 351 of the study). On (b) (6) ((b) (6) days after the last dose of LCZ696), the patient delivered a normal baby girl by cesarean section.
- One patient had a medical pregnancy termination at about 10 weeks gestation once the pregnancy was identified. There was no mention of any fetal malformations.
- Two patients had spontaneous abortions (SAB); one patient had a SAB at six weeks gestation, and the other patient had a SAB at seven weeks gestation.

Reviewer Comments
Current valsartan labeling notes that oligohydramnios, hypotension, hyperkalemia, oliguria, neonatal skull hypoplasia, anuria, renal failure, and fetal or neonatal death have been observed when AT-II receptor antagonists were used in the second or third trimester of pregnancy. Although there are no studies or case reports with sacubitril use alone in pregnant women, there are four pregnancies in clinical trials that have been done with sacubitril/valsartan. In these four cases, there was one normal pregnancy, two SABs and one medical termination. There was no known evidence of fetal malformations in the abortions, but the number of pregnant women exposed was small, and it is difficult to know if sacubitril has teratogenic effects when it is used in combination with valsartan, which is already known to adversely affect a fetus.

Proposed sacubitril/valsartan labeling recommends that sacubitril/valsartan is discontinued as soon as pregnancy is found. However, heart failure can worsen during pregnancy and can

[6] Drugs@FDA: Valsartan. Pregnancy 8.1, Revised 9/26/2014. Accessed 5/15/15.

be fatal to the pregnant mother. Therefore, a risk/benefit statement should be made in labeling that considers the benefit of the drug to the mother versus the risk to the mother if the drug is withdrawn.

Sacubitril/valsartan and Lactation

A search of published literature in the Drugs and Lactation Database (Lactmed)[7] and Pubmed for available human lactation data was performed to update the Lactation subsection of labeling for this application. Although there is no information on sacubitril or valsartan in published literature, animal studies have shown that LBQ657, sacubitril's metabolite, is present in the milk of lactating rats.

In addition, serious adverse reactions were observed in pediatric patients less than the age of six in clinical trials with valsartan.[8] In a study (n=90) of pediatric patients (1 to 5 years of age), two deaths and three cases of on-treatment transaminase elevations were seen in the one-year open-label extension phase. These five events occurred in a study population in which patients frequently had significant co-morbidities. A causal relationship to valsartan has not been established. In a second study, in which 75 children aged 1 to 6 years were randomized, no deaths and one case of marked liver transaminase elevations occurred during a 1 year open-label extension. Currently, valsartan is not recommended for pediatric patients under 6 years of age.[9]

Reviewer Comments:
The characteristics of sacubitril/valsartan suggest that sacubitril/valsartan may be present in breast milk. Sacubitril/valsartan has a high pH (8.15), and a moderate half-life of 11.5 hours (for LBQ657, sacubitril's metabolite)), which may increase the presence of the drug in the mother's circulation and may increase infant exposure to the drug via breast milk. However, this drug has a high molecular weight (957.99 Daltons). Drugs with molecular weights more than 800 Daltons are more likely to be excluded from the milk compartment than drugs with molecular weights less than 800 Daltons.[10]

Proposed sacubitril/valsartan lactation labeling states that sacubitril/valsartan is present in rat milk and that the drug is not recommended during breastfeeding. Given the risk of serious adverse events (liver transaminase elevation and death) as seen in pediatric patients in clinical trials with valsartan, breastfeeding with maternal use of sacubitril/valsartan is not recommended due to the potential for these serious adverse reactions in a breastfed infant.

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[7] The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. http://toxnet.nlm nih.gov/cgi-bin/sis/htmlgen?LACT

[8] Current applicant proposed labeling sacubitril/valsartan: Section 5: Warnings and Precautions.

[9] Drugs@FDA: Valsartan Labeling, section 6.1 Adverse Reactions: Pediatric Hypertension. Accessed 5/15/2015.

[10] Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. Journal of the American Pharmacists Association. 2012; 51 (1): 86-94.

DPMH agrees with the applicant's recommendation against breastfeeding with maternal use of sacubitril/valsartan.

Sacubitril/valsartan and Fertility

(b) (4)

There is no infertility noted in animal studies, and there are no infertility concerns in humans. (b) (4)

CONCLUSIONS

LCZ696 (sacubitril/valsartan) labeling has been updated to comply with the PLLR. A review of the applicant's submitted data and the published literature revealed no new information with LCZ696 (sacubitril/valsartan) use in pregnant or lactating women and regarding fertility in males and females of reproductive potential. DPMH has the following recommendations for LCZ696 (sacubitril/valsartan) labeling:

- **Warnings and Precautions, Section 5.1**
  - A subsection describing embryo- and/or fetal risks ("Embryofetal Toxicity") as well as mitigation measures must be placed in the Warnings and Precautions section of labeling as required by regulation (21 CFR 201.57(c)(9)(i)(A)(4))
- **Pregnancy, Section 8.1**
  - The "Pregnancy" subsection of LCZ696 (sacubitril/valsartan) labeling was formatted in the PLLR format to include the "Risk Summary," "Clinical Considerations," and "Data" subsections.[11]
- **Lactation, Section 8.2**
  - The "Lactation" subsection of LCZ696 (sacubitril/valsartan) labeling was formatted in the PLLR format to include the "Risk Summary" and "Data" subsections.[12]

Because the applicant has voluntarily complied with the PLLR requirements prior to the June 30, 2015 effective date, language waiving the current labeling requirements should be included in the approval letter. The following approval letter language is suggested.

"WAIVER OF PREGNANCY, LABOR AND DELIVERY, AND NURSING MOTHERS SUBSECTIONS

We are waiving the current requirements of 21CFR 201.56(d)(1) and 201.57(c)(9)(i) through (iii), regarding the content and format of labeling for subsections 8.1 Pregnancy, 8.2 Labor and Delivery, and 8.3 Nursing Mothers of prescribing information. Your approved labeling for subsections 8.1, 8.2, and 8.3 reflects the content and format requirements of the Pregnancy and Lactation Labeling Rule (79 FR 72063, December 4, 2014) which implements on June 30, 2015."

[11] Draft Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

[12] Draft Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

APPENDIX B: LCZ696B (sacubitril/valsartan), NDA 207620 Novartis Response to FDA Information Request, April 14, 2015

Narratives of patients with pregnancy and /or spontaneous abortion

Patient B2314-0665-00076

Patient details: 31 years, female, Asian
Randomized treatment group: LCZ696 200 mg bid

The patient had a history of chronic heart failure (0-3 months, NYHA class II, LVEF 18%). The primary etiology was non-ischemic (idiopathic cardiomyopathy). Her alcohol consumption was less than 1 drink per day. There was no other relevant medical history for this patient. Relevant concomitant medications included amiodarone, atorvastatin, bisoprolol (2.5 mg qd), digoxin (0.25 mg qd), and spironolactone-furosemide (50/20 mg half tablet daily, Osyrol-Lasix). The patient was on ramipril (5 mg qd) prior to start of the study.

The patient entered the run-in phase on 01 Oct 2012. She received enalapril 10 mg bid from 01 Oct 2012 to 14 Oct 2012, LCZ696 100 mg bid from 16 Oct 2012 to 22 Oct 2012 and LCZ696 200 mg bid from 23 Oct 2012 to 05 Nov 2012. She was randomized on 06 Nov 2012 and started with LCZ696 200 mg bid on Day 1 (07 Nov 2012).

On Day 465 (14 Feb 2014), while on LCZ696 200 mg bid, the patient was found to be pregnant. The patient's last menstrual period was on Day 402 (13 Dec 2013). The reason for contraception failure was uncertain. Treatment with LCZ696 was temporarily interrupted from Day 466 (15 Feb 2014) due to this event. On Day [redacted] (b) (6), the patient had a medical termination of her pregnancy. Treatment with LCZ696 was restarted on Day 476 (25 Feb 2014).

The patient received the last dose of LCZ696 on Day 535 (25 Apr 2014) as per protocol and completed the study on the next day (26 Apr 2014).

The Investigator did not suspect a relationship between the event (pregnancy) and LCZ696.

Patient B2314-1187-00030

Patient details: 18 years, female, black
Randomized treatment group: LCZ696 200 mg bid

The patient had a history of chronic heart failure (0-3 months, NYHA class II, LVEF 22.30%). The primary etiology was non-ischemic (peripartum cardiomyopathy). Her alcohol consumption was less than 1 drink per day. The patient's relevant medical history type 1 diabetes mellitus (since 2011) and a previous normal delivery. Relevant concomitant medications included carvedilol (3.125 mg bid), furosemide (40 mg bid), spironolactone (25 mg qd), and insulin. The patient was on perindopril (4 mg qd) prior to start of the study.

The patient entered the run-in phase on 01 Jun 2012. She received enalapril 10 mg bid from 01 Jun 2012 to 17 Jun 2012, LCZ696 100 mg bid from 19 Jun 2012 to 01 Jul 2012 and LCZ696 200 mg bid from 02 Jul 2012 to 15 Jul 2012. She was randomized on 16 Jul 2012 and started with LCZ696 200 mg bid on Day 1 (17 Jul 2012).

On Day 198 (30 Jan 2013), while on LCZ696 200 mg bid, the patient was found to be pregnant. The patient used norethisterone enantate pills as her contraceptive method since May-2012. After the patient was noted to be pregnant, it was reported that the patient did not use contraception as instructed. Treatment with LCZ696 was permanently discontinued due to this event and the patient received the last dose on Day 351 (02 Jul 2013). On [redacted] (b) (6) days after the last dose of LCZ696, the patient delivered a normal baby girl by LSCS (lower segment caesarean section). It was reported that patient's baby had two episodes of body twitching on [redacted] (b) (6) days after delivery by c-section. After this no more twitching was reported.

The patient completed the study and attended the End-of-Study visit on 08 Apr 2014.

The Investigator did not suspect a relationship between the event (pregnancy) and the LCZ696.

Patient B2314-1176-00009

Patient details: 39 years, female, black
Randomized treatment group: LCZ696 200 mg bid

The patient had a history of chronic heart failure (>1-2 years, NYHA class II, LVEF 30%). The primary etiology was non-ischemic (idiopathic cardiomyopathy). Her alcohol consumption was less than 1 drink per day. The patient's relevant medical history and active medical conditions included insomnia (since 2011) and 2 normal pregnancies with 2 normal fetuses. Relevant concomitant medications included bisoprolol (2.5 mg qd), furosemide (40 mg qd), spironolactone (25 mg qd), and ethinyl estradiol-levonorgestrel (Triphasil). The patient was on perindopril (10 mg qd) prior to start of the study.

The patient entered the run-in phase on 12 Jul 2012. She received enalapril 10 mg bid from 13 Jul 2012 to 25 Jul 2012, LCZ696 100 mg bid from 27 Jul 2012 to 07 Aug 2012 and LCZ696 200 mg bid from 08 Aug 2012 to 21 Aug 2012. She was randomized on 22 Aug 2012 and started with LCZ696 200 mg bid on Day 1 (23 Aug 2012).

On an unspecified day in February 2013, the patient had her last menstrual period. Treatment with LCZ696 was temporarily interrupted from Day 164 (02 Feb 2013) due to pregnancy. The patient was using contraceptive pills (ethinyl estradiol-levonorgestrel). The patient showed poor compliance with contraceptive pill use and LCZ696 200 mg at the time of conception. On Day 239 (18 Apr 2013), an ultrasound confirmed 6 weeks pregnancy. On Day [redacted] (b) (6), the patient had a spontaneous abortion at [redacted] (b) (4) weeks gestation. The patient received doxycycline and metronidazole post spontaneous abortion. The event (abortion spontaneous) was considered resolved on the same day [redacted] (b) (6). Treatment with LCZ696 was restarted on Day 355 (12 Aug 2013).

The patient received the last dose of the LCZ696 on Day 601 (15 Apr 2014) as per protocol and completed the study on the next day (16 Apr 2014).

The Investigator did not suspect a relationship between the event (abortion spontaneous) and LCZ696.

Patient B2314-1187-00032

Patient details: 34 years, female, black
Randomized treatment group: LCZ696 200 mg bid

The patient had a history of chronic heart failure (>1-2 years, NYHA class II, LVEF 29.10%). The primary etiology was non-ischemic (peripartum cardiomyopathy). Her alcohol consumption was less than 1 drink per day. The patient's medical history and active medical condition included 3 normal deliveries (38 weeks gestation). Relevant concomitant medications included carvedilol (6.25 mg bid), digoxin (0.125 mg qd), furosemide (60 mg bid), and spironolactone (25 mg qd). The patient was on perindopril (4 mg qd) prior to the start of the study.

The patient entered the run-in phase on 15 Jun 2012. She received enalapril 10 mg bid from 16 Jun 2012 to 28 Jun 2012, LCZ696 100 mg bid from 30 Jun 2012 to 11 Jul 2012 and LCZ696 200 mg bid from 12 Jul 2012 to 26 Jul 2012. She was randomized on 27 Jul 2012 and started with LCZ696 200 mg bid on Day 1 (28 Jul 2012).

