CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207620Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ADDENDUM to CLINICAL PHARMACOLOGY REVIEW

NDA Number:	207620
Submission Dates:	December 17, 2014
Submission Type:	Priority
Brand Name:	ENTRESTO®
Generic Name:	LCZ696 (sacubitril/valsartan)
Drug Class:	Angiotensin receptor-Neprilysin Inhibitor
Dosage Form/Route:	Film-coated Tablets/Oral
Dosage Strengths:	50 mg, 100 mg and 200 mg
Proposed Indication:	Treatment of heart failure (NYHA class II – IV) (b) (4)
Proposed Dose:	Target dose is 200 mg twice daily (BID). The starting dose is 100 mg BID. Double dose every 2-4 weeks as tolerated.
Applicant:	Novartis Pharmaceuticals
OCP Division:	DCP1
OND Division:	Division of Cardiovascular and Renal Products (DCRP)
Reviewers:	Luning Zhuang, PhD & Sreedharan Sabarinath, PhD
Team Leaders:	Jeffry Florian, PhD & Rajanikanth Madabushi, PhD

INTRODUCTION:

The objectives of this review addendum are:

(1) To compare the mean daily dose of enalapril, the active comparator used in PARADIGM-HF Phase III study, to that in SOLVD-Treatment study (SOLVD-T), and

(2) To document revised estimates for apparent volume of distribution of sacubitril and valsartan.

Reference ID: 3784800

(1) Mean Daily Dose of Enalapril in PARADIDGM-HF versus SOLVD-T

Background:

In the PRADIGM-HF study, the target dose for enalapril, the active comparator, was 10 mg twice daily (BID). The applicant stated that this target dose was selected because enalapril demonstrated a significant reduction of mortality in SOLVD-Treatment study (SOLVD-T) in patients with NYHA Class II-IV . The reported mean daily dose in all randomized patients for enalapril was 11.2 mg in SOLVD-T. The mean daily dose, among patients on the study medication at final visit, was 16.6 mg in SOLVD-T. In an attempt to compare the dose of enalapril across the two trials, the Applicant computed mean enalapril daily dose from PARADIGM-HF. The mean enalapril daily dose was calculated to be 15.7 mg and 18.9 mg, respectively, in patients who survived to the final visit (i.e., patients who died before their final visits were excluded) and in those patients taking study medication.

The applicant also submitted mean daily dose calculations for enalapril from SOLVD-T. The main assumption for this calculation method was that all mean doses described in the publication were based on the final dose of patients who survived to the final study visit (i.e., patients who died before their final visits were excluded).

The calculations provided by the applicant are listed below:

Methodology of how final mean enalapril doses were calculated in SOLVD-T (From Applicant)

Number of patients randomized to enalapril: 1285

Number of enalapril patients who died before the study final visit: 452

Number of enalapril patients who survived to the final visit: 1285 – 452 = 833

Number of patients who were on enalapril 2.5 mg/d at the final visit: 1.8% × 833 = 15

Number of patients who were on enalapril 5 mg/d at the final visit: 6.7% × 833 = 56

Number of patients who were on enalapril 10 mg/d at the final visit: 9.5% × 833 = 79

Number of patients who were on enalapril 20 mg/d at the final visit: 49.3% × 833 = 411

Number of enalapril patients on study medication at the final visit: 15 + 56 + 79 + 411 = 561

Number of enalapril patients who stopped blinded medication by end of study: 833 – 561 = 272

Final mean daily dose of enalapril:

$$\frac{(15 \times 2.5mg/d) + (56 \times 5mg/d) + (79 \times 10mg/d) + (411 \times 20mg/d) + (272 \times 0mg/d)}{(15 + 56 + 79 + 411 + 272)}$$

$$= \frac{9327.5}{833} = 11.2\ mg/d$$

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Mean enalapril daily dose among patients taking study medication:

$$\frac{(15 \times 2.5mg/d) + (56 \times 5mg/d) + (79 \times 10mg/d) + (411 \times 20mg/d)}{(15 + 56 + 79 + 411)} = \frac{9327.5}{561}$$

$$= 16.6\ mg/d$$

Review Team's Comments:

We agree that the proposed calculation method was able to reproduce the reported mean daily dose of enalapril. However, it should be noted that the SOLVD-T publication provided only the percentage of patients at each dose level at the final visit, total number of deaths and the total number of patients who were randomized. It is not clear from the publication whether the percentages of patients at each dose level are based on the overall population or those patients who were alive at the final visit (as proposed by the applicant). The review team tested the alternative assumption i.e., 'all randomized patients' as referring to the overall study population and not just those patients who were alive at the end of the study (See Figure 1 below for a snapshot of the publication). The "final visit" is interpreted as the visit prior to the study end date or the visit prior to an event.

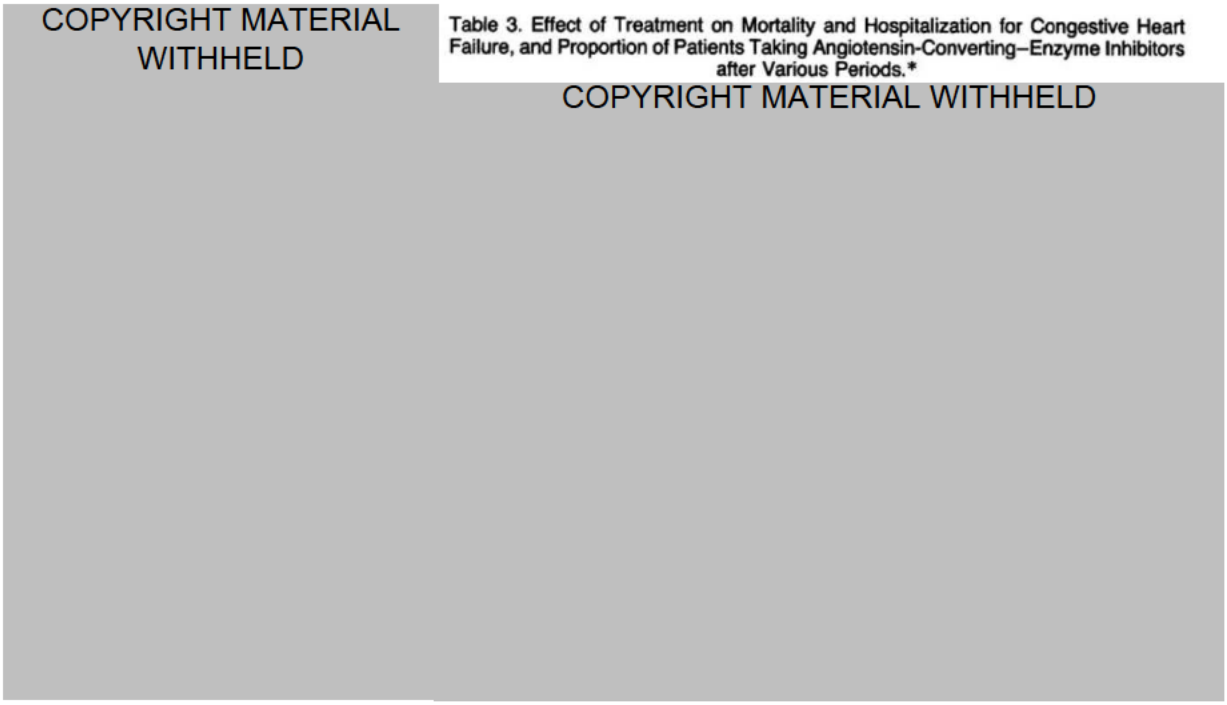

Figure 1. Relevant section of SOLVD-T publication showing mean daily dose of enalapril

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Using the same information available from the publication, we can reproduce the reported mean daily dose of enalapril even if we use all patients that are randomized in the SOLVD-T (i.e., using N=1258, without excluding patients who died before final study visit). This is because both calculation methods rely only on the reported percentage of patients at each dose level. Our calculations are illustrated below:

Methodology of how final mean enalapril doses were calculated in SOLVD-T (From FDA)

Number of patients randomized to enalapril: 1285

Number of patients who were on enalapril 2.5 mg/d at the final visit: 1.8% × 1285 = 23

Number of patients who were on enalapril 5 mg/d at the final visit: 6.7% × 1285 = 86

Number of patients who were on enalapril 10 mg/d at the final visit: 9.5% × 1285 = 122

Number of patients who were on enalapril 20 mg/d at the final visit: 49.3% × 1285 =634

Number of enalapril patients on study medication at the final visit: 23 + 86 + 122 + 634 = 865

Number of enalapril patients who stopped blinded medication by end of study: 1285 – 865 = 420

Final mean daily dose of enalapril:

$$\frac{(23 \times 2.5mg/d) + (86 \times 5mg/d) + (122 \times 10mg/d) + (634 \times 20mg/d) + (420 \times 0mg/d)}{(23 + 86 + 122 + 634 + 420)}$$

$$= \frac{14379.2}{1285} = 11.2\ mg/d$$

Mean enalapril daily dose among patients taking study medication:

$$\frac{(23 \times 2.5mg/d) + (86 \times 5mg/d) + (122 \times 10mg/d) + (634 \times 20mg/d)}{(23 + 86 + 122 + 634)} = \frac{14379.2}{865}$$

$$= 16.6\ mg/d$$

This suggests that the actual method applied in SOLVD-T publication could be either as proposed by the applicant or as illustrated above, without excluding patients who died before final study visit. The same calculation methodologies can be used for PARADIGM-HF and the results are summarized in Table 2.