In August 2012, the patient was found to be pregnant. The patient was using oral contraceptives and compliance with contraception was uncertain. Treatment with LCZ696 was temporarily interrupted from Day 77 (12 Oct 2012) due to pregnancy. On Day (b) (6), she had bleeding, and an incomplete spontaneous abortion was suspected. She was referred to a gynecologist, who confirmed a spontaneous abortion. The event (abortion spontaneous) was considered resolved on Day 82 (17 Oct 2012) at the 7th week of pregnancy. Treatment with LCZ696 was re-started on Day 113 (17 Nov 2012).

The patient received the last dose of the LCZ696 on Day 620 (08 Apr 2014) as per protocol and completed the study on the next day (09 Apr 2014).

The Investigator did not suspect a relationship between the events (pregnancy, abortion spontaneous) and the LCZ696.

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/s/

MIRIAM C DINATALE
05/26/2015

LYNNE P YAO
05/26/2015

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	207620
Generic Name	LCZ696
Sponsor	Novartis Pharmaceuticals, Corp
Indication	Treatment of Heart Failure
Dosage Form	Tablet
Drug Class	Angiotensin receptor neprilysin inhibitor (ARNI)
Therapeutic Dosing Regimen	400 mg
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Unknown
Submission Number and Date	SDN 005; 17 Dec 2014
Review Division	DCRP

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1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of LCZ696 (400 mg and 1200 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between LCZ696 (400 mg and 1200 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 8, indicating that assay sensitivity was established.

In this randomized, blinded, four-period crossover study, 84 healthy male subjects received LCZ696 400 mg, LCZ696 1200 mg, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for LCZ696 (400 mg and 1200 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
LCZ696 400 mg	1	3.1	(2.0, 4.2)
LCZ696 1200 mg	1	3.7	(2.6, 4.8)
Moxifloxacin 400 mg	1	12.0	(10.6, 13.5)

* Multiple endpoint adjustment of 4 time points was applied.

The mean C_{max} values for all LCZ696 analytes with the supratherapeutic dose (1200 mg) were 7780 ng/mL for sacubitril (a.k.a. AHU377), 40700 ng/mL for LBQ657 and 9360 ng/mL for valsartan. These values were 2.4-fold, 3.0-fold, and 2.0-fold the mean Cmax (3210 ng/mL, 13700 ng/mL, 4690 ng/mL, respectively) values with the therapeutic dose (400 mg). These supratherapeutic concentrations are higher than those for the expected worst case scenario (AHU377 (4960 ng/mL), LBQ657 (30650 ng/mL) and valsartan (5852 ng/mL) at steady state in subjects with severe renal impairment receiving 400 mg LCZ696 once daily for 5 days).

2 PROPOSED LABEL

The following is the sponsor's proposed labeling language related to QT.

12.2 Pharmacodynamics

In a thorough QTc clinical study in healthy male subjects, single doses of (b) (4) had no effect on cardiac repolarization.

QT-IRT's comments: The proposed labeling is acceptable. We defer final labeling decisions to the Division.

3 BACKGROUND

3.1 Product Information

LCZ696 (sacubitril/valsartan) is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI) currently under development for the treatment of hypertension and heart failure. Following oral administration, LCZ696 dissociates into the pro-drug sacubitral (which is further metabolized to LBQ657, the neprilysin inhibitory moiety) and valsartan. LCZ696 has the mechanism of action of an angiotensin receptor neprilysin inhibitor (ARNI), simultaneously inhibiting neprilysin (neutral endopeptidase, NEP) via LBQ657, and blocking the antiotensin II type-1 (AT1) receptor via valsartan, resulting in complementary effects on the cardiovascular system that are beneficial in heart failure patients.

3.2 Market approval status

Valsartan was approved as a monotherapy. However, LCZ696 is not approved for marketing in any country.

3.3 Preclinical Information

Pre-clinical studies suggest no increased risk of QTc interval prolongation with LCZ696 (see Appendix 6.1).

3.4 Previous Clinical Experience

Data from the extensive LCZ696 clinical development and clinical pharmacology programs show that in general, cardiac safety events in controlled LCZ696 studies occur

with low incidence and are reported either with an incidence lower than active comparator (enalapril, olmesartan) or with an incidence that is comparable with placebo (in the hypertension studies). Syncope is a commonly reported adverse event in LCZ696 treated patients. It is likely that the observed events of syncope are more closely related to the identified risk of hypotension, and not a symptom of cardiac adverse effects. In PARADIGM-HF the frequency of reported AEs of syncope is similar between LCZ696 and enalapril.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of LCZ696's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT did not review the protocol prior to conducting this study. The sponsor submitted the study report CLCZ696B2123 for LCZ696, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A randomized, partially blinded, placebo-controlled crossover study to assess the effects of single therapeutic and supratherapeutic doses of LCZ696 on baseline- and placebo-corrected QTc intervals in healthy male volunteers

4.2.2 Protocol Number

CLCZ696B2123

4.2.3 Study Dates

10 Oct 2012 - - 28 Dec 2012

4.2.4 Objectives

The primary objective was to to assess whether a therapeutic and supratherapeutic dose of LCZ696 (AHU377, LBQ657 and valsartan) causes changes in the baseline-corrected mean Fridericia's correction of QT interval (QTcF interval) as compared to placebo (ΔΔQTc) in healthy male subjects.

The secondary objectives were as the follows:

- To evaluate the effect of moxifloxacin on the baseline-corrected mean QTcF as compared to placebo (ΔΔQTc) in healthy male subjects to confirm assay sensitivity.
- To evaluate the exposure-QTcF relationship of LCZ696 (AHU377, LBQ657 and valsartan) in healthy male subjects.
- To assess the tolerability of therapeutic and supratherapeutic single oral doses of LCZ696 in healthy male subjects.
- To evaluate baseline-corrected changes in heart rate, PR interval, and QRS duration for LCZ696 (AHU377, LBQ657 and valsartan) as compared to placebo.
- To evaluate ECG morphologic changes related to cardiac repolarization (ST segment and T waves) for LCZ696 (AHU377, LBQ657 and valsartan).

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, 12-sequence, crossover design with four dosing occasions. Each dosing occasion was followed by a washout period of at least 4 days.

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The positive (moxifloxacin) control was not blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There were 4 treaments:

- Treatment A: LCZ696 400 mg
- Treatment B: LCZ696 1200 mg
- Treatment C: Moxifloxacin 400 mg
- Treatment D: Placebo

4.2.6.2 Sponsor's Justification for Doses

A single therapeutic dose of LCZ696 400 mg and a supratherpeutic dose of 1200 mg were selected to assess the effect of LCZ696 over a wide exposure range. The supratherapeutic dose of LCZ696 1200 mg provided a 3-fold exposure multiple, and was consistent with the ICH E14 regulatory recommendation to evaluate the QT effect at exposures that are significantly higher than those achieved with the therapeutic dose, thus accounting for potential exposure increase due to drug-drug interactions or in special population

Reviewer's Comment: The selected doses appear to be reasonable considering the fact that the largest exposure of LBQ657 was observed with the proposed therapeutic dose of 200 mg in patients with severe renal impairment and their observed exposure was similar to the projected exposure of LBQ657 with 1200 mg of LCZ696. No significant drug-drug interaction or drug accumulation is anticipated.

4.2.6.3 Instructions with Regard to Meals

Doses will be administered with or without food.

Reviewer's Comment: A preliminary single-dose food effect study showed no clinically significant food effect on drug exposures with 200 mg LCZ696. Thus the proposed instruction appears to be reasonable.

4.2.6.4 ECG and PK Assessments

A total of 84 subjects were enrolled into the study and 81 subjects completed the study.

Twelve (12)-lead Holter recordings for ECG extraction were obtained using validated 24-hour Holter ECG recorders at 1000 Hz resolution on baseline days (Day -1) and on profiling days (Day 1) of each treatment period, and assessed in a blinded fashion by a core ECG laboratory that was assigned to the study. The Holter recorders were removed after completion of the study procedures on Day 2 of each period.

- The ECGs were extracted for primary analysis at the following times:On Day 1 during the terminal portion of the 15 min-ECG collection time window (ECTW) starting at -1 h, -35 min and -15 min relative to the nominal dosing time (baseline).
- On Day 1 during the terminal portion of the ECTW ending at 0.5, 1, 2, 3, 4, 5, 8, 12 and 24 hours relative to the dosing time.

All blood samples for pharmacokinetics analysis were taken at 0.5, 1, 2, 3, 4, 5, 8, 12 and 24 hours relative to the dosing time.

Reviewer's Comment: Considering median Tmax values (0.5 hours for sacubitril, 2.0 hours for valsartan,and 2.1 hours for LBQ657) and mean half-lives (1.4 hours for sacubitril, 9.9 hours for valsartan, and 11.5 hours for LBQ657), these samplings for ECG and PK assessments were reasonable to describe both absorption phase and the elimination phase of LCZ696.

4.2.6.5 Baseline

The average of predose QT/QTc values on dose administration day of each period was used as baseline for that period.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Standard 12-Lead ECGs were obtained while subjects were recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 84 healthy male volunteers were enrolled and randomized to the study. 81 subjects completed the study per protocol. No replacement subjects were enrolled. All subjects were included in the safety and PD analysis set. 83 subjects were included in PK analysis set.

The mean age (SD) of subjects enrolled in study was 32.8 (7.44) years, ranging from 19 to 46 years. All subjects were male (84/84, 100%) with a mean (SD) height of 179.4 (7.19) cm and mean (SD) weight of 79.0 (8.81) kg. With respect to race, the majority of subjects were Caucasians (81/84, 96%), followed by Black (2/84, 2%) and Asian subjects (1/84, 1%).

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The upper bounds of the two-sided 90% CI for all baseline- and placebo-corrected QTcF values (ΔΔQTcF) after administration of therapeutic (400 mg) and supratherapeutic (1200 mg) doses of LCZ696 remained below the threshold of 10 ms.

The following Table 2 displays the sponsor's results for primary analysis.

Table 2: Treatment Comparisons for Placebo-corrected Change from Mean Baseline in QTc (ΔΔQTc) by Time and LCZ696 Dose (Sponsor's Results Based on Pharmacodynamic Analysis Set)

		LCZ696 400mg - Placebo			LCZ696 1200mg - Placebo		
Parameter	Hours post dose (hh:mm)	Estimated difference	SE	90% CI	Estimated difference	SE	90% CI
QTcF (ms)	0:30	0.895	0.440	(0.16, 1.63)	1.36	0.456	(0.61, 2.11)
	1:00	2.902	0.609	(1.89, 3.91)	3.60	0.532	(2.71, 4.48)
	2:00	2.857	0.646	(1.78, 3.93)	2.57	0.584	(1.60, 3.54)
	3:00	1.265	0.576	(0.31, 2.22)	1.79	0.542	(0.88, 2.69)
	4:00	1.248	0.650	(0.17, 2.33)	1.22	0.705	(0.05, 2.40)
	5:00	1.084	0.556	(0.16, 2.01)	1.54	0.707	(0.36, 2.71)
	8:00	-1.246	0.554	(-2.17, -0.32)	-1.41	0.676	(-2.54, -0.29)
	12:00	-2.674	0.665	(-3.78, -1.57)	-1.75	0.661	(-2.85, -0.65)
	24:00	-1.371	0.599	(-2.37, -0.37)	-0.41	0.583	(-1.38, 0.56)
QTcB (ms)	0:30	1.590	0.791	(0.27, 2.91)	3.46	0.876	(2.01, 4.91)
	1:00	4.511	0.982	(2.89, 6.14)	6.36	0.748	(5.11, 7.60)
	2:00	6.003	0.994	(4.35, 7.66)	6.97	0.886	(5.50, 8.44)
	3:00	4.697	0.894	(3.21, 6.18)	6.58	0.949	(5.00, 8.16)
	4:00	4.372	0.959	(2.78, 5.97)	6.49	0.861	(5.06, 7.93)
	5:00	4.597	0.951	(3.01, 6.18)	5.87	1.021	(4.17, 7.57)
	8:00	4.142	0.954	(2.55, 5.73)	4.83	1.085	(3.03, 6.64)
	12:00	0.836	1.126	(-1.04, 2.71)	2.00	1.150	(0.08, 3.91)
	24:00	-0.000	0.997	(-1.66, 1.66)	1.71	0.865	(0.28, 3.15)

Baseline = Mean of the pre-dose measurements at −1 h, −35 min and −15 min
Lack of QTc prolongation for one treatment when all upper 90% limits < 10 ms

Source: clinical study report CLCZ696B2123, Table 11-3, page 62

Reviewer's Comments: Please see the reviewer's analysis in section 5.2.

4.2.8.2.2 Assay Sensitivity

Assay sensitivity was demonstrated in this study based on the results. The maximum ΔΔQTcF effect was 11.903 ms and observed at 1 h post dose. The corresponding lower bound of the two-sided 90% CI at this time point was 10.91 ms.

The following Table 3 displays the sponsor's results for assay sensitivity analysis.

Table 3: Treatment Comparisons of Placebo-corrected Change from Mean Baseline in QTc (ΔΔQTc) by Time for Moxifloxacin (Sponsor's Results Based on Pharmacodynamic Analysis Set)

		Moxifloxacin 400mg- Placebo			
Parameter	Hours post dose (hh:mm)	Estimated difference	SE	90% CI	p-value
QTcF (ms)	0:30	8.360	0.661	(7.26, 9.46)	<.001
	1:00	11.903	0.602	(10.91, 12.90)	<.001
	2:00	10.555	0.608	(9.54, 11.57)	<.001
	3:00	10.311	0.551	(9.39, 11.23)	<.001
	4:00	9.703	0.691	(8.55, 10.85)	<.001
	5:00	9.986	0.648	(8.91, 11.06)	<.001
	8:00	8.450	0.577	(7.49, 9.41)	<.001
	12:00	6.726	0.779	(5.43, 8.02)	<.001
	24:00	5.268	0.640	(4.20, 6.33)	<.001
QTcB (ms)	0:30	11.019	1.060	(9.26, 12.78)	<.001
	1:00	16.603	1.021	(14.91, 18.29)	<.001
	2:00	12.238	0.956	(10.66, 13.82)	<.001
	3:00	11.235	0.876	(9.78, 12.69)	<.001
	4:00	9.738	1.059	(7.99, 11.49)	<.001
	5:00	10.018	0.905	(8.51, 11.52)	<.001
	8:00	9.688	0.868	(8.24, 11.13)	<.001
	12:00	7.313	0.951	(5.73, 8.89)	<.001
	24:00	4.783	0.962	(3.18, 6.38)	<.001

Baseline = Mean of the pre-dose measurements at −1 h, −35 min and −15 min

Assay sensitivity when at least one p-value < 0.0125

Source: clinical study report CLCZ696B2123, Table 11-4, page 64

Reviewer's Comments: Please see the reviewer's analysis in section 5.2.

4.2.8.2.3 Categorical Analysis

The categorical analysis of QTcF did not reveal any subjects with treatment-emergent QTcF values > 480 ms in any of the study groups. The overall incidence of treatment-emergent QTcF > 450 ms was low (1%) and noted only in one subject receiving moxifloxacin 400 mg at all post dose timepoints between 1 h and 5 h.

There were no subjects with QTcF increases from baseline of more than 30 or 60 ms.

4.2.8.3 Safety Analysis

There were no deaths, SAEs or AEs leading to discontinuation from the study.

A total of 52 AEs were reported in 29 subjects (34.5%) at least once during the study. Most frequently observed AEs were similarly distributed across all treatment groups. All AEs were either mild or moderate in intensity and resolved by the end of the study or during the 30-day follow-up period. Approximately 50% of AEs were drug related.

There were no cardiovascular AEs reported during the study that may suggest a pro-arrhythmic potential for LCZ696. There were no clinically significant abnormalities in vital signs, safety ECGs and laboratory measurements.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 4 and Figure 1 for AHU377, Table 5 and Figure 2 for LBQ657, Table 6 and Figure 3 for valsartan. The mean C_{max} values for all LCZ696 analytes with the supratherapeutic dose (1200 mg) were 7780 ng/mL for sacubitril (a.k.a. AHU377), 40700 ng/mL for LBQ657 and 9360 ng/mL for valsartan. These values were 2.4-fold, 3.0-fold, and 2.0-fold the mean Cmax (3210 ng/mL, 13700 ng/mL, 4690 ng/mL, respectively) values with the therapeutic dose (400 mg). The intended clinical dose is 200 mg BID.

Table 4. Summary statistics for PK parameters for AHU377 following a single oral dose of LCZ696 400 mg or LCZ696 1200 mg

		LCZ696 400 mg			LCZ696 1200 mg		
Parameter	Unit	n	Arithmetic mean (SD)	CV%	n	Arithmetic mean (SD)	CV%
AUC0-24h	hr*ng/mL	81	4400 (1780)	40.4	82	13200 (4640)	35.3
AUClast	hr*ng/mL	82	4390 (1760)	40.2	82	13100 (4640)	35.3
Cmax	ng/mL	82	3210 (1690)	52.6	82	7780 (3830)	49.2
Tmax[1]	hr	82	0.517 (0.500;3.08)		82	1.05 (0.483;4.02)	

Figure 1. Mean (SD) plasma concentration-time profiles for AHU377 following a single oral dose of LCZ696 400 mg or LCZ696 1200 mg

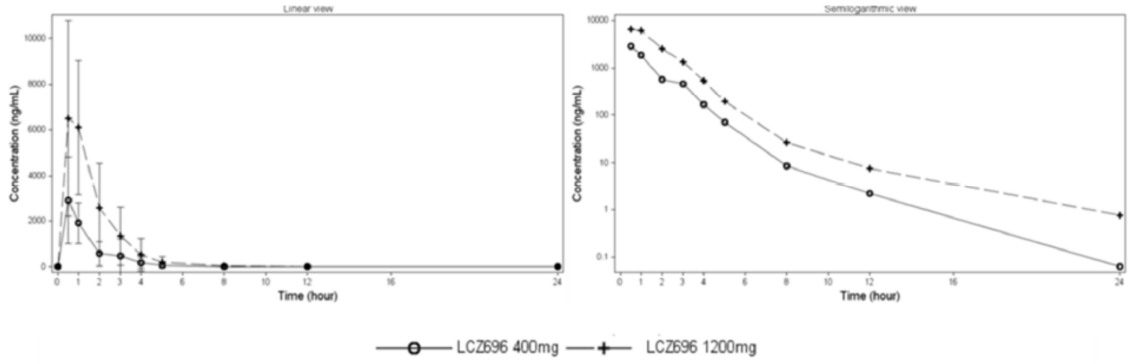


Table 5. Summary statistics for PK parameters for LBQ657 following a single oral dose of LCZ696 400 mg or LCZ696 1200 mg

		LCZ696 400 mg			LCZ696 1200 mg		
Parameter	Unit	n	Arithmetic mean (SD)	CV%	n	Arithmetic mean (SD)	CV%
AUC0-24h	hr*ng/mL	81	122000 (19700)	16.2	82	364000 (62300)	17.1
AUClast	hr*ng/mL	82	121000 (22200)	18.3	82	364000 (62400)	17.1
Cmax	ng/mL	82	13700 (2490)	18.2	82	40700 (6990)	17.2
Tmax[1]	hr	82	2.07 (1.05;5.07)		82	3.05 (2.05;5.07)	

Figure 2. Mean (SD) plasma concentration-time profiles for LBQ657 following a single oral dose of LCZ696 400 mg or LCZ696 1200 mg

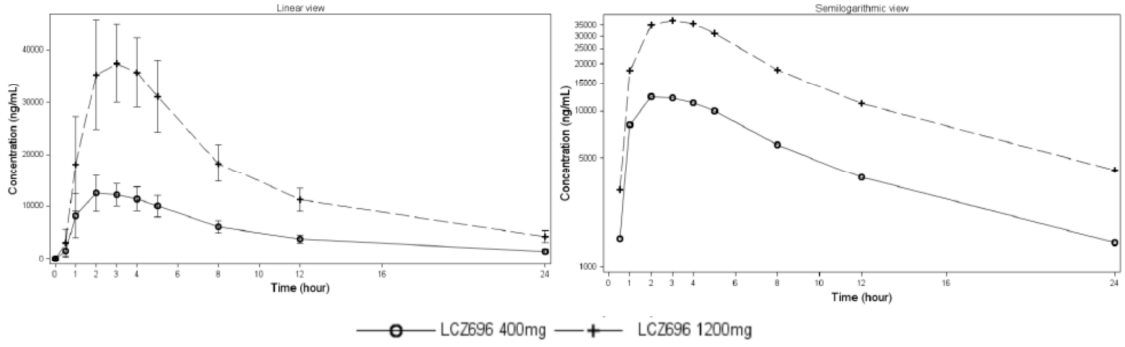
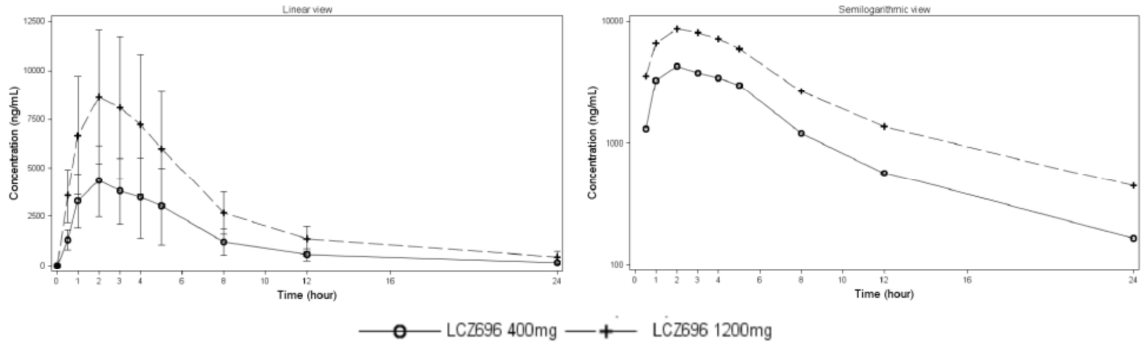


Table 6. Summary statistics for PK parameters for valsartan following a single oral dose of LCZ696 400 mg or LCZ696 1200 mg

		LCZ696 400 mg			LCZ696 1200 mg		
Parameter	Unit	n	Arithmetic mean (SD)	CV%	n	Arithmetic mean (SD)	CV%
AUC0-24h	hr*ng/mL	81	30500 (14500)	47.5	82	66000 (25400)	38.5
AUClast	hr*ng/mL	82	30300 (14500)	47.9	82	66000 (25400)	38.5
Cmax	ng/mL	82	4690 (2210)	47.2	82	9360 (3790)	40.5
Tmax[1]	hr	82	2.07 (1.05;5.07)		82	2.07 (1.03;4.07)	

Figure 3. Mean (SD) plasma concentration-time profiles for valsartan following a single oral dose of LCZ696 400 mg or LCZ696 1200 mg



4.2.8.4.2 Exposure-Response Analysis

The plasma concentration-response relationships for the placebo-corrected change from mean baseline in QTcF (ΔΔQTcF) and all LCZ696 analytes are presented in Figure 4 to Figure 6. Statistically significant but relatively flat slopes were reported for all LCZ696 analytes.

Figure 4. Concentration response relationship for the placebo-corrected change from mean baseline in QTcF (ΔΔQTcF) and AHU377

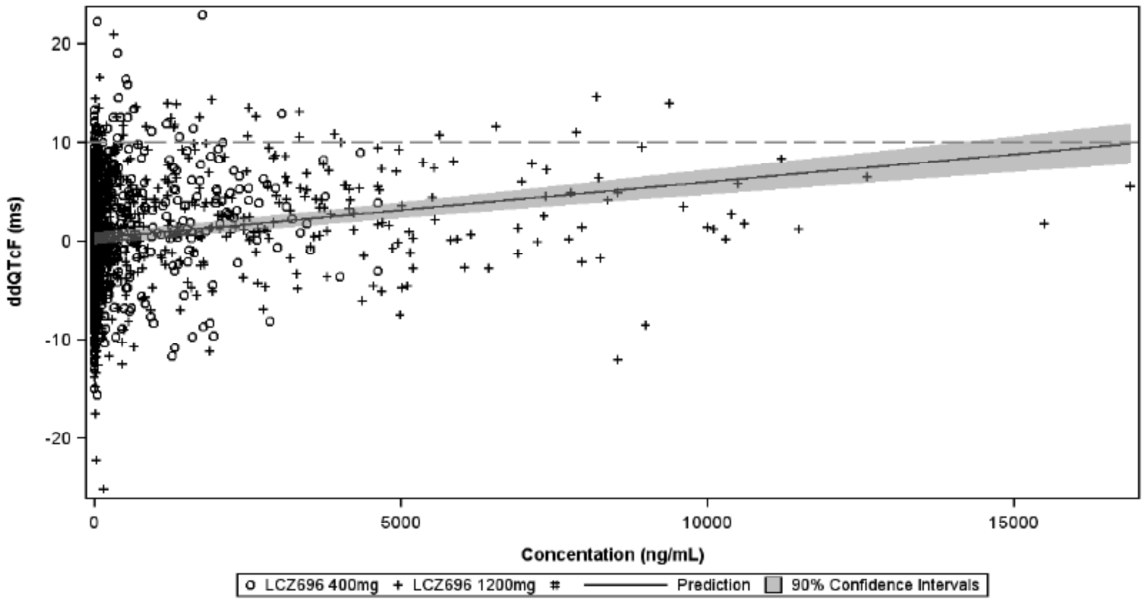


Figure 5. Concentration response relationship for the placebo-corrected change from mean baseline in QTcF (ΔΔQTcF) and LBQ657