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Table 2. Mean daily dose of enalapril from SOLVD-T and PARADIGM-HF

Study	Approach Used	Mean daily dose	Mean daily dose for those taking medication
SOLVD-T	All Randomized Patients (FDA's interpretation)	**11.2 mg/d**	16.6 mg/d
	Excluding deaths* (Applicant's interpretation)	11.2 mg/d	16.6 mg/d
PARADIGM-HF	All Randomized Patients (FDA's interpretation)	**14.2 mg/d**	18.9 mg/d
	Excluding deaths** (Applicant's interpretation)	15.6 mg/d	18.9 mg/d

*Excluded 452 patients who died before final study visit

** Excluded 848 patients who died before final study visit

Summary/Conclusion:

Both calculation approaches were able to reproduce the reported enalapril daily dose for SOLVD-T. This is because of the limited information from the publication. PARADIGM-HF study had average daily dose of 14.2 mg of enalapril in all randomized patients and 15.6 mg in survivors (patients who died were excluded from the calculation), respectively. When compared to the best available mean enalapril daily dose from SOLVD-T, i.e., 11.2 mg, the mean enalapril daily dose in PARADIGM-HF (calculated either way) is numerically higher. Hence, it can be concluded that the daily dose of enalapril in PARADIGM-HF is no less than that reported from SOLVD-T.

(2) Apparent volume of distribution of sacubitril and valsartan

In the NDA, the average apparent volume of distribution (Vz/F) parameter was reported as (b) (4) L and (b) (4) L, respectively, for sacubitril and valsartan. This was based on the data obtained from 82 healthy subjects following single dose administration of 200 mg LCZ696 from clinical studies LCZ696A1101 (N=8), LCZ696A2102 (N=8), LCZ696B2115 (N=10), LCZ696B2203 (N=16, matching healthy subjects), LCZ696B2126 (N=40). The clinical pharmacology review (DARRTS dated 5/15/2015) also reported these values on page 19.

However, it was later determined that the dose used for the calculation of Vz/F for the study LCZ696B2126 was not correct. (b) (4)

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(b) (4)

Therefore, correction to the dose for study LCZ696B2126 was required and Vz/F was recalculated (Reference: Labeling communication with the applicant, dated 6/22/2015). Based on these revised estimates, average Vz/F value is corrected to 103.4 L for sacubitril and 75.4 L for valsartan. These changes are implemented in Section 12.3 of the label.

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/s/

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CLINICAL PHARMACOLOGY REVIEW

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1. EXECUTIVE SUMMARY

Novartis Pharmaceuticals has submitted an original new drug application (NDA 207620) for LCZ696 (sacubitril/valsartan). The applicant is seeking approval for the indication: treatment of heart failure (NYHA Class II-IV) (b) (4). LCZ696 is a (b) (4) which dissociates to a prodrug sacubitril and valsartan up on oral administration. Sacubitril is further metabolized by esterases to form an active moiety called LBQ657, which is a neprilysin inhibitor. Valsartan is an angiotensin II receptor blocker, approved in the US for the treatment of hypertension and heart failure. The proposed mechanism of action of LCZ696 is simultaneous blockade of neprilysin and angiotensin II receptors.

The primary evidence of efficacy and safety are based on a single phase III study (PARADIGM-HF), comparing LCZ696 200 mg twice daily (BID) with an active comparator, enalapril 10 mg BID. The study was stopped early by the recommendation of the Data Monitoring Committee (DMC) at a pre-specified interim analysis due to compelling evidence for efficacy. LCZ696 was superior to enalapril in reducing the risk of the composite primary endpoint with a 20 % relative risk reduction (HR 0.8, 95 % CI 0.73-0.87, P<0.0001). LCZ696 was also superior to enalapril in delaying time to cardiovascular (CV) death, with a relative risk reduction of 20 %.

The submission also includes two phase II studies in patients with heart failure and supportive clinical pharmacology studies, including intrinsic and extrinsic factor studies. The pivotal efficacy study used final marketing image (FMI) formulations, except for the 50 mg strength. A pivotal bioequivalence study bridges the 50 mg clinical service formulation to the 50 mg FMI tablet.

1.1 Recommendations

The new drug application (NDA 207620) for LCZ696 (sacubitril/valsartan) is acceptable and can be approved from a clinical pharmacology perspective.

We have the following dosing recommendations:

Use a lower starting dose of 50 mg BID in patients with (1) severe renal function impairment or (2) moderate hepatic impairment.

1.2 Phase 4 Study Commitments

None.

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1.3 Summary of OCP Findings

1.3.1 Pharmacokinetics

- 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.
- LCZ696 tablets can be administered with no regard to food.
- The LCZ696 analytes have high plasma protein binding (97 % for sacubitril and LBQ657 and 94 % for valsartan)
- No significant CYP isozyme involvement in the metabolism of LCZ696 analytes. LBQ657, formed from sacubitril by esterases, is not metabolized further into any major metabolites. CYP2C9 plays a minor role for valsartan (~ 9 %). 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.

1.3.2 Exposure-Response Relationships

There was limited pharmacokinetic (PK) data collected from the Phase III study PRADIGM-HF (~ 7 %). Moreover, the study employed a dose titration scheme based on tolerability to attain the target dose (200 mg BID) of LCZ696. No dose/exposure response analysis was feasible.

1.3.3 Intrinsic Factors

Age, race, gender or body weight did not have any significant impact on the exposure of LCZ696 analytes. Pre-specified sub-group analyses on primary efficacy endpoint of cardiovascular death or hospitalization for worsening heart failure also showed consistent treatment effect across all

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subpopulations for LCZ696 relative to enalapril, the active comparator. No dose adjustments are required for age, race, gender or as per body weight.

1.3.3.1 Renal impairment

In subjects with mild (CrCL 50 to ≤ 80 mL/min) and moderate (CrCL 30 to ≤ 50 mL/min) renal impairment, exposure to LQB657 increased by about 2X. Subjects with severe renal impairment (CrCL<30 mL/min) showed a 2.7X increase in exposure to LBQ657. However, the exposure to sacubitril and valsartan were not significantly altered in renal function impairment. Patients with mild to moderate renal impairment were enrolled in the pivotal efficacy study and there were no increase in adverse events associated with the increased exposure to LQB657 in those patients. Therefore, no dose adjustments are proposed for mild and moderate renal impairment.

LCZ696 is a fixed dose combination of sacubitril (prodrug for LBQ657) and valsartan. Therefore adjusting dose levels for LBQ657 alone without affecting the dose of valsartan is not feasible. Moreover, LCZ696 is titrated to the target dose based on tolerability in each patient. The incremental increase in exposure seen in severe renal impairment is 2.7X relative to healthy subjects and is closer to the 2.2X increase seen in patients with moderate renal impairment. There is clinical experience with LCZ696 in patients with moderate renal impairment in Phase III, where no dose adjustments were employed. Therefore, no change to the target dose is proposed in patients with severe renal impairment. However a lower starting dose of 50 mg BID should be used in patients with severe renal impairment. A lower starting dose and slower titration to target may reduce tolerability issues.

1.3.3.2 Hepatic impairment

Subjects with mild hepatic impairment (Child-Pugh Class A) showed increased exposure to sacubitril, LBQ657 and valsartan by about 53 %, 48 % and 19 % respectively. The increase in exposure seen in moderate hepatic impairment (Child-Pugh Class B) was about 245 %, 90 % and 109 % for sacubitril, LBQ657 and valsartan respectively. No studies were conducted in subjects with severe hepatic impairment (Child-Pugh Class C). Sacubitril is an inactive pro-drug and has no significant safety issues identified. No dose adjustments are proposed for mild hepatic impairment. Use of a lower starting dose of 50 mg BID is recommended in patients with moderate hepatic impairment. Use of LCZ696 in patients with severe hepatic impairment is not recommended.