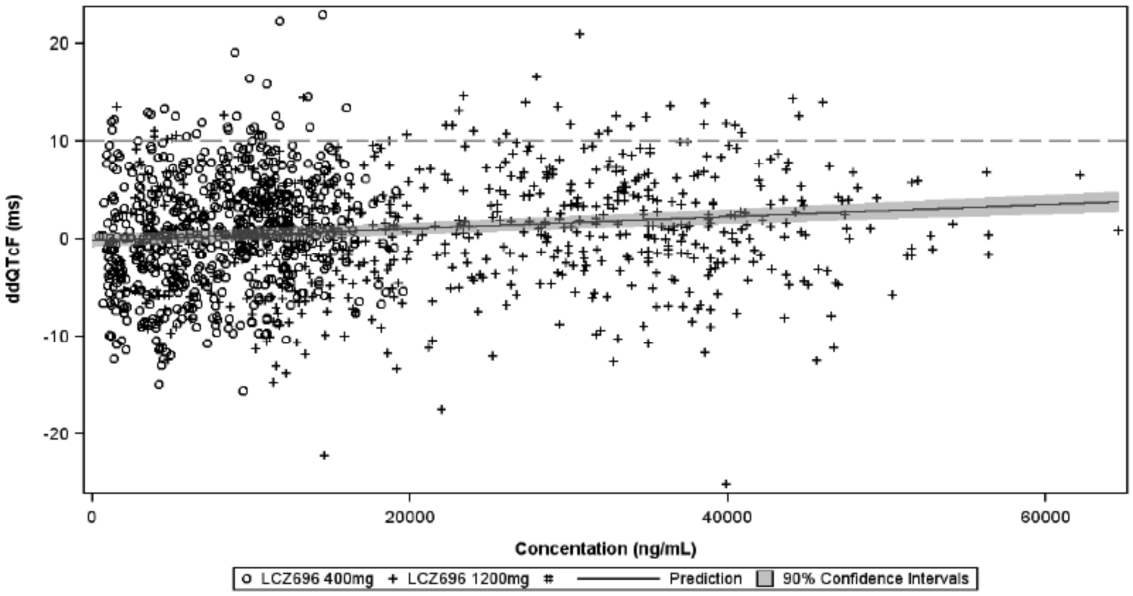
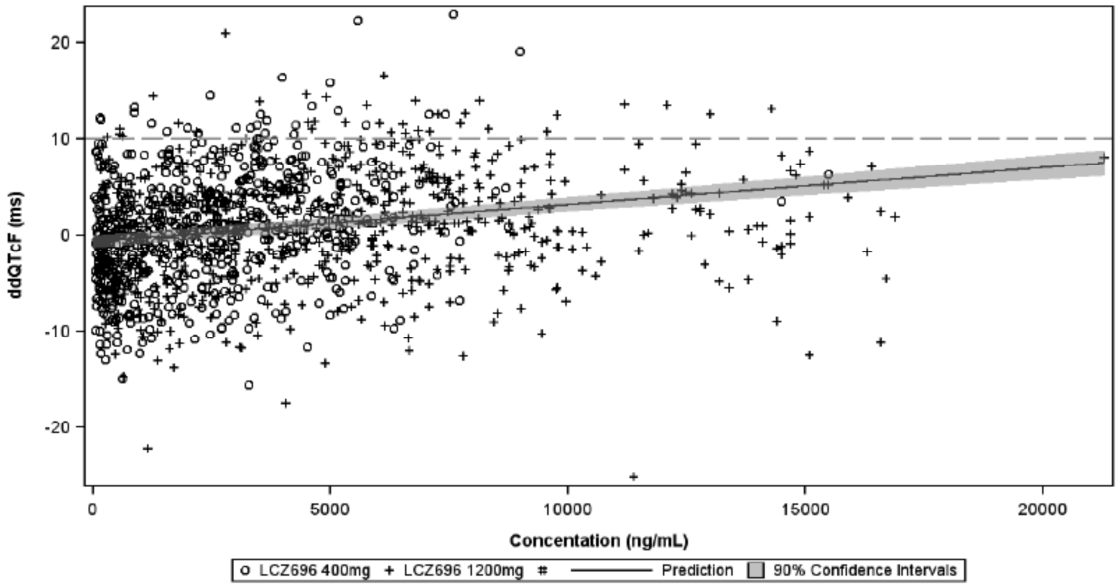


Figure 6. Concentration response relationship for the placebo-corrected change from mean baseline in QTcF (ΔΔQTcF) and Valsartan



(Source: Sponsor's study report, page 75)

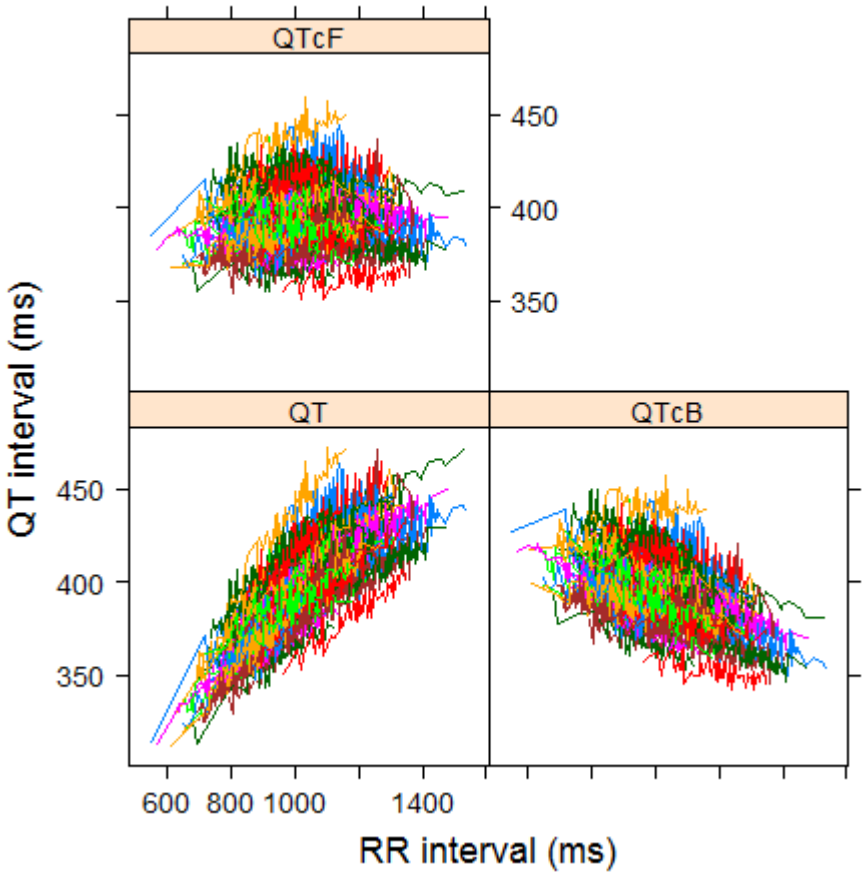
Reviewer's Comments: The reviewer's independent analysis is is presented in Figure 9.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The relationship between different correction methods and RR is presented in Figure 7. This statistical reviewer used QTcF for the primary statistical analysis.

Figure 7: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for LCZ696

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes treatment, sequence, period, time point, and treatment by time point as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

Table 7: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group = A: LCZ696 400 mg

	ΔQTcF (ms) LCZ696 400 mg	ΔQTcF (ms) Placebo	ΔΔQTcF (ms) LCZ696 400 mg	
Time (hour)	**LSmean**	**LSmean**	**LSmean**	**90% CI**
0.5	-2.3	-3.2	1.1	(-0.0, 2.2)
1	-0.0	-2.9	3.1	(2.0, 4.2)
2	-0.3	-3.2	3.0	(1.9, 4.1)
3	-1.7	-2.9	1.4	(0.3, 2.5)
4	-1.6	-2.8	1.4	(0.3, 2.5)
5	-1.6	-2.6	1.2	(0.1, 2.3)
8	-10.9	-9.6	-1.1	(-2.2, 0.0)
12	-7.0	-4.3	-2.7	(-3.8, -1.5)
24	-2.5	-1.1	-1.3	(-2.4, -0.2)

Table 8: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group = B: LCZ696 1200 mg

	ΔQTcF (ms) LCZ696 1200 mg	ΔQTcF (ms) Placebo	ΔΔQTcF (ms) LCZ696 1200 mg	
Time (hour)	**LSmean**	**LSmean**	**LSmean**	**90% CI**
0.5	-1.8	-3.2	1.5	(0.4, 2.6)
1	0.7	-2.9	3.7	(2.6, 4.8)
2	-0.6	-3.2	2.7	(1.6, 3.8)
3	-1.2	-2.9	1.9	(0.8, 3.0)
4	-1.6	-2.8	1.4	(0.2, 2.5)
5	-1.1	-2.6	1.7	(0.5, 2.8)
8	-11.0	-9.6	-1.2	(-2.3, -0.1)
12	-5.9	-4.3	-1.5	(-2.6, -0.4)
24	-1.5	-1.1	-0.3	(-1.4, 0.9)

The largest upper bounds of the 2-sided 90% CI for the mean differences between LCZ696 400 mg and placebo, and between LCZ696 1200 mg and placebo were 4.2 ms and 4.8 ms, respectively.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 9. The largest unadjusted 90% lower confidence interval was 10.9 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval was 10.6 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

Table 9: Analysis Results of ΔQTcF and ΔΔQTcF for Moxifloxacin

	ΔQTcF (ms) Moxifloxacin 400 mg	ΔQTcF (ms) Placebo	ΔΔQTcF (ms) Moxifloxacin 400 mg		
Time (hour)	**LSmean**	**LSmean**	**LSmean**	**90% CI**	**Adjust 90% CI***
0.5	5.1	-3.2	8.5	(7.4, 9.6)	(7.0, 9.9)
1	9.0	-2.9	12.0	(10.9, 13.1)	(10.6, 13.5)
2	7.4	-3.2	10.7	(9.6, 11.8)	(9.2, 12.1)
3	7.4	-2.9	10.4	(9.3, 11.5)	(9.0, 11.9)
4	6.9	-2.8	9.8	(8.7, 10.9)	(8.4, 11.3)
5	7.3	-2.6	10.1	(9.0, 11.2)	(8.6, 11.5)
8	-1.3	-9.6	8.5	(7.4, 9.6)	(7.1, 10.0)
12	2.4	-4.3	6.8	(5.7, 7.9)	(5.4, 8.3)
24	4.2	-1.1	5.4	(4.3, 6.5)	(3.9, 6.8)

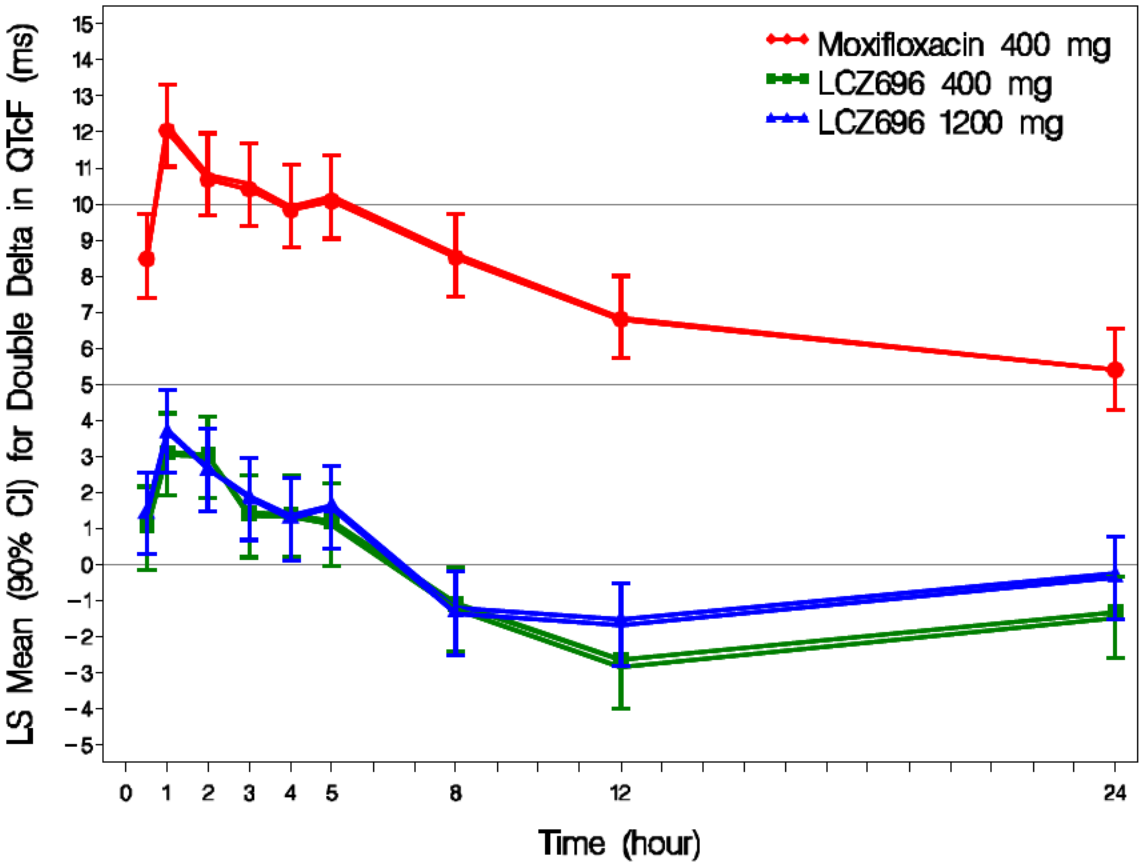
* Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

5.2.1.3 Graph of ΔΔQTcF Over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups.

(Note: CIs are all unadjusted including moxifloxacin)

Figure 8: Mean and 90% CI ΔΔQTcF Timecourse



5.2.1.4 Categorical Analysis

Table 10 lists the number of subjects as well as the number of observations whose QTcF values were ≤ 450 ms and between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 10: Categorical Analysis for QTcF

	Total N		QTcF<=450 ms		450<QTcF<=480 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Day 1 & Day 2 Predose	84	4564	83 (98.8%)	4563 (100%)	1 (1.2%)	1 (0.0%)
Placebo	82	735	82 (100%)	735 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	81	729	80 (98.8%)	724 (99.3%)	1 (1.2%)	5 (0.7%)
LCZ696 400 mg	81	723	81 (100%)	723 (100%)	0 (0.0%)	0 (0.0%)
LCZ696 1200 mg	82	732	82 (100%)	732 (100%)	0 (0.0%)	0 (0.0%)

Table 11 lists the categorical analysis results for ΔQTcF. No subject's change from baseline in QTcF was above 30 ms.

Table 11: Categorical Analysis of ΔQTcF

	Total N		ΔQTcF<=30 ms		30<ΔQTcF<=60 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Placebo	82	735	82 (100%)	735 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	81	729	81 (100%)	729 (100%)	0 (0.0%)	0 (0.0%)
LCZ696 400 mg	81	723	81 (100%)	723 (100%)	0 (0.0%)	0 (0.0%)
LCZ696 1200 mg	82	732	82 (100%)	732 (100%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

Similar statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper limits of 90% CI for the HR mean differences between LCZ696 400 mg and placebo, and between LCZ696 1200 mg and placebo were 6.2 bpm and 6.9 bpm, respectively.

The outlier analysis results for HR are presented in Table 13.

Table 12: Analysis Results of ΔHR and ΔΔHR

	LCZ696 400 mg			LCZ696 1200 mg		
	ΔHR (bpm)		**ΔΔHR (bpm)**	**ΔHR (bpm)**		**ΔΔHR (bpm)**
Time (hour)	**LSmean**	**LSmean Placebo**	**LSmean (90% CI)**	**LSmean**	**LSmean Placebo**	**LSmean (90% CI)**
0.5	0.4	-0.2	0.5 (-0.5, 1.6)	1.6	-0.2	1.6 (0.5, 2.6)
1	0.8	-0.6	1.4 (0.3, 2.4)	1.8	-0.6	2.2 (1.1, 3.3)
2	2.6	-0.1	2.7 (1.6, 3.7)	3.8	-0.1	3.6 (2.6, 4.7)
3	4.1	1.1	2.9 (1.9, 4.0)	5.4	1.1	4.0 (3.0, 5.1)
4	4.5	1.7	2.7 (1.7, 3.8)	6.4	1.7	4.5 (3.4, 5.5)
5	5.8	2.7	3.1 (2.0, 4.2)	6.5	2.7	3.6 (2.6, 4.7)
8	10.5	5.2	5.1 (4.0, 6.2)	11.4	5.2	5.9 (4.8, 6.9)
12	9.8	6.3	3.4 (2.3, 4.5)	9.8	6.3	3.2 (2.1, 4.2)
24	4.8	3.6	1.1 (0.1, 2.2)	5.3	3.6	1.5 (0.4, 2.5)

Table 13: Categorical Analysis for HR

	Total N	HR<=100 bpm	HR>100 bpm	HR>45 bpm	HR<=45 bpm
Treatment Group	**Subj. #**	**Subj. #**	**Subj. #**	**Subj. #**	**Subj. #**
Day 1 & Day 2 Predose	84	84 (100%)	0 (0.0%)	73 (86.9%)	11 (13.1%)
Placebo	82	81 (98.8%)	1 (1.2%)	78 (95.1%)	4 (4.9%)
Moxifloxacin 400 mg	81	80 (98.8%)	1 (1.2%)	75 (92.6%)	6 (7.4%)
LCZ696 400 mg	81	81 (100%)	0 (0.0%)	79 (97.5%)	2 (2.5%)
LCZ696 1200 mg	82	82 (100%)	0 (0.0%)	80 (97.6%)	2 (2.4%)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 14. The largest upper limits of 90% CI for the PR mean differences between LCZ696 400 mg and placebo, and between LCZ696 1200 mg and placebo were -3.9 ms with a 90% CI of -5.4 to -2.4 ms and -5.5 ms with a 90% CI of -6.9 to -4.0 ms, respectively.

The outlier analysis results for PR are presented in Table 15.

Table 14: Analysis Results of ΔPR and ΔΔPR

	LCZ696 400 mg			LCZ696 1200 mg		
	ΔPR (ms)		ΔΔPR (ms)	ΔPR (ms)		ΔΔPR (ms)
Time (hour)	**LSmean**	**LSmean Placebo**	**LSmean (90% CI)**	**LSmean**	**LSmean Placebo**	**LSmean (90% CI)**
0.5	-1.6	-0.6	-1.0 (-2.5, 0.4)	-2.5	-0.6	-1.8 (-3.2, -0.3)
1	-2.1	-0.2	-2.0 (-3.4, -0.5)	-3.3	-0.2	-2.9 (-4.4, -1.5)
2	-3.3	-2.0	-1.3 (-2.8, 0.2)	-5.2	-2.0	-3.0 (-4.4, -1.5)
3	-4.4	-2.4	-2.0 (-3.4, -0.5)	-5.9	-2.4	-3.3 (-4.7, -1.8)
4	-5.5	-3.0	-2.6 (-4.0, -1.1)	-7.0	-3.0	-3.8 (-5.3, -2.4)
5	-7.2	-3.4	-3.8 (-5.3, -2.3)	-7.5	-3.4	-3.9 (-5.3, -2.4)
8	-10.2	-7.1	-3.1 (-4.6, -1.6)	-11.4	-7.1	-4.2 (-5.6, -2.7)
12	-8.9	-8.8	-0.2 (-1.6, 1.3)	-11.0	-8.8	-2.1 (-3.6, -0.6)
24	-5.0	-1.1	-3.9 (-5.4, -2.4)	-6.8	-1.1	-5.5 (-6.9, -4.0)

Table 15: Categorical Analysis for PR

	Total N		PR<=200 ms		PR>200 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Day 1 & Day 2 Predose	84	4563	83 (98.8%)	4562 (100%)	1 (1.2%)	1 (0.0%)
Placebo	82	735	82 (100%)	735 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	81	729	81 (100%)	729 (100%)	0 (0.0%)	0 (0.0%)
LCZ696 400 mg	81	723	81 (100%)	723 (100%)	0 (0.0%)	0 (0.0%)
LCZ696 1200 mg	82	732	82 (100%)	732 (100%)	0 (0.0%)	0 (0.0%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 16. The largest upper limits of 90% CI for the QRS mean differences between LCZ696 400 mg and placebo, and between LCZ696 1200 mg and placebo were 0.6 ms and 0.8 ms, respectively.

There were 32 (39.5%) and 36 (43.9%) subjects who experienced QRS interval greater than 110 ms in LCZ696 400 mg group and LCZ696 1200 mg group, respectively. 39 (46.4%) subjects experienced QRS greater than 110 ms prior to dose administration (profiling day 1 and day 2 predose).

The outlier analysis results for QRS are presented in Table 17.

Table 16: Analysis Results of ΔQRS and ΔΔQRS

	LCZ696 400 mg			LCZ696 1200 mg		
	ΔQRS (ms)		ΔΔQRS (ms)	ΔQRS (ms)		ΔΔQRS (ms)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
0.5	0.2	-0.0	0.2 (-0.0, 0.5)	0.3	-0.0	0.3 (0.1, 0.6)
1	0.3	-0.0	0.4 (0.1, 0.6)	0.5	-0.0	0.5 (0.3, 0.8)
2	0.1	0.1	0.1 (-0.2, 0.4)	0.2	0.1	0.1 (-0.1, 0.4)
3	0.2	0.1	0.1 (-0.2, 0.4)	0.3	0.1	0.2 (-0.1, 0.5)
4	0.3	0.1	0.1 (-0.1, 0.4)	0.3	0.1	0.2 (-0.1, 0.4)
5	0.4	0.4	0.1 (-0.2, 0.3)	0.4	0.4	0.0 (-0.2, 0.3)
8	-0.6	-0.3	-0.3 (-0.5, 0.0)	-0.4	-0.3	-0.1 (-0.3, 0.2)
12	-0.6	-0.1	-0.5 (-0.7, -0.2)	-0.1	-0.1	0.0 (-0.2, 0.3)
24	-0.1	0.0	-0.0 (-0.3, 0.2)	0.0	0.0	0.0 (-0.2, 0.3)

Table 17: Categorical Analysis for QRS

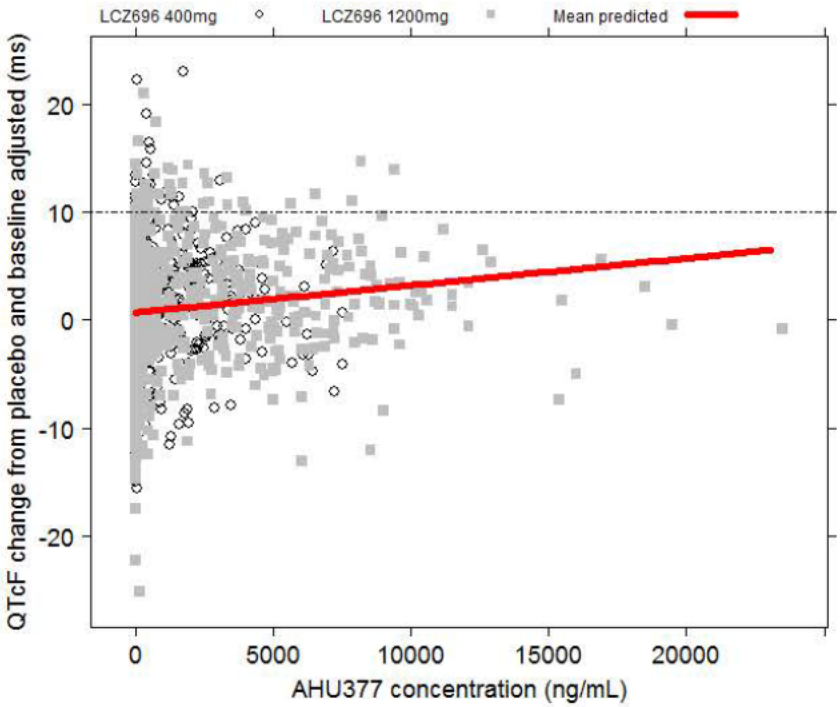
	Total N		QRS<=110 ms		QRS>110 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Day 1 & Day 2 Predose	84	4563	45 (53.6%)	3067 (67.2%)	39 (46.4%)	1496 (32.8%)
Placebo	82	735	50 (61.0%)	503 (68.4%)	32 (39.0%)	232 (31.6%)
Moxifloxacin 400 mg	81	729	51 (63.0%)	481 (66.0%)	30 (37.0%)	248 (34.0%)
LCZ696 400 mg	81	723	49 (60.5%)	461 (63.8%)	32 (39.5%)	262 (36.2%)
LCZ696 1200 mg	82	732	46 (56.1%)	460 (62.8%)	36 (43.9%)	272 (37.2%)

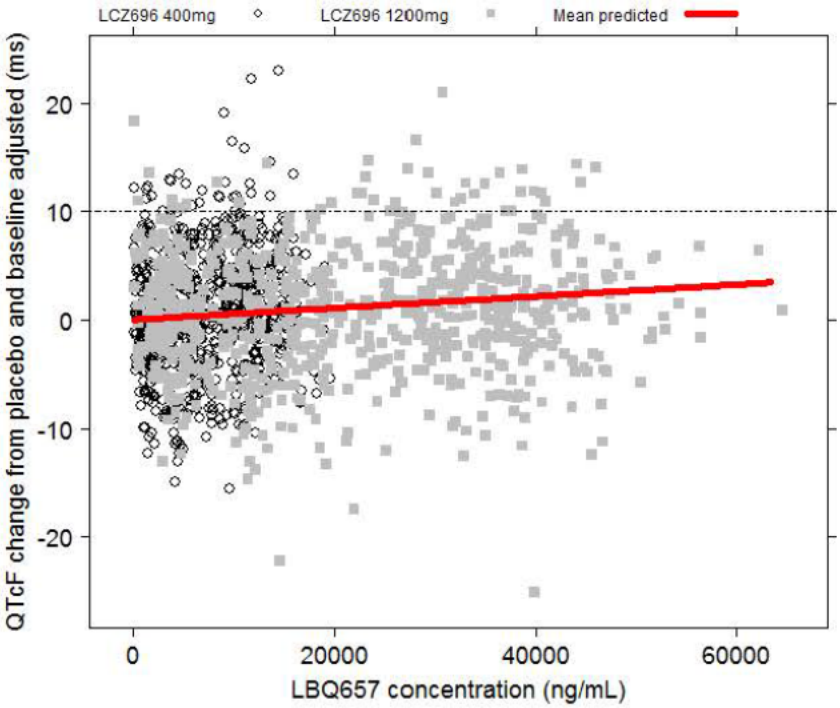
5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

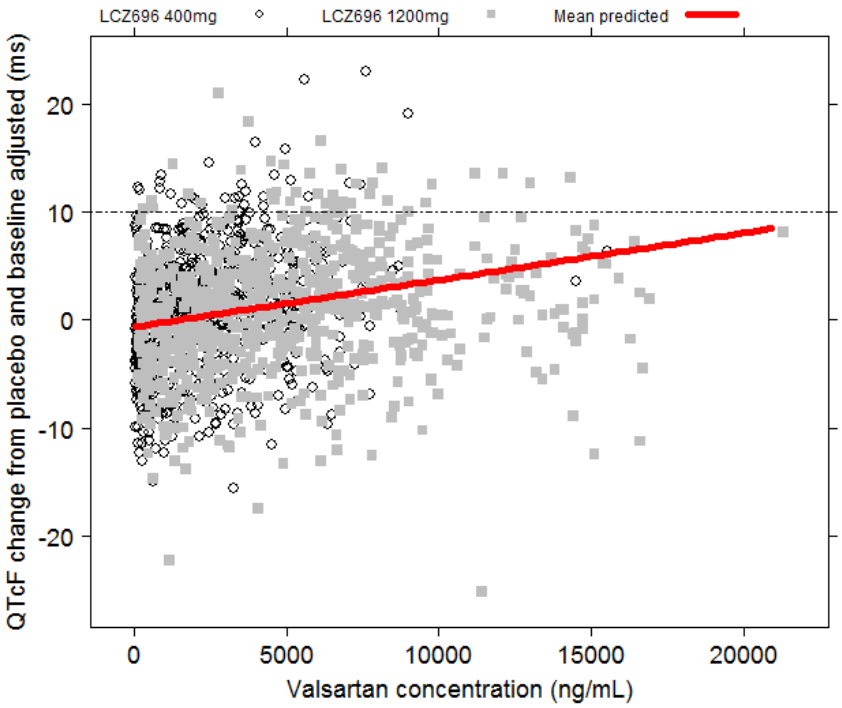
The relationships between ΔΔQTcF and concentrations of all analytes are visualized in Figure 9. Statistically significant but relatively flat slopes were observed for all LCZ696

analytes. Clinically relevant QTc prolongation (10 ms) is not expected within the studied concentration ragnes of all analytes.