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1.3.4 Extrinsic Factors

1.3.4.1 Drug-Drug Interactions

The involvement of CYPs for the biotransformation of sacubitril, LBQ657 and valsartan is considered minimal. Therefore, the DDI potential of LCZ696 as a victim when co-administered with drugs that may affect the CYP system is considered to be low.

No clinically relevant interaction was observed when LCZ696 was co-administered with carvedilol, furosemide, nitroglycerine, digoxin, warfarin, metformin, omeprazole, hydrochlorothiazide, amlodipine, and oral contraceptives. Co-administration of sildenafil and LCZ696 resulted in additional reduction in blood pressure (BP), possibly due to additive pharmacodynamic effects (~4-5 mmHg additional reduction in SBP/DBP). Patients should be advised about potential adverse effects due to BP lowering effects when sildenafil or other phosphodiesterase-5 inhibitors are to be initiated while on treatment with LCZ696.

Co-administration of LCZ696 increased the C_{max} of atorvastatin and its metabolites by up to 2X and AUC by 1.3X. These effects may potentially be due to the OATP1B1 and OATP1B3 inhibitory effects of sacubitril. However, atorvastatin was used as a co-medication in the Phase III study for LCZ696 (~31 % of patients in LCZ696 and enalapril treatment groups) and no significant adverse events related to atorvastatin were reported in them. No dose adjustments are proposed for atorvastatin when co-administered with LCZ696.

1.3.5 Biopharmaceutics

The pivotal efficacy study PARADIGM-HF used final marketing image (FMI) formulations for 100 mg and 200 mg tablet strengths. The 50 mg strength clinical service form tablet used in Phase III was bridged to FMI 50 mg tablet with a pivotal bioequivalence study.

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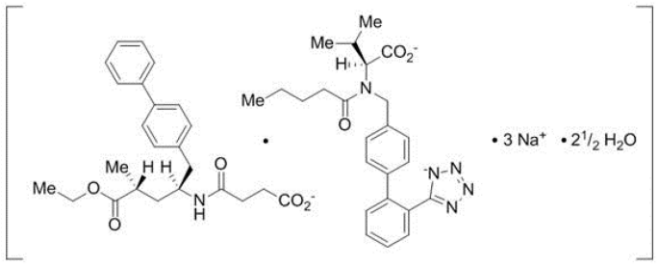
2. QUESTION BASED REVIEW (QBR)

2.1 General Attributes

LCZ696 is a (b) (4) of a pro-drug sacubitril, which forms the active moiety LBQ657, and valsartan. LBQ657 is a neprilysin inhibitor. There are no approved neprilysin inhibitors in the US. Valsartan is an angiotensin II receptor Type 1 blocker (ARB) and is approved in the US for the treatment of hypertension and heart failure. The clinical pharmacology information on valsartan is available in the USPI[1] and in its approval package[2]. Hence, this review does not discuss the clinical pharmacology aspects of valsartan in detail.

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Drug Substance:

Appearance:	(b) (4)	
Molecular Formula (hemipentahydrate):	$C_{48}H_{55}N_6O_8Na_3.2.5H_2O$	
Molecular Weight (hemipentahydrate):	957.99	
Structural Formula:	 *Source: Quality overview summary- Drug substance, Section 2.3*	
Solubility:	Conc. of sacubitril (mg/mL)	Conc. of valsartan (mg/mL)
0.1 N HCl	0.052	0.032
Water	>100	>100
Phosphate buffer, pH 6.8	>50	>50
Partition coefficients:	Log D o/w at pH 6.8 =1.29 for sacubitril,	

[1] DIOVAN® (valsartan) USPI: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021283s044lbl.pdf

[2] NDA 21283 (Diovan®) Approval Package: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/021283_ORIGINAL_APPROVAL_PACKAGE.PDF

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	-1.49 at pH 7.4 for valsartan
pKa	4.6 for sacubitril, 3.9 and 4.7 for valsartan

Source: Quality overview summary- Drug substance, Section 2.3

Drug Product:

LCZ696 (sacubitril/valsartan) is formulated as immediate release, film-coated tablets for oral administration in 50 mg, 100 mg and 200 mg strengths (differentiated by debossing and color). The excipients included microcrystalline cellulose, low substituted hydroxypropylcellulose crospovidone, magnesium stearate, talc and colloidal silicone dioxide.

2.1.2 What are the proposed therapeutic indication and mechanism of action?

The proposed indication for LCZ696 is the treatment of heart failure (NYHA class II-IV) (b) (4) [redacted]. The proposed label claims include (b) (4) [redacted]

LCZ696 contains sacubitril, a pro-drug for a neprilysin inhibitor LBQ657, and valsartan. The proposed mechanism of action of LCZ696 involves simultaneously inhibiting neprilysin via LBQ657 and angiotensin II Type-1 (AT-1) receptors via valsartan. The mechanism of action for valsartan is well understood and is depicted in the schematic below (Figure 1). LBQ657 is believed to enhance the effects of natriuretic peptides, including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-Type natriuretic peptide (CNP). ANP and BNP are released into circulation by the heart in response to myocardial stress. CNP is synthesized by endothelial and renal epithelial cells. These peptides are cleared from circulation by neprilysin dependent proteolytic degradation and through natriuretic peptide clearance receptors. The natriuretic peptides act by activating membrane bound guanylyl cyclase-coupled receptors and by increasing concentrations of cyclic guanosine monophosphate (cGMP). The cGMP is thus considered as an indirect marker for neprilysin inhibition.

The proposed mechanism of action of LCZ696 and potential beneficial effects in patients with heart failure (HF) are illustrated in Figure 1:

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*Neprilysin substrates listed in order of relative affinity for NEP: ANP, CNP, Ang II, Ang I, adrenomedullin, substance P, bradykinin, endothelin-1, BNP
Ang=angiotensin; ANP=atrial natriuretic peptide; AT1=angiotensin II type 1; BNP=B-type natriuretic peptide; CNP=C-type natriuretic peptide; NEP=neprilysin; RAAS=renin angiotensin aldosterone system

Lavin et al. N Engl J Med 1998;339:321–8;
Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42;
Schrier & Abraham N Engl J Med 2009;341:577–85;
Langenickel & Dole. Drug Discov Today: Ther Strateg 2012;9:e131–9;
Feng et al. Tetrahedron Letters 2012;53:275–6

Figure 1 Proposed mechanism of action of LCZ696. Source: Applicant's slides - Topline results meeting PARADIGM-HF

2.1.3 What are the current treatments available for the proposed indication?

The guideline recommended treatments available for the proposed indication include[3]:

- Angiotensin converting enzyme (ACE) inhibitors, Angiotensin II receptor blockers (ARBs), if ACE inhibitors are not tolerated (Class I, Level A)

  AND

- Beta blockers (Class I, Level A) – carvedilol, bisoprolol or extended release metoprolol
- Diuretics, if there is evidence of fluid retention (Class I , Level C)
- Spironolactone, provided estimated creatinine clearance is >30 mL/min and K^+ < 5 mEq/L (Class I, Level A)
- Hydralazine/isosorbide dinitrate for self-identified African Americans with symptomatic NYHA class III-IV heart failure receiving optimal therapy with ACE inhibitors and beta blockers (Class I, Level A)
- Digoxin (Class IIa, Level B)

[3] ACCF/AHA Guideline for the management of heart failure, 2013

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- Ivabradine, approved in April 2015 to reduce risk of hospitalizations for worsening heart failure in patients with symptomatic heart failure with left ventricular ejection fraction <35%, who are on sinus rhythm with resting heart rate >70 bpm and either on maximally tolerated doses of beta blockers or have a contra indication to beta blocker use. Ivabradine is thought to act by reducing heart rate in these patients.

In addition to the pharmacotherapies listed above, implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT) are also used in patients with heart failure with reduced ejection fraction[3].

2.1.4 What are the proposed dosages and route of administration?

LCZ696 is available as film coated tablets for oral administration in 50 mg (24 mg of sacubitril/ 26 mg of valsartan), 100 mg (49 mg of sacubitril/ 51 mg of valsartan) or 200 mg (97 mg of sacubitril/ 103 mg of valsartan) strengths.

The proposed target dose is 200 mg twice daily (BID). The starting dose is 100 mg BID. A lower starting dose of 50 mg BID is recommended in patients not currently taking an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), and for patients previously taking low doses of these drugs. The dose should be doubled every 2-4 weeks, as tolerated by the patient, to the target dose of 200 mg BID.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The efficacy and safety claims of LCZ696 are primarily based on a single, pivotal Phase III study, PARADIGM-HF in heart failure patients with systolic dysfunction (See Section 2.2.4).