Figure 9: ΔΔ QTcF vs. Concentrations of Analytes of LCZ696







5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

No clinically relevant effect on PR or QRS was seen.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	Include maximum proposed clinical dosing regimen LCZ696 200mg BID
Maximum tolerated dose	Include if studied or NOAEL dose The maximum tolerated dose was not established. A maximum single dose of LCZ696 1200 mg was tested in healthy subjects; maximum multiple doses of LCZ696 900 mg administered once daily for 14 days were tested in healthy subjects. There were no dose-limiting adverse events (AEs) identified at these doses. (Study LCZ696A2102) Please refer to the preclinical safety section below for NOEL doses.
Principal adverse events	Include most common adverse events; dose limiting adverse events Most common adverse events (>10%) are derived from the LCZ696 phase 3 study in patient with HF (CLCZ696B2314; PARADIGM-HF) because this study represents the majority of HF patients enrolled in the LCZ696 clinical development program (N=8842). Most common adverse events (AEs) in study CLCZ696B2314 were hypotension (17.6%), hyperkalemia (11.6%), and renal impairment (10.1%). These AEs are also the ones that most commonly led to drug discontinuation. In addition, cardiac failure was seen in 17.4% of patients, but this AE is reflective of the disease state of HF and the population studied. (Source: Summary of Clinical Safety section 2.1.1.1.2, Table 2-3) As described in the previous row, the highest doses studied were LCZ696 1200 mg single dose and LCZ696 900 mg once daily administered for 14 days in healthy subjects. No AEs occurred after administration of a single dose of 1200 mg LCZ696 in the single ascending dose study (CLCZ696A2102). In the TQT study (CLCZ696B2123), healthy subjects received single doses of LCZ696 400 mg and 1200 mg. The overall incidence of AEs was comparable in the LCZ696 400 mg, LCZ696 1200 mg, moxifloxacin 400 mg and placebo groups. In the LCZ696 1200 mg group, headache, nausea and pruritus (2 of 82 subjects each) were the most common AEs. After administration of LCZ696 900 mg once daily for 14 days in the multiple ascending dose study (CLCZ696A2102), 6 out of 8 subjects enrolled in this cohort reported mild AEs of orthostatic hypotension and postural orthostatic tachycardia syndrome that were considered to be related to study drug by the investigator. Of these, 5 subjects received LCZ696 900 mg qd and 1 subject

<table>
<tr><td></td><td colspan="2">received placebo. None of the reported AEs were considered dose-limiting. It is therefore concluded that LCZ696 was safe and well tolerated in healthy subjects at single doses up to 1200 mg and multiple doses up to 900 mg once daily for 14 days in healthy subjects.</td></tr>
<tr><td rowspan="2">Maximum dose tested</td><td>Single Dose</td><td>Specify dose

1200 mg LCZ696</td></tr>
<tr><td>Multiple Dose</td><td>Specify dosing interval and duration

900 mg once daily for 14 days</td></tr>
<tr><td rowspan="2">Exposures Achieved at Maximum Tested Dose</td><td>Single Dose</td><td>Mean (%CV) Cmax and AUC

The pharmacokinetic parameters of LCZ696 analytes following single dose administration of LCZ696 1200 mg in healthy subjects are as follows (Study A2102):

<table>
<tr><th>LCZ696 analytes</th><th>Cmax (ng/mL)</th><th>AUC0-24 (ng*h/mL)</th></tr>
<tr><td>sacubitril</td><td>4475 (41.7%)</td><td>10410.4 (42.2%)</td></tr>
<tr><td>LBQ657</td><td>30050 (18.3%)</td><td>290920.3 (19.9%)</td></tr>
<tr><td>valsartan</td><td>7447.5 (37.6%)</td><td>60118.4 (49.1%)</td></tr>
</table></td></tr>
<tr><td>Multiple Dose</td><td>Mean (%CV) Cmax and AUC

The pharmacokinetic parameters of LCZ696 following once daily administration of LCZ696 900 mg for 14 days in healthy subjects are as follows (A2102):

<table>
<tr><th>sacubitril</th><th>Day 1</th><th>Day 14</th></tr>
<tr><td>Cmax (ng/mL)</td><td>5350 (33.3%)</td><td>6524.3 (31.5%)</td></tr>
<tr><td>AUC (0-24) (ng*h/mL)</td><td>8996.7 (21.7%)</td><td>9999 (22.1%)</td></tr>
</table>
<table>
<tr><th>LBQ657</th><th>Day 1</th><th>Day 14</th></tr>
<tr><td>Cmax (ng/mL)</td><td>31050 (13.7%)</td><td>38257.1 (25.1%)</td></tr>
<tr><td>AUC (0-24) (ng*h/mL)</td><td>263526.7 (18.3%)</td><td>326627.6 (21.7%</td></tr>
</table>
<table>
<tr><th>valsartan</th><th>Day 1</th><th>Day 14</th></tr>
<tr><td>Cmax (ng/mL)</td><td>8722.5 (29%)</td><td>8960 (33.6%)</td></tr>
<tr><td>AUC (0-24)</td><td>45281.8</td><td>54920.1</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td></td><td>(ng*h/mL) | (24.6%) | (29%)</td></tr>
<tr><td>Range of linear PK</td><td colspan="2">Specify dosing regimen

Dose proportionality was assessed using power model, Y = α * Doseβ, where Y, α, and β correspond to the PK parameter, proportionality constant, and exponent, respectively. Over a dose range of 50 – 400 mg LCZ696, with 2-fold increase in dose, the exposure of sacubitril increased proportionally, and LBQ657 and valsartan exposures increased by 1.87-fold and 1.69-fold, respectively. The slope (95% CI) for exposure of LCZ696 analytes vs. dose over a dose range of 50 mg to 400 mg is given below.

<table>
<tr><th>PK parameter</th><th>sacubitril</th><th>LBQ657</th><th>valsartan</th></tr>
<tr><td>AUCinf</td><td>1.00 (0.97 –1.02)</td><td>0.90 (0.88 – 0.92)</td><td>0.76 (0.72 – 0.79)</td></tr>
<tr><td>AUClast</td><td>1.00 (0.97 - 1.02)</td><td>0.89 (0.87 – 0.91)</td><td>0.76 (0.72 – 0.79)</td></tr>
<tr><td>Cmax</td><td>0.85 (0.80 –0.89)</td><td>0.91 (0.89 – 0.93)</td><td>0.72 (0.69 – 0.76)</td></tr>
</table></td></tr>
<tr><td>Accumulation at steady state</td><td colspan="2">Mean (%CV); specify dosing regimen

No significant accumulation of LCZ696 analytes was observed with once daily administration of 400mg LCZ696.
At the proposed dosing regimen of 200 mg BID LCZ696, sacubitril, LBQ657, and valsartan are accumulated by 1.04-fold, 1.6-fold, and 1.21-fold, respectively.</td></tr>
<tr><td>Metabolites</td><td colspan="2">Include listing of all metabolites and activity
Sacubitril is an inactive prodrug. LBQ657 is the primary metabolite of sacubitril formed by ester hydrolysis. LBQ657 is responsible for NEP inhibition activity of sacubitril. LBQ657 accounts for ~86% of the total administered sacubitril dose excreted via urine and feces. Several minor metabolites accounting for <1% of total administered dose are also observed.

Valsartan is minimally metabolized by CYP2C9, forming 4-hydroxyvaleryl metabolite (< 10% of total dose). None of the metabolites are active.</td></tr>
<tr><td rowspan="2">Absorption</td><td>Absolute/Relative Bioavailability</td><td>Mean (%CV)

The absolute bioavailability of sacubitril is estimated to be >60.7% (11.4%) following oral administration of LCZ696. The oral absolute bioavailability of valsartan is reported to be 23%.</td></tr>
<tr><td>Tmax</td><td>Median (range) for parent
sacubitril: 0.5 hours (0.3 – 4.0)
valsartan: 2.0 hours (0.7 – 5.1)

Median (range) for metabolites
LBQ657: 2.1 hours (1.0 – 6.0)</td></tr>
<tr><td>Distribution</td><td>Vd/F or Vd</td><td>Mean (%CV)</td></tr>
</table>

<table>
<tr><td></td><td></td><td>sacubitril: 157.4 (56.5%) L
valsartan: 107.8 (66.6%) L
LBQ657: Not reported as it is a metabolite</td></tr>
<tr><td></td><td>% bound</td><td>Mean (%CV)

sacubitril: 96.7% (5 %)
LBQ657: 97% (3 %)
valsartan: 94.1% (1.6 %)</td></tr>
<tr><td>Elimination</td><td>Route</td><td>Primary route; percent dose eliminated

sacubitril/LBQ657: 60.7% via urinary excretion following oral administration

valsartan: biliary pathway accounts for 86% of excretion of valsartan following intravenous administration</td></tr>
<tr><td></td><td>Terminal t½</td><td>Mean (%CV) for parent

sacubitril: 1.4 hours (44.8%)
valsartan: 9.9 hours (51.9%)

Mean (%CV) for metabolites
LBQ657: 11.5 hours (22.2%)</td></tr>
<tr><td></td><td>CL/F or CL</td><td>Mean (%CV)

sacubitril: 76.8 L/h (42.8%)
valsartan: 8.2 L/h (71.1%)</td></tr>
<tr><td>Intrinsic Factors</td><td>Age</td><td>Specify mean changes in Cmax and AUC

Geometric mean ratio (elderly (>65 yrs) vs. young (18 – 45 yrs) and corresponding 90% CI (Study A2109)

<table><tr><th>PK parameter</th><th>LBQ657</th><th>valsartan</th></tr><tr><td>AUCinf</td><td>1.42 (1.24 – 1.61)</td><td>1.30 (1.08 – 1.55)</td></tr><tr><td>AUClast</td><td>1.41 (1.24 – 1.61)</td><td>1.31 (1.10 – 1.56)</td></tr><tr><td>Cmax</td><td>1.04 (0.92 – 1.18)</td><td>1.24 (1.01 – 1.51)</td></tr></table></td></tr>
<tr><td></td><td>Sex</td><td>No effect of gender on the pharmacokinetics of LCZ696 analytes was observed.
Geometric mean ratio (male vs. female) and corresponding 90% CI (Study B2109)

<table><tr><th>PK parameter</th><th>LBQ657</th><th>valsartan</th></tr><tr><td>AUCinf</td><td>0.99 (0.87 – 1.13)</td><td>1.02 (0.85 – 1.22)</td></tr><tr><td>AUClast</td><td>0.99 (0.87 – 1.12)</td><td>1.02 (0.86 – 1.22)</td></tr><tr><td>Cmax</td><td>0.90 (0.80 – 1.02)</td><td>0.99 (0.81 – 1.22)</td></tr></table></td></tr>
</table>

	Race	Specify mean changes in Cmax and AUC No significant impact of race was observed on pharmacokinetics of LCZ696 analytes following single dose administration of LCZ696 200 mg. Summary of sacubitril PK parameters by race following single dose administration of 200 mg LCZ696