There were two Phase II studies, PARAMOUNT-HF and TITRATION (See Section 2.2.5). The PARAMOUNT-HF study compared the effect of 200 mg BID LCZ696 t 160 mg BID valsartan on biomarkers in patients with heart failure with preserved ejection fraction. TITRATION was a safety and tolerability study, comparing two titration regimens for LCZ696 in heart failure patients with reduced ejection fraction. A total of 30 clinical pharmacology studies in healthy subjects, patients with heart failure or hypertension and special populations were used to support the application.

2.2.2 What is the basis for selecting response endpoints in clinical studies?

The major goal of treating heart failure is to reduce fatal and non-fatal consequences associated with the disease. These consequences are cardiovascular (CV) death and hospitalizations for worsening of heart failure. The primary efficacy endpoint for the

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PARADIGM-HF was the time to first occurrence of CV death or hospitalization for worsening heart failure. The components of this composite endpoint are disease specific and were employed in previous clinical trials in heart failure. The composite endpoint of CV death and hospitalizations associated with heart failure have also been shown to be modifiable by treatments improving this disease, such as ACE inhibitors, mineralocorticoid receptor antagonists, beta blockers and devices such as ICD/CRT[4].

2.2.3 Were correct moieties identified and properly measured to access clinical pharmacology?

Upon oral administration, LCZ696 dissociates quickly, resulting in systemic exposure of the pro-drug sacubitril, active metabolite of sacubitril (LBQ657) and valsartan. These moieties were identified and quantified in various biological matrices using validated LC-MS/MS methods in clinical studies[5].

2.2.4 What are the key features of the Phase III trial of LCZ696?

The pivotal Phase III study was an active controlled outcome study in heart failure patients with reduced ejection fraction. The primary objective was to test superiority of LCZ696 to enalapril (active comparator) in delaying time to first occurrence of cardiovascular (CV) death or heart failure hospitalization (composite primary efficacy endpoint). The study was powered to demonstrate a CV mortality benefit. A schematic of the study design is shown below (Figure 2).

The study consisted of three periods: (1) screening (2) single blind active run in period ranging from 5 to 10 weeks and (3) double blind treatment period for randomized patients.

The active run in period prior to randomization consisted of a 2-4 week treatment with enalapril 10 mg BID, followed by treatment with LCZ696 100 mg BID and then with 200 mg BID for an additional 3-6 weeks. During the run in period, patients were on their background medications for heart failure but were required to discontinue any existing ACE inhibitor or ARB therapy. Patients unable to tolerate enalapril 10 mg BID or LCZ696 during the run in period were not eligible for randomization and were discontinued from the study.

During and after the run-in period, two short washout periods (approximately 36 hours each) were introduced between the enalapril and LCZ696 treatments in order to minimize the potential risk of angioedema due to overlapping (angiotensin converting enzyme-neprilysin) ACE-NEP inhibition.

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[4] ACCF/AHA Guideline for the management of heart failure, 2013

[5] CTD 2.7.1 Summary of bioanalytical methods for LCZ696 studies

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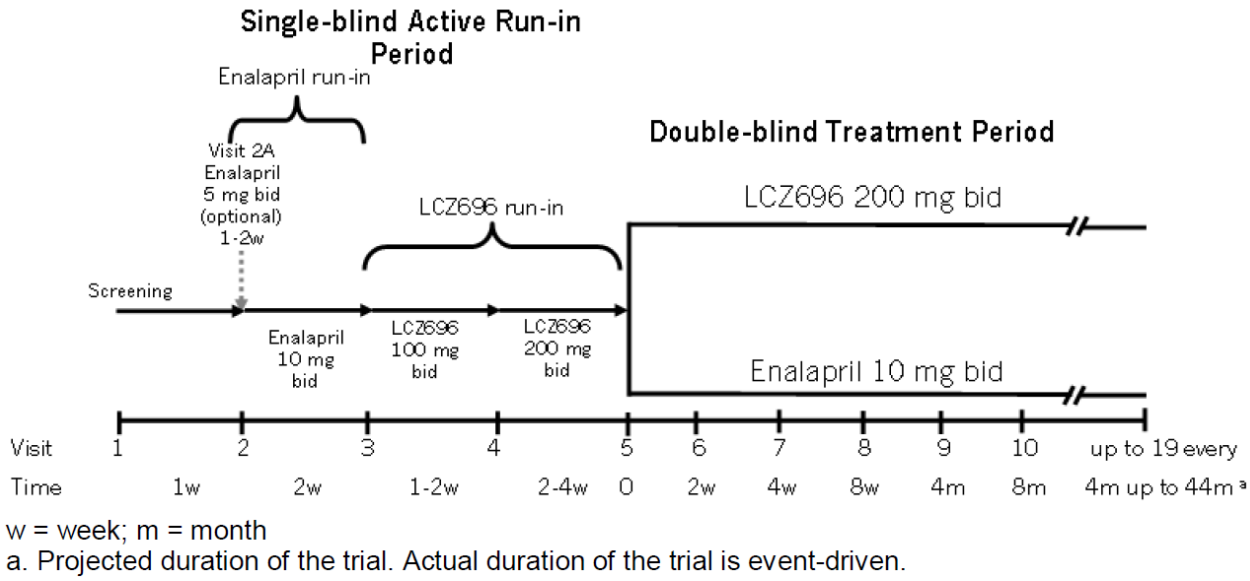

Figure 2. Schematic of PARADIGM-HF study design. Source: Summary of clinical efficacy, Figure 2-2

A total of 8442 heart failure patients with reduced ejection fraction were randomized to either LCZ696 or enalapril in a 1:1 ratio. Patients had a mean age of 63.8 years, and the majority of patients were either NYHA class II (70.3%) or III (24.1%). The majority of randomized patients had left ventricular ejection fraction (LVEF) ≤ 35%. A total of 963 patients (11.4%) had LVEF > 35%, with a mean LVEF of 29.5 % for the overall study population. The LCZ696 and enalapril groups were well-balanced with respect to baseline demographics, CV-related comorbidities, and HF disease characteristics. Majority of patients were treated with guideline-recommended standard of care HF pharmacotherapies prior to enrollment, including ACEIs (77.7 %), ARBs (22.6 %), beta-blockers (94.3 %), and aldosterone antagonists (58.4%). The median duration of follow-up was 27 months.

2.2.5 How was the Phase III dose and regimen selected?

Using cGMP as an indirect marker for neprilysin inhibition, a study in healthy subjects suggested near maximal increase in cGMP with 200 mg or greater doses of LCZ696 (Multiple ascending dose study B2102). An E_{max} model described the relationship between cGMP change from baseline in area under the effect curve on Day 6 (ΔAUEC) and LCZ696 doses over a range of 0 to 900 mg (Figure 3). Model predicted means overlaid with individual cGMP AUEC change from baseline are shown below. No additional neprilysin inhibition (seen as increase in cGMP) is expected by increasing the LCZ696 dose beyond 200 mg/day. This formed the basis for limiting the dose of LCZ696 to 200 mg.

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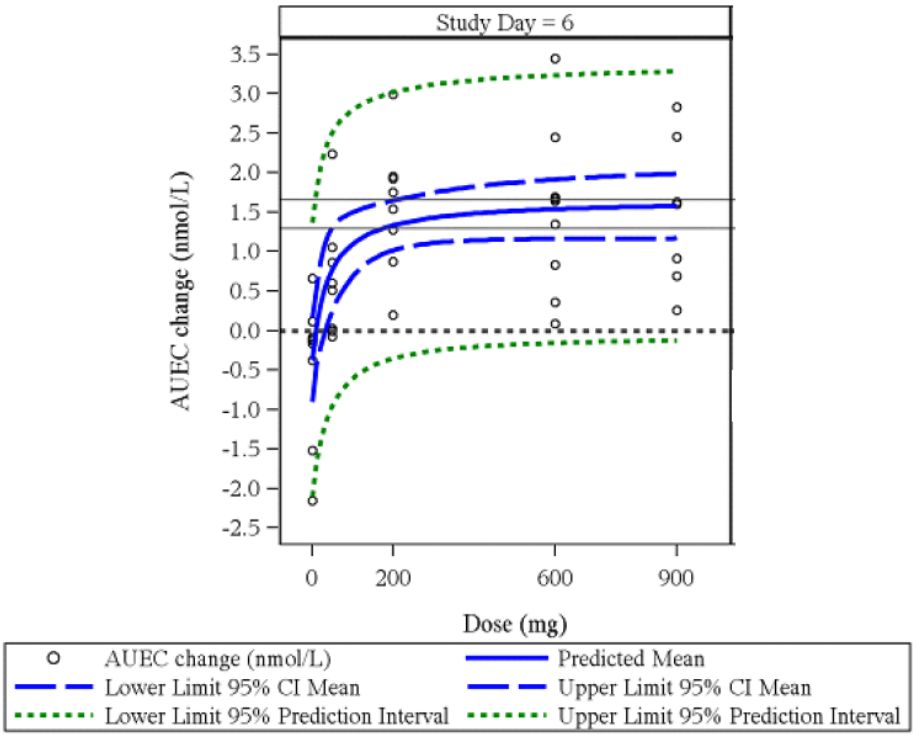

Figure 3. Dose-response curve for cGMP (indirect marker for neprilysin inhibition) from multiple ascending dose study B2102. cGMP levels measured at pre-dose, 4, 12 and 24 h post dose. Change from baseline in cGMP AUEC is shown. Source: Clinical Pharmacology Summary, Page 130, Figure 3-12

However, once daily dosing with LCZ696 did not sustain the elevation in cGMP for 24 hours. So a BID regimen was adopted to prolong the duration of cGMP elevation to 24 hours (Figure 4). In addition, the potential for adverse events such as hypotension was lower when the same total daily dose was administered as BID instead of once daily (Study B2223).

In addition, the approved target maintenance dose of valsartan for heart failure is 160 mg BID[6]. The systemic exposure to valsartan from LCZ696 200 mg (97 mg of sacubitril/103 mg of valsartan) is similar to that from 160 mg valsartan. This observation and the valsartan dosing frequency may also have been considered when selecting the dose/regimen for PARADIGM-HF study.

[6] DIOVAN® USPI: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021283s044lbl.pdf

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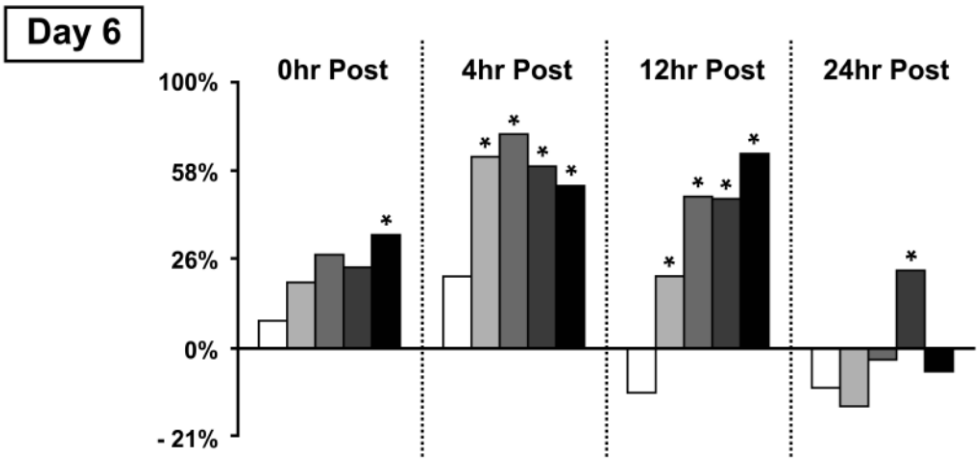
In summary, the dose/regimen selected for the pivotal efficacy study was justifiable based on the indirect pharmacological response of LCZ696 and to reduce the risk for potential adverse events and to align with the valsartan dosing frequency in patients with HF.



Note: * P <0.05 versus placebo.

Figure 4 Geometric Mean of % Change from Baseline for cGMP over time. Source: Clinical study report for A2102, Page 67, Figure 11-8

2.2.5 Was any alternate dose titration scheme evaluated for LCZ696?

The PARADIGM-HF study included a single-blind active run-in period during which patients were administered enalapril 5 to 10 mg bid for 2 to 4 weeks followed by LCZ696 up-titrated from 100 mg bid to 200 mg bid over a duration of 3 to 6 weeks. This design allowed tolerability assessments of patients to the target doses of enalapril and LCZ696 prior to randomization. Only those patients who tolerated the target dose of enalapril and LCZ696 entered the double-blind phase with long-term follow-up. During the run-in period, there were 10.5 % patients who discontinued from the enalapril run-in period and 9.3 % of patients who discontinued from the LCZ696 run-in period. Among those, approximately 6.1 % and 5.5 % of patients discontinued study medication due to AEs during the enalapril and the LCZ696 run-in periods, respectively. The most common AEs that led to discontinuation during the run-in periods were hypotension, hyperkalemia, and renal impairment.

A phase II safety and tolerability study (TITRATION, N~ 498) in patients with HF evaluated two titration schemes for LCZ696, both using the target dose of 200 mg BID. A schematic of the study design is shown below (Figure 5):

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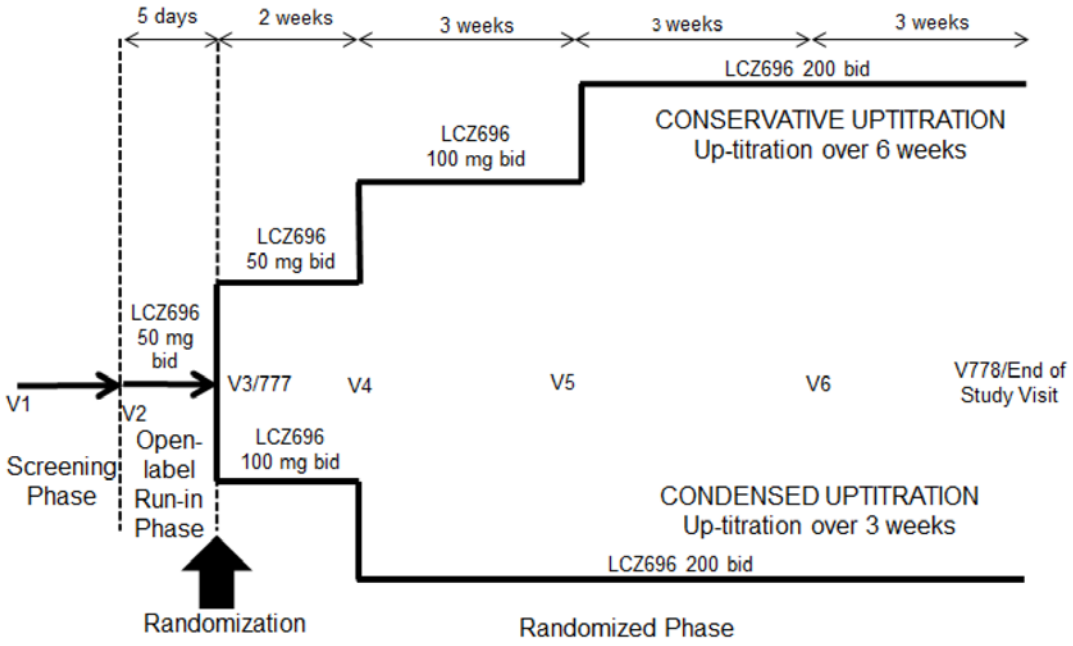

Figure 5. Schematic of TITRATION study design. Source: Summary of Clinical Efficacy, Page 24, Figure 2-1

Patients were randomized to one of the following two treatment arms in a 1:1 ratio in a double-blind manner: (1) Conservative up-titration: LCZ696 was up-titrated from 50 mg BID to 200 mg BID over 6 weeks (including the run-in phase) and (2) Condensed up-titration: LCZ696 was up-titrated from 50 mg BID to 200 mg BID over 3 weeks (including the run-in phase).

The result showed that LCZ696 was well tolerated in terms of the commonly observed adverse events (such as hypotension, hyperkalemia, renal dysfunction and angioedema) following either a condensed or conservative up-titration regimens to achieve the target dose of 200 mg BID (Table 1). Patients who were ACEI/ARB naïve or taking lower pre-study doses of ACEIs/ARBs (low RAS stratum) were better able to achieve and maintain the target dose of LCZ696 200 mg BID if they were up-titrated more gradually, whereas the rate of up-titration was less important in patients who were taking higher pre-study doses of ACEIs/ARBs (high RAAS stratum). The incidence of hyperkalemia was relatively higher with the condensed titration scheme for both strata. See Table 1 below:

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Table 1. Adverse events reported in TITRATION study.