Parameter	Asian (N=18)	Black (N=11)	Caucasian (N=51)	Pacific Islander (N=1)	Other (N=1)
AUCinf (h*ng/mL)	2559.47 ± 498.851 (19.5%)	1937.75 ± 524.773 (27.1%)	1904.12 ± 493.012 (25.9%)	1303.61	2645.82
AUClast (h*ng/mL)	2555.77 ± 499.204 (19.5%)	1933.43 ± 525.256 (27.2%)	1899.98 ± 492.663 (25.9%)	1301.65	2643.36
Cmax (ng/mL)	2129.98 ± 1176.640 (55.2%)	1776.36 ± 965.930 (54.4%)	1775.33 ± 731.433 (41.2%)	1300.00	1810.00
t1/2 (h)	1.43 ± 0.822 (57.6%)	1.50 ± 0.486 (32.4%)	1.44 ± 0.619 (43.0%)	0.83	1.35
Tmax (h)	0.50 (0.5-1.5)	0.50 (0.5-1.0)	0.50 (0.5-4.0)	0.48 (0.5-0.5)	0.50 (0.5-0.5)

Data is presented as mean ± standard deviation (CV%)

Summary of LBQ657 PK parameters by race following single dose administration of 200 mg LCZ696

Parameter	Asian (N=18)	Black (N=11)	Caucasian (N=51)	Pacific Islander (N=1)	Other (N=1)
AUCinf (h*ng/mL)	80314.01 ± 14075.850 (17.5%)	73288.66 ± 13612.558 (18.6%)	82762.31 ± 18364.874 (22.2%)	88802.86	84601.54

		AUClast (h*ng/mL)	79881.74 ± 13960.480 (17.5%)	72734.82 ± 13424.013 (18.5%)	82070.55 ± 18352.996 (22.4%)	87727.15	84119.60
		Cmax (ng/mL)	8740.00 ± 1495.134 (17.1%)	7005.45 ± 1656.553 (23.6%)	7733.53 ± 1538.860 (19.9%)	7890.00	8080.00
		t1/2 (h)	11.00 ± 2.396 (21.8%)	10.78 ± 1.751 (16.2%)	11.79 ± 2.767 (23.5%)	12.66	10.67
		Tmax (h)	2.00 (1.5-4.0)	2.07 (1.0-6.0)	2.00 (1.0-4.0)	2.10 (2.1-2.1)	3.00 (3.0-3.0)
		Vz/F (L)	25.05 ± 4.766 (19.0%)	39.00 ± 6.206 (15.9%)	39.20 ± 7.585 (19.4%)		36.40
		Data is presented as mean ± standard deviation (CV%)					
		Summary of valsartan PK parameters by race following single dose administration of 200 mg LCZ696					
		Parameter	Asian (N=18)	Black (N=11)	Caucasian (N=51)	Pacific Islander (N=1)	Other (N=1)
		AUCinf (h*ng/mL)	25355.76 ± 7505.116 (29.6%)	16369.24 ± 2685.440 (16.4%)	22160.31 ± 8977.822 (40.5%)	18362.14	42524.82
		AUClast (h*ng/mL)	25169.18 ± 7454.814 (29.6%)	16045.48 ± 2813.385 (17.5%)	21763.29 ± 8695.828 (40.0%)	18311.35	42315.40
		Cmax (ng/mL)	4255.00 ± 1127.453 (26.5%)	2888.18 ± 634.899 (22.0%)	3880.18 ± 1583.964 (40.8%)	3110.00	8180.00
		t1/2 (h)	12.05 ± 7.866 (65.3%)	11.23 ± 6.253 (55.7%)	8.81 ± 3.060 (34.7%)	6.68	12.20
		Tmax (h)	1.73 (1.0-3.0)	1.50 (1.0-3.0)	1.50 (1.0-4.0)	2.10 (2.1-2.1)	2.00 (2.0-2.0)
		Vz/F (L)	83.43 ± 75.143 (90.1%)	149.33 ± 81.037 (54.3%)	109.06 ± 66.400 (60.9%)	54.06	82.77
		Data is presented as mean ± standard deviation (CV%)					
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC The effect of hepatic impairment on Cmax and AUC of LCZ696 analytes following single dose administration of LCZ696 200 mg (study LCZ696B2203) is presented below:					
				sacubitril	LBQ657	valsartan	
		Parameter	Hepatic impairment group*	GMR (90% CI)	GMR (90% CI)	GMR (90% CI)	

AUCinf	Mild	1.53 [1.13, 2.07]	1.48 [1.16, 1.89]	1.19 [0.80, 1.78]
	Moderate	3.44 [2.53, 4.69]	1.90 [1.27, 2.85]	2.09 [1.23, 3.54]
Cmax	Mild	1.57 [1.09, 2.28]	1.03 [0.94, 1.14]	0.96 [0.61, 1.50]
	Moderate	3.10 [2.33, 4.13]	1.01 [0.84, 1.21]	1.05 [0.65, 1.69]

* No study has been conducted to evaluate the impact of severe hepatic impairment on pharmacokinetics of LCZ696.

The effect of renal impairment on steady-state Cmax and AUC of LCZ696 analytes following multiple dose administration of LCZ696 400 mg once daily for 5 days (study LCZ696A2204 and LCZ696A2205) is presented below:

By CrCL classification (calculated by Cockgroft Gault formula)

		sacubitril	LBQ657	valsartan
Parameter	Renal impairment group	GMR (90% CI)	GMR (90% CI)	GMR (90% CI)
AUCinf	Mild (n=8)	1.05 [0.77,1.43]	2.10 [1.67, 2.65]	1.37 [0.82, 2.30]
	Moderate (n=8)	0.90 [0.66,1.23]	2.24 [1.78, 2.82]	1.01 [0.61, 1.69]
	Severe (n=6)	1.14 [0.72,1.79]	2.7 [2.04, 3.57]	1.27 [0.60, 2.68]
Cmax	Mild (n=8)	1.27 [0.88 ,1.83]	1.60 [1.33,1.92]	1.03 [0.68,1.56]
	Moderate (n=8)	1.10 [0.76,1.60]	1.54 [1.29,1.85]	1.01 [0.67,1.54]
	Severe (n=6)	1.36 [0.65,2.86]	1.61 [1.28,2.04]	0.88 [0.46,1.67]

By eGFR classification

			sacubitril	LBQ 657	valsartan
Parameter	Renal impairm	eGFR mL/min/1.73m	GMR (90% CI)	GMR (90%	GMR (90% CI)

			ent group	2		CI)
		AUCinf	Mild (n=19)	60 - 89	1.20 [0.91 - 1.60]	1.27 [1.01 - 1.59] 1.35 [0.85 - 2.14]
			Moderate (n=7)	30 - 59	1.04 [0.74 - 1.45]	2.29 [1.75 - 3.0] 1.33 [0.77 - 2.29]
			Severe (n=9)	15 - 29	1.12 [0.82 - 1.54]	2.90 [2.24 - 3.75] 1.58 [0.94 - 2.65]
			ESRD (n=3 no dialysis)	<15 no dialysis / Require dialysis	0.91 [0.59 - 1.39]	3.27 [2.32 - 4.61] 0.77 [0.38 - 1.54]
		Cmax	Mild (n=19)	60 - 89	1.03 [0.68 - 1.55]	1.22 [1.03 - 1.45] 1.33 [0.92 - 1.92]
			Moderate (n=7)	30 - 59	0.97 [0.60 - 1.58]	1.76 [1.43 - 2.16] 1.07 [0.7 - 1.66]
			Severe (n=9)	15 - 29	1.25 [0.79 - 1.99]	1.83 [1.50 - 2.22] 1.31 [0.87 - 1.99]
			ESRD (n=3 no dialysis)	<15 no dialysis / Require dialysis	1.09 [0.59 - 2.02]	2.05 [1.58 - 2.67] 0.62 [0.35 - 1.07]
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC Effect of LCZ696 200 mg BID on pharmacokinetics of co-administered medicines:				
		Study no.	**Co-med**	**Dosing regimen of Comed**	**AUC**	**Cmax**
		B2111	digoxin	digoxin 0.25 mg for 14 days (with LCZ 200mg from day 11 to 14)	0.92 (0.88 - 0.96)	0.96 (0.89 - 1.03)

B2112	R-warfarin	LCZ696 200 mg + warfarin 25 mg (on day 5) / Placebo + warfarin 25 mg (on day 5)	0.98 (0.96 - 1.00)	0.96 (0.91 - 1.03)
	S-warfarin		0.97 (0.95 - 1.00)	0.95 (0.88 - 1.03)
B2115	atorvastatin	atorvastatin 80 mg for 4 days	1.34 (1.23 - 1.45)	1.74 (1.49 - 2.02)
	o-hydroxy-atorvastatin		1.22 (1.12 - 1.32)	1.68 (1.49 - 1.91)
	p-hydroxy-atorvastatin		1.26 (1.15 - 1.39)	2.08 (1.75 - 2.49)
B2116	furosemide	furosemide 40 mg for 1 day	0.72 (0.67 - 0.77)	0.50 (0.45 - 0.56)

Data is presented as geometric mean ratio (test/reference) and 90% CI

Effect of co-medications on the pharmacokinetics of LCZ696 analytes:

Study no.	Co-med	Dosing regimen of Comed	LCZ696 analyte	AUC	Cmax
B2122	metformin	400 mg QD for 5 Days	sacubitril	1.09 (1.02 - 1.17)	1.03 (0.89 - 1.21)
			LBQ657	1.09 (1.04 - 1.13)	1.08 (1.01 - 1.15)
			valsartan	0.98 (0.82 - 1.17)	0.98 (0.80 - 1.20)
A2120	hydrochloro-thiazide	400 mg QD for 5 Days	sacubitril	1.07 (1.02 - 1.11)	1.05 (0.94 - 1.17)
			LBQ657	1.20 (1.17 - 1.23)	1.19 (1.10 - 1.28)
			valsartan	1.14 (1.00 - 1.29)	1.16 (0.98 - 1.37)
B2225	sildenafil	400 mg QD for 5 Days	sacubitril	1.10 (1.04 - 1.17)	0.90 (0.74 - 1.10)
			LBQ657	1.02 (1.01 - 1.04)	0.94 (0.88 - 0.99)

					valsartan	0.71 (0.62 - 0.80)	0.61 (0.53 - 0.71)
		A2119	amlodipine	400 mg QD for 5 Days	sacubitril	1.00 (0.98 - 1.02)	0.97 (0.93 - 1.02)
					valsartan	1.21 (1.07 - 1.36)	1.17 (1.02 - 1.35)
		B2113	omeprazole	400 mg QD on Day 1	sacubitril	0.93 (0.87 - 0.99)	0.93 (0.77 - 1.13)
					LBQ657	1.02 (0.99 - 1.06)	1.04 (0.98 - 1.11)
					valsartan	0.89 (0.73 - 1.09)	0.87 (0.69 - 1.09)
		A2124	OC (LVG/EES)	400 mg QD for 7 Days	LBQ657	1.03 (1.01 - 1.05)	1.13 (1.07 - 1.20)
					valsartan	0.86 (0.73 - 1.01)	0.84 (0.67 - 1.06)
		B2125	carvedilol	400 mg QD for 5 Days	LBQ657	1.04 (1.02 - 1.06)	0.97 (0.93 - 1.02)
					valsartan	0.91 (0.82 - 1.01)	0.88 (0.78 - 0.98)
		B2111	digoxin	200 mg BID for 3 Days and 200 mg QD on 4th day	sacubitril	0.97 (0.89 - 1.07)	0.98 (0.75 - 1.27)
					LBQ657	1.13 (1.10 - 1.17)	1.14 (1.06 - 1.22)
					valsartan	1.07 (0.93 - 1.24)	1.06 (0.89 - 1.25)
		B2112	warfarin	200 mg BID for 10 Days	sacubitril	1.02 (0.95 - 1.08)	1.18 (0.94 - 1.46)
					LBQ657	1.07 (1.05 - 1.09)	1.07 (1.03 - 1.11)

					valsartan	0.94 (0.83 - 1.07)	0.93 (0.82 - 1.05)
		B2115	atorvastatin	200 mg BID for 4 Days and 200 mg QD on 5th day	LBQ657	1.02 (0.99 - 1.06)	1.08 (1.01 - 1.16)
					valsartan	0.81 (0.71 - 0.92)	0.91 (0.79 - 1.04)
		B2116	furosemide	200 mg BID for 5 Days	sacubitril	1.01 (0.96 - 1.07)	1.04 (0.91 - 1.19)
					LBQ657	1.08 (1.07 - 1.10)	1.08 (1.03 - 1.12)
					valsartan	1.16 (1.02 - 1.31)	1.16 (1.02 - 1.32)
		Data is presented as geometric mean ratio (test/reference) and 90% CI					
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)					

Effect of food on pharmacokinetics of LCZ696 analytes was evaluated following LCZ696 200 mg and 400 mg single dose administration and with CSF, FMI, and (b) (4) formulation (Study B2107, Study A1101, Study B2126).