Response variable	Stratum	LCZ696 Condensed n/N (%)	LCZ696 Conservative n/N (%)
Hypotension	High RAAS	5/120 (4.2)	7/127 (5.5)
	Low RAAS	19/127 (15.0)	14/124 (11.3)
	All	24/247 (9.7)	21/251 (8.4)
Renal dysfunction	High RAAS	5/120 (4.2)	9/127 (7.1)
	Low RAAS	13/127 (10.2)	10/124 (8.1)
	All	18/247 (7.3)	19/251 (7.6)
Hyperkalemia	High RAAS	8/120 (6.7)	5/127 (3.9)
	Low RAAS	11/127 (8.7)	6/124 (4.8)
	All	19/247 (7.7)	11/251 (4.4)
Angioedema	High RAAS	0/120 (0.0)	1/127 (0.8)
	Low RAAS	0/127 (0.0)	1/124 (0.8)
	All	0/247 (0.0)	2/251 (0.8)

Safety/tolerability in HFrEF, LVEF ≤ 35%, N ~ 498, 5.6 % discontinuations due to AEs in run-in phase

Source: TITRATION Study CLCZ696B2228 Report, Page 91, Table 11-5

The TITRATION study was relatively small but supports the proposed dose titration scheme for LCZ696, which involves a starting dose of 100 mg BID for most patients with dose doubling in every 2-4 weeks, based on tolerability, up to the target dose of 200 mg BID. Patients who are naïve to ACE inhibitors/ARBs or are taking low doses of these drugs should use a lower starting dose (50 mg BID) of LCZ696.

2.2.6 Is the washout period between stopping ACE inhibitors and starting LCZ696 justified?

Clinical experience from omapatrilat[7], a combined ACE and neprilysin inhibitor indicated higher incidence of angioedema. Therefore, to minimize the potential risk of angioedema due to overlapping ACE-neprilysin inhibition, two short washout periods of approximately 36 hours each, were introduced between the enalapril and LCZ696 treatments during and after the run-in period in the PRADIGM-HF study. The wash out period of 36 hours corresponds to duration of at least 3X reported elimination half-life for most ACE inhibitors[8].

[7] Circulation, 111:1697-1702, 2005

[8] Elimination half-life for few ACE inhibitors after multiple dosing reported in USPIs: Enalapril 11 h, Lisinopril 12 h, ramiprilat 13-17 h, captopril <2 h, benzaprilat 10-11 h, fosinoprilat 11.5 h, moexiprilat 12 h, quinaprilat 3 h, trandopril 6 h

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The incidence of angioedema cases reported to the Angioedema Adjudication Committee was similar between LCZ696 and enalapril treatment arms during the run in period (total 54 cases reported, 25 from enalapril and 29 from LCZ696) and the double-blind phase (total 93 cases reported, 45 from enalapril and 48 from LCZ696). The AAC confirmed angioedema cases were 15 patients (0.14 %) during enalapril run in and 10 patients (0.11 %) during LCZ696 run in periods. There were no cases of angioedema involving airway compromise or death on either run in periods. Among the 10 cases of AAC-confirmed angioedema during the LCZ696 run-in period, 1 and 3 cases occurred within 1 and 7 days, respectively, after switching from enalapril to LCZ696. For the other 6 cases, 2 occurred within 14 days, 3 within 28 days, and 1 within 42 days.

During the double blind period, there were 19 (0.45 %) AAC confirmed cases of angioedema in LCZ696 group and 10 (0.24 %) in enalapril group. The applicant states that only one case of AAC confirmed angioedema occurred within 1-2 days after switching from LCZ696 run in period to double blind enalapril treatment. Two patients experienced angioedema within 30 days from the start of double blind treatment and majority of the cases occurred sporadically thereafter. These observations suggest that the 36 h washout period implemented may have helped in reducing the incidence of angioedema due to overlapping ACE and neprilysin inhibition. This seems appropriate for most ACE inhibitors.

2.2.7 What are the characteristics of the exposure or dose-response relationships for efficacy or safety?

The PK sampling from the pivotal efficacy study was limited (~ 7 % of patients). In addition, the PARADIGM-HF study employed a dose titration scheme based on tolerability to attain the target dose (200 mg BID) of LCZ696. No dose/exposure response analysis was feasible for the study.

2.2.8 Does LCZ696 prolog QT or QTc interval?

As per the QT-IRT review[9], no significant QTc prolongation effect of LCZ696 (400 mg and 1200 mg doses) was detected in a TQT study (N~84 healthy subjects). The largest upper bounds of the two-sided 90 % CI for the mean difference between LCZ696 and placebo (ΔΔQTcF) were below 10 ms, the threshold for regulatory concern as per ICH E14 guidelines. The largest lower bound of the two-sided 90 % CI for the ΔΔQTcF for the positive control moxifloxacin was greater than 5 ms in the TQT study.

[9] QT-IRT Review in DARRTS dated 2/27/2015

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2.3 Pharmacokinetics of Drug and Metabolite(s)

After oral administration the LCZ696 dissociates rapidly to the pro-drug sacubitril and valsartan. Sacubitril undergoes ester hydrolysis to form the active moiety LBQ657.

2.3.1 What are the single and multiple dose PK parameters?

Single and multiple doses of LCZ696 were evaluated in healthy volunteers, in hypertensive subjects and in patients with heart failure. The highest dose tested was 1200 mg as single dose and 900 mg once daily for 14 days in healthy subjects (Study A2102). Following oral administration, LCZ696 completely dissociates and as such there is no systemic exposure to LCZ696. Absorption was rapid for sacubitril, LBQ657 and valsartan after LCZ696 dose administration (see Section 2.3.2). The average terminal elimination half-lives were 1.4 h, 9.9 and 11.5 h respectively for sacubitril, valsartan and LBQ657. The PK was linear but less than proportional for 200-900 mg dose range for sacubitril and valsartan. Linear PK was seen for LBQ657 for 200-1200 mg dose range. Deviation from dose linearity was observed for valsartan and sacubitril at 1200 mg dose level. Based on the C_{max} and AUC_{24h} values on Day 1 and Day 14 from the multiple dose study, there was no significant accumulation for sacubitril, valsartan or LBQ657 in this study with once daily dosing. With the recommended twice daily dosing regimen for LCZ696, no significant accumulation was observed for sacubitril and valsartan, while LBQ657 accumulated 1.6 fold.

2.3.2 What are the characteristics of drug absorption?

As shown in Section 2.1.2, LCZ696 dissociates into sacubitril (pro-drug) and valsartan after oral administration and gets absorbed from the GI tract. The median time to reach peak plasma concentrations of sacubitril, LBQ657 and valsartan were 30 minutes, 2 h and 1.5 h respectively. The systemic exposure of valsartan from a 400 mg dose of LCZ696 (i.e., 206 mg of valsartan) was equivalent to that from a 320 mg of commercially available valsartan tablet. This suggests that the absolute oral bioavailability of valsartan from LCZ696 is greater than that reported (F~23 %) for valsartan given alone. The reason behind the increased bioavailability of valsartan from LCZ696 is not clear. The absolute oral bioavailability of sacubitril is estimated to be at least 60 % based on urinary excretion data from a mass balance study (See Section 2.3.6).

2.3.3 What are the characteristics of drug distribution, including plasma protein binding?

Based on *in vitro* studies, both sacubitril and LBQ657 are highly protein bound (~97 %). Protein binding of valsartan is about 94 %. A study in healthy subjects (A2126) showed that a small portion of LBQ657 can cross the blood brain barrier (~ 0.3 %). The apparent volume of distribution (V_z/F) of sacubitril and valsartan were relatively high (157 L and 108 L, respectively).

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2.3.4 What are the characteristics of drug metabolism?

Sacubitril, the pro-drug (AHU377), is converted to the active moiety LBQ657 by ester hydrolysis (Figure 6). No other significant metabolites were identified for sacubitril or LBQ657. The CYP450 isozymes do not have a major role in the biotransformation of LCZ696.

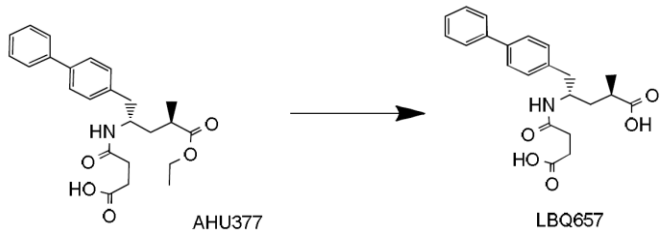

Figure 6. Conversion of sacubitril (named as AHU377) to the active moiety LBQ657 by ester hydrolysis. Source: Report ADME R0300249, Page 30, Figure 7-7

Valsartan is minimally metabolized and approximately 20 % of the dose is recovered as metabolites. CYP2C9 plays a minor role for valsartan metabolism, with the primary metabolite accounting for about 9 % of the dose[10].

2.3.5 What are the characteristics of drug excretion?

About 52-68 % of sacubitril (mainly as LBQ657) and 13 % of valsartan/metabolite are excreted in urine. About 86 % of valsartan/metabolite and 37-48 % of sacubitril (as LBQ657) are excreted in feces.

2.3.6 Does the mass balance study suggest renal or hepatic as the major route of elimination for LCZ696?

A mass balance study (B2105, N=4 healthy male subjects) evaluated the ADME of LCZ696. A single 200 mg [^{14}C]-labeled LCZ696, where sacubitril was radiolabeled, was used in this study. Almost 100 % of radioactivity was recovered in 7 days. Peak radioactivity was seen in 1-2 hours after dose administration in systemic circulation and the mean terminal elimination half-life for the sacubitril was about 1.3 hours.

The elimination of sacubitril was primarily as LBQ657, with unchanged sacubitril accounting for about 0.8-2.8 % in urine and 0.3-0.9 % in feces, respectively. The peak plasma concentration of LBQ657 was seen in 1-2 hours and the average terminal elimination half-life was about 12 hours. About 51.7-67.8 % of the sacubitril dose was excreted in urine and 36.9-48.3 % was in

[10] DIOVAN USPI: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021283s044lbl.pdf

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feces, suggesting renal excretion is the predominant route of elimination for LBQ657, the neprilysin inhibitor.

About 83 % of valsartan and its primary metabolite were excreted in feces, with about 13 % recovered in urine, suggesting that renal route is not dominant for valsartan excretion. This is supported by the results of the renal impairment study (See Section 2.4.1.2). Given the low bioavailability, the contribution of hepatic route in the elimination via biliary excretion cannot be clearly identified. However, the results of the hepatic impairment study suggest that hepatic route is important for valsartan (See Section 2.4.1.3).

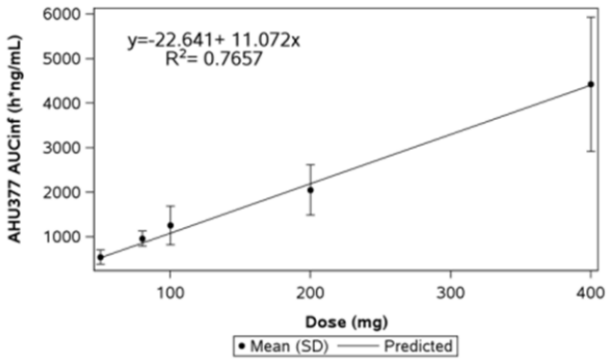
2.3.7 How does the PK of the drug and metabolite(s) in healthy volunteers compare to that in patients?

The applicant conducted a pooled PK analysis using two Phase II studies in patients with heart failure and five clinical pharmacology studies in healthy subjects following 200 mg BID LCZ696 (Studies A2117, B2111, B2112, B2115, B2116, B2128, and B2223). The AUC_{12h} of sacubitril, LBQ657 and valsartan was higher by about 55 %, 110 % and 132 % in patients with heart failure (N~43), compared to healthy subjects (N~144). The observed increase in exposure was attributed to organ impairment (renal/hepatic) seen in patients with heart failure.

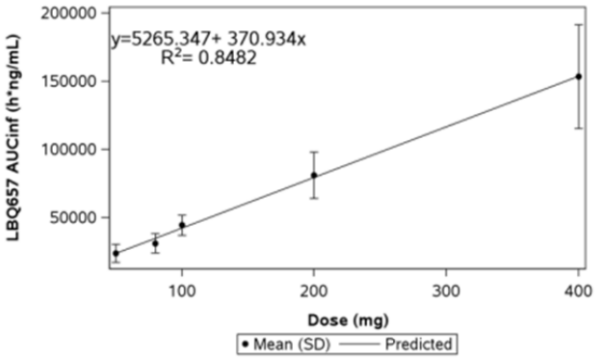
2.3.8 Based on the PK parameters, what is the degree of linearity or non-linearity in dose-concentration relationship?

The exposures (AUCs) of sacubitril, LBQ657 and valsartan from LCZ696 were linear in the dose range of 50-400 mg of LCZ696 (Figure 6). Deviation from dose linearity was observed at higher dose levels (1200 mg) for valsartan and sacubitril (See Section 2.3.2).

Sacubitril



LBQ657



Valsartan

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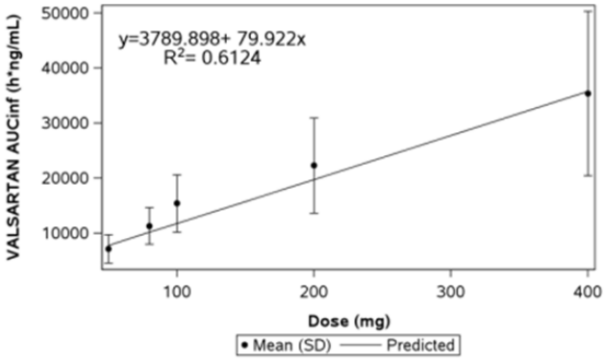

Figure 7 Dose vs. AUC relationship of LCZ696 analytes in healthy subjects

Source: 2.7.2 Summary of clinical pharmacology studies, Figure3-1, Page 84

2.3.9 What is the variability of PK parameters and what are the major causes of variability?

The reported inter individual variability (% CV) for AUC_{12h} at steady state from a pooled analysis (N~144) were 34 %, 29 % and 48 % for sacubitril, LBQ657 and valsartan, respectively in healthy subjects. The observed % CV for clearance (CL/F) was 46 %, 36 % and 55 % for sacubitril, LBQ657 and valsartan, respectively. A population analysis conducted by the applicant identified age, renal and hepatic function as major causes of variability.

2.4 Intrinsic Factors

2.4.1 What intrinsic factors (age, sex, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The treatment benefit associated with LCZ696 in reducing the risk of the composite primary endpoint (CV death or HF hospitalization) when compared to enalapril was consistent across all pre-specified subgroups including intrinsic and extrinsic factors). Similarly, no significant safety risks were reported for any specific subpopulation.

2.4.1.1 Age, Race, Gender and Body weight

In elderly subjects (>65 years), the exposure of LBQ657 and valsartan was higher by 42 % and 30 %, respectively, compared to young subjects, with no significant change in their terminal elimination half-life values. The observed differences in the exposure of the LCZ696 analytes in the elderly are not considered clinically relevant because LCZ696 was safe and well tolerated in the age/gender clinical pharmacology study and in patients > 65 years in the pivotal Phase III

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study. The safety and efficacy of LCZ696 in pediatric patients aged below 18 years has not been established. Race and gender has no significant effect on the PK of LCZ696 analytes. A population PK analysis conducted by the applicant indicated that body weight has no significant impact on the exposure to LCZ696 analytes. Effect of intrinsic factors on valsartan and LBQ657 are shown in Figure 9. No dose adjustment of LCZ696 is required in geriatric/elderly or as per gender or body weight.

2.4.1.2 Renal Impairment

Study A2204 compared the PK of LCZ696 (400 mg once daily for 5 days) in subjects with mild (CrCL 50 to ≤ 80 mL/min) and moderate (CrCL 30 to ≤ 50 mL/min) renal impairment (N=8 per group) with that in matched healthy subjects (N=16). There was no significant increase in C_{max} or AUC_{24h} values in subjects with mild/moderate renal impairment relative to healthy subjects for sacubitril and valsartan. However, the AUC_{24h} for LBQ657 was increased by 110-124 % for mild/moderate renal impairment (Figure 8).