Effect of food on pharmacokinetics of LBQ657 following single dose administration of LCZ696:

	400 mg LCZ696 formulation		200 mg LCZ696 CSF	200 mg LCZ696 (b) (4)
	Low fat	High fat	Japanese meal	High fat
AUCinf	1.0 (0.97 – 1.02)	1.04 (1.01 – 1.06)	0.92 (0.90 – 0.95)	1.02 (1.00 – 1.04)
AUClast	0.91 (0.8 – 1.03)	1.04 (0.92 – 1.18)	0.92 (0.90 – 0.95)	1.02 (1.00 – 1.04)
Cmax	0.81 (0.7 – 0.92)	0.72 (0.63 – 0.82)	0.73 (0.70 – 0.77)	0.81 (0.77 – 0.85)

Data is presented as geometric mean ratio (90% CI) for test (fed)/reference (fasted)

Effect of food on pharmacokinetics of valsartan following single dose administration of LCZ696:

	400 mg LCZ696 formulation		200 mg LCZ696 CSF	200 mg LCZ696 (b) (4)
PK parameter	Low fat	High fat	Japanese meal	High fat

		AUCinf	0.66 (0.57 – 0.75)	0.91 (0.79 – 1.04)	0.60 (0.45 – 0.81)	0.60 (0.54 – 0.66)
		AUClast	0.67 (0.58 – 0.76)	0.91 (0.79 – 1.04)	0.60 (0.45 – 0.81)	0.59 (0.54 – 0.65)
		Cmax	0.61 (0.51 – 0.71)	0.6 (0.51 – 0.70)	0.49 (0.33 – 0.73)	0.43 (0.38 – 0.48)
		Data is presented as geometric mean ratio (90% CI) for test (fed)/reference (fasted)				

Expected High Clinical Exposure Scenario

Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.

Based on results from clinical pharmacology studies, the largest increases in mean AUC and Cmax for sacubitril and valsartan were observed in patients with moderate hepatic impairment following single dose administration of 200 mg LCZ696 (LCZ696B2203). For LBQ657, the largest increase in mean AUC and Cmax were observed in patients with severe renal impairment following multiple dose administration of 400 mg LCZ696 once daily for 5 days (LCZ696A2205).

Parameter	sacubitril	LBQ657	valsartan
	Moderate hepatic impairment (LCZ696B2203)	Severe renal impairment (LCZ696A2205)	Moderate hepatic impairment (LCZ696B2203)
*AUCinf (ng*h/mL)	6200 (47.9%)	538342 (49.9%)	65600 (76.4%)
Cmax (ng/mL)	4430 (39.7%)	30650 (37.4%)	4180 (56%)
Data is presented as mean (CV%)			
* - Steadystate AUC0-24 was presented for LBQ657			

The observed mean (CV%) of AUC and Cmax for LCZ696 analytes in the TQT study at the supra-therapeutic dose of LCZ696 1200 mg (LCZ696B2123) are summarized in the table below:

Parameter	sacubitril	LBQ657	valsartan
AUC0-24 (ng*h/mL)	13200 (35.3%)	364000 (17.1%)	66000 (38.5%)
Cmax (ng/mL)	7780 (49.2%)	40700 (17.2%)	9360 (40.5%)
Data is presented as mean (CV%)			

It is therefore concluded that maximal increases in Cmax observed in the clinical pharmacology program, which are considered to be most relevant to QT-prolongation, were covered by the TQT study.

Preclinical Cardiac Safety	Summarize *in vitro* and *in vivo* results per S7B guidance. *In vitro* hERG IC50 LCZ696: >3 mM [Study 0670356] NDA Module 4.2.1.3 [1.8 ± 0.6% at 10 µM (n=3), 1.7 ± 0.2% at 100 µM (n=3), 2.9 ± 0.3% at 787 µM (n=3) and by 32.4 ± 0.7% at 3,000 µM (n=4), vs 0.7 ± 0.2% in control (n=4)]. Assuming 3000 µM LCZ696 dissociates into approximately 3,000 µM valsartan and 3,000 µM sacubitril, this concentration is greater than 2700X the clinical exposure to valsartan and sacubitril (unbound Cmax) associated with a 200 mg LCZ696 BID dose. hERG IC50 sacubitril:>1 mM [Study 0359201] NDA Module 4.2.1.3 In this non-GLP study, cells (n=5) were exposed to AHU377 at 1 mM (383.5 µg/mL). This AHU377 concentration was greater than 5000X the clinical exposure to AHU377 (unbound Cmax) associated with a 200 mg BID dose. *In vivo* Telemeterized cynomolgus monkey study: LCZ696 NOEL > 100 mg/kg [Study 0670360] NDA Module 4.2.1.3 Single oral doses of LCZ696 (0, 25, 100 mg/kg) were tested. The 100 mg/kg dose in primates provided valsartan Cmax exposures similar to those achieved at the 200 mg BID clinical dose; exposures to AHU377 and LBQ657 were approximately 10X and 8X the clinical Cmax at LCZ696 200 mg BID (when corrected for differences in protein bindings). Telemeterized beagle dog study: AHU377 NOEL >250 mg/kg/day [Study 0470026] NDA Module 4.2.1.3 Single oral doses of AHU377 (0, 50, 250 mg/kg/day) were tested. LBQ657 Cmax exposure at 250 mg/kg (extrapolated from study from Study CRA-11-014 Main Report was 11-fold higher than LBQ657 exposure at LCZ696 200 mg BID (when corrected for differences in protein bindings). No dedicated cardiovascular safety studies were performed with valsartan (valsartan NDA was approved prior to issuance of ICH S7a and S7b guidance). However, by virtue of the dissociation of LCZ696 into valsartan and AHU377 in aqueous solutions, the hERG inhibitory potential of valsartan was assessed in *in vitro* studies with LCZ696 and, clinically relevant valsartan exposure were achieved in *in vivo* studies with LCZ696.
Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths). The effects of LCZ696 on cardiac conduction (PR interval, QRS duration) and repolarization (QT interval) were investigated in a randomized, partially blinded (open label moxifloxacin), placebo and active-controlled (moxifloxacin), single-dose, cross-over study in healthy male

	subjects using Holter-monitoring (Study LCZ696B2123). This study was designed in accordance with the ICH E14 Guidance for Industry 2005 and subsequent Q&A documents issued by the ICH E14 Implementation Working Group. LCZ696 did not affect cardiac conduction and repolarization following single dose administration of 400 mg and 1200 mg. There were no adverse events of QT prolongation, syncope, seizure, ventricular arrhythmia, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden death reported in this study. Consistent with this negative TQT study, there was no evidence for an increased incidence of cardiac safety events across the LCZ696 clinical development program. Please see Section 2.1 for more information on Clinical Cardiac Safety.

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/s/

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REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Application: 207620

Application Type: New NDA

Name of Drug/Dosage Form: ENTRESTO (sacubitril/valsartan) Tablets

Applicant: Novartis Pharmaceuticals

Receipt Date: December 17, 2014

Goal Date: August 15, 2015

1. Regulatory History and Applicant's Main Proposals

LCZ696, developed by Novartis is a novel combination of sacubitril and valsartan for the treatment of heart failure (NYHA class II-IV) [redacted] (b) (4). Novartis has had several interactions with the FDA throughout the development process from Pre-IND meetings through pre-NDA and Top- Line results meetings.

The Phase 3 trial, CLCZ696B2314 (PARADIGM-HF) was a randomized, double-blind pivotal outcome study comparing the efficacy and safety of LCZ696 to enalapril in patients with heart failure and reduced ejection fraction (HFrEF). In March 2014, the Data Monitoring Committee recommended early closure of the trial because of compelling efficacy. Novartis was granted fast track and rolling review.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in Day 60 letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by 25 February 2015. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

NO 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required

• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

NO 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES

21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

NO 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"*[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 36. In the BW, all text should be **bolded**.

Comment:

YES 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"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."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). 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."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

NO 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

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

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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

/s/

ALEXIS T CHILDERS
02/12/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

<table>
<tr><th colspan="3">Application Information</th></tr>
<tr><td>NDA # 207620</td><td>NDA Supplement #: S- N/A
BLA Supplement #: S-</td><td>Efficacy Supplement Category:
☐ New Indication (SE1)
☐ New Dosing Regimen (SE2)
☐ New Route Of Administration (SE3)
☐ Comparative Efficacy Claim (SE4)
☐ New Patient Population (SE5)
☐ Rx To OTC Switch (SE6)
☐ Accelerated Approval Confirmatory Study (SE7)
☐ Animal Rule Confirmatory Study (SE7)
☐ Labeling Change With Clinical Data (SE8)
☐ Manufacturing Change With Clinical Data (SE9)
☐ Pediatric</td></tr>
<tr><td colspan="3">Proprietary Name: Entresto
Established/Proper Name: LCZ696 (sacubitril/valsartan)
Dosage Form: tablets
Strengths: 50 mg, 100 mg, 200 mg</td></tr>
<tr><td colspan="3">Applicant: Novartis Pharmaceuticals Corporation
Agent for Applicant (if applicable): N/A</td></tr>
<tr><td colspan="3">Date of Application: 17 December 2014
Date of Receipt: 17 December 2014
Date clock started after UN: N/A</td></tr>
<tr><td colspan="2">PDUFA/BsUFA Goal Date: 15 August 2015</td><td>Action Goal Date (if different): N/A</td></tr>
<tr><td colspan="2">Filing Date: 15 February 2015</td><td>Date of Filing Meeting: 26 January 2015</td></tr>
<tr><td colspan="3">Chemical Classification (original NDAs only) :
☒ Type 1- New Molecular Entity (NME); NME and New Combination
☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination
☐ Type 3- New Dosage Form; New Dosage Form and New Combination
☐ Type 4- New Combination
☐ Type 5- New Formulation or New Manufacturer
☐ Type 7- Drug Already Marketed without Approved NDA
☐ Type 8- Partial Rx to OTC Switch</td></tr>
<tr><td colspan="3">Proposed indication(s)/Proposed change(s): treatment of heart failure (NYHA II-IV) in patients with [redacted] (b) (4)</td></tr>
<tr><td colspan="2">Type of Original NDA:
AND (if applicable)
Type of NDA Supplement:

If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:
http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</td><td>☒ 505(b)(1)
☐ 505(b)(2)

☐ 505(b)(1)
☐ 505(b)(2)</td></tr>
</table>

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☒ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☒ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 104628, (b) (4)	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.			X	
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐	X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov)*: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☐ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☐	☒		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☒	☐	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it;*	☒	☐	☐	(b) (4) [redacted]

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☒	☐	☐	Submitted even though electronic submission
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☒	☐	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage*	☒	☐		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	Waiver
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm

Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	QT consult 1/13/15 Carci stats 1/21/15
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☒	☐		Pre-NDA 6/25/14 Top-Line 9/22/14
Any Special Protocol Assessments (SPAs)? **Date(s):** 1/20/10 carci, 7/16/09 clinical ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		Agreement on 2 carci SPAs No agreement on clinical SPA

ATTACHMENT

MEMO OF FILING MEETING

DATE: 26 January 2015

BACKGROUND: LCZ696, developed by Novartis is a novel combination of sacubitril and valsartan for the treatment of heart failure (NYHA class II-IV) (b) (4) .

The Phase 3 trial, CLCZ696B2314 (PARADIGM-HF) was a randomized, double-blind pivotal outcome study comparing the efficacy and safety of LCZ696 to enalapril in patients with heart failure and reduced ejection fraction (HFrEF). In March 2014, the Data Monitoring Committee recommended early closure of the trial because of compelling efficacy.

In addition to the Phase 3 trial, there are two supportive phase 2 studies in patients with heart failure, CLZ696B2214 (PARAMOUNT) and CLCZ696B2228 (TITRATION). Safety data is provided from completed studies in patients with hypertension as well.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alexis Childers	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Aliza Thompson		Y
Division Director	Norman Stockbridge		Y
Office Director	Ellis Unger		Y
Clinical	Reviewer:	Kim Smith Tzu-Yun McDowell	Y
	TL:	Aliza Thompson	Y
Social Scientist Review (*for OTC products*)	Reviewer:	NA	
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology	Reviewer:		N
	TL:		
Clinical Pharmacology	Reviewer:	Sreedharan Sabarinath	Y
	TL:	Raj Madabushi	Y

Biostatistics	Reviewer:	John Lawrence	Y
	TL:	Jim Hung	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Tim Link	Y
	TL:	Al DeFelice	Y
Statistics (carcinogenicity)	Reviewer:	Feng Zhou	N
	TL:	Karl Lin	N
Immunogenicity (assay/assay validation) *(for protein/peptide products only)*	Reviewer:	NA	
	TL:	NA	
Product Quality (CMC)	Reviewer:	Sherita McLamore Hines Anamitro Banerjee	Y
	TL:	Wendy Wilson	Y
Biopharmaceutics	Reviewer	Salah Hamed	Y
	TL:		N
Quality Microbiology	Reviewer:	Robert Mello	Y
	TL:		
CMC Labeling Review	Reviewer:	NA	
	TL:	NA	
Facility Review/Inspection	Reviewer:	Bogdan Kurtyka	N
	TL:	Zhong Li	N
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Sharon Gershon	Y
	TL:	Susan Thompson	
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Pharmacometrics	Reviewer:	Luning Zhuang	Y
	TL:		
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments
CLINICAL **Comments**: only IRs	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO

• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: no comments	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments: no comments	☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: no comments	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (protein/peptide products only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: IR will be sent seperately	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☒ YES ☐ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☐ YES ☒ NO ☒ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> • Was the Microbiology Team consulted for validation of sterilization? **Comments**:	☒ Not Applicable ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**: none	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☒ YES ☐ NO ☒ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	NA
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority:

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): March 11, 2015

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments: in progress scheduling

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	351(k) BLA/supplement: If filed, send filing notification letter on day 60

☒	If priority review: • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

ALEXIS T CHILDERS
02/12/2015