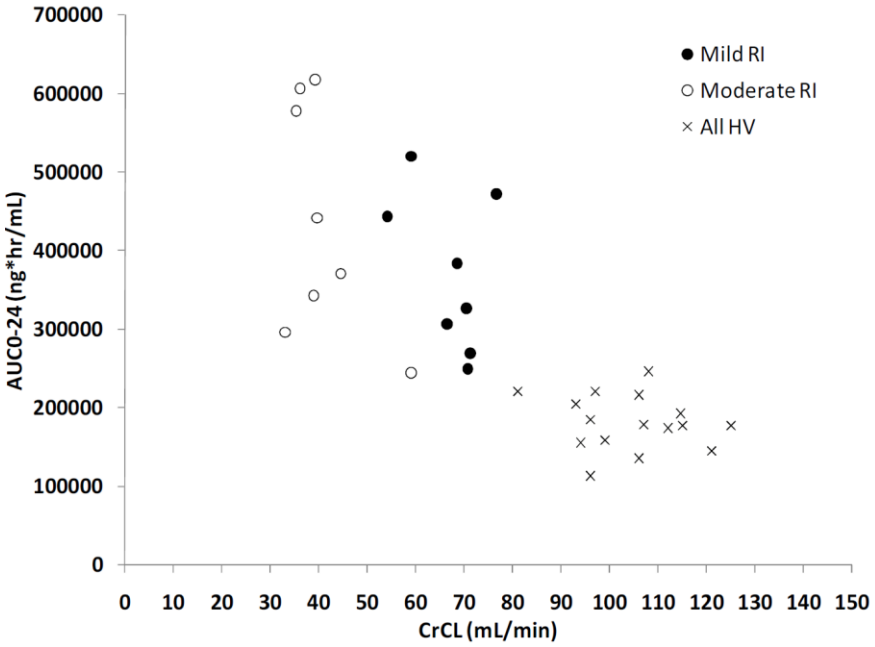

Figure 8 Individual exposures (AUC24h) for LBQ657 and creatinine clearance values. Source: Clinical Study report CLCZ696A2204, Page 57.

The PK of LCZ696 in subjects with severe renal function impairment (CrCL<30 mL/min) was studied separately (Study A2205). Six subjects were enrolled in each group and received 400 mg LCZ696 once daily for 5 days. The exposure to LBQ657 (AUC_{24h}) increased by about 170 % in subjects with severe renal impairment relative to healthy subjects. The increase in exposures (AUC) seen with sacubitril (~30 %) and valsartan (~36%) were not considered significant. Figure

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9 illustrates the influence of renal impairment on the exposure (AUC) to the active moiety LBQ657 and valsartan from LCZ696.

In both Study A2204 and Study A2205, renal impairment was categorized based on creatinine clearance values as per FDA guidance of 1998. The analyses described in this section used the same renal impairment categories as in these dedicated studies and the results are similar when classification as per FDA Guidance 2010 (mild eGFR 60-90, moderate 30-60 and severe <30 mL/min/1.73m^2) was used. So the recommendations described here are applicable to renal impairment categorizations as per 2010 guidance as well. No studies were performed in patients undergoing dialysis. Because of the high plasma protein binding of LCZ696 components, they are not expected to be dialyzable.

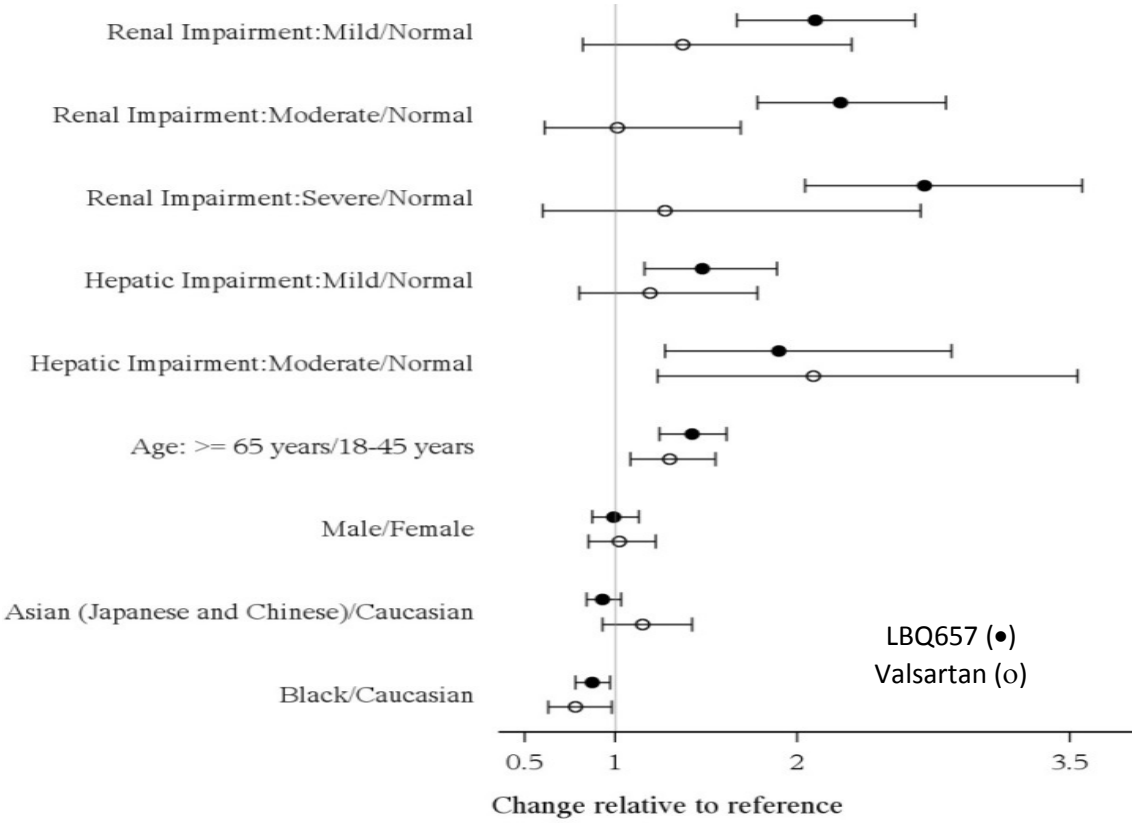

Figure 9 Effect of intrinsic factors on the exposure (AUC) of LBQ657 and valsartan. Source: Summary of Clinical Pharmacology, Page 12.

The Phase III study included patients with mild/moderate renal function impairment. Tables 2A and 2B below show the disposition of patients by their baseline renal function status, who were at target dose and who had dose adjustments during the double blind phase. The proportion of

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patients who required at least one dose reduction related to an adverse event (AE) was higher in those with impaired renal function. However, this trend was seen in both LCZ696 and enalapril treatment group. The number of patients who were maintained on target dose with no dose adjustments was also similar, for each renal function category, between LCZ696 and enalapril groups. These observations suggest that increased exposure to LCZ696 analytes due to reduced renal function may not be the reason behind these dose reductions associated with AEs. Additionally, the clinical benefits of LCZ696 relative to enalapril were similar across different renal function categories, as shown in the Figure 10 below. Therefore, no dose adjustments are proposed for patients with mild or moderate renal impairment.

Table 2 Reasons for study drug dose reduction in patients with varying degree of renal function during double-blind period by treatment group for LCZ696 (A) and enalapril (B) treatment groups

(A) LCZ696	All Patients (N=4203)	CrCL≥80 (N=1726)	50≤CrCL<80 (N=1784)	30≤CrCL<50 (N=631)	CrCL<30 (N=65)
On target dose throughout study duration	2445 (58.2)	1124 (65.1)	1014 (56.8)	291 (46.1)	20 (30.8)
At least one dose reduction	1758 (42.8)	603 (34.9)	771 (43.2)	341 (54.0)	46 (70.8)
Dose reduction due to AEs	1614 (38.4)	506 (29.3)	710 (39.8)	350 (55.5)	47 (72.3)
Hyperkalemia	139 (3.3)	34 (2.0)	62 (3.5)	35 (5.5)	8 (12.3)
Hypotension	415 (9.9)	127 (7.4)	190 (10.7)	92 (14.6)	6 (9.2)
Renal dysfunction	180 (4.3)	38 (2.2)	79 (4.4)	51 (8.1)	12 (18.5)
Angioedema*	13 (0.3)	5 (0.3)	6 (0.3)	2 (0.3)	0
Cough	40 (1.0)	17 (1.0)	15 (0.8)	8 (1.3)	0

(B) Enalapril	All Patients (N=4229)	CrCL≥80 (N=1752)	50≤CrCL<80 (N=1787)	30≤CrCL<50 (N=643)	CrCL<30 (N=51)
On target dose throughout study duration	2433 (57.5)	1122 (64.0)	1010 (56.5)	286 (44.5)	19 (37.3)
At least one dose reduction	1796 (42.5)	631 (36.0)	778 (43.5)	358 (55.7)	33 (64.7)
Dose reduction due to AEs	1635 (38.7)	526 (30.0)	720 (40.3)	353 (54.9)	36 (70.6)

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Hyperkalemia	156 (3.7)	42 (2.4)	82 (4.6)	27 (4.2)	5 (9.8)
Hypotension	300 (7.1)	102 (5.8)	137 (7.7)	57 (8.9)	4 (7.8)
Renal dysfunction	221 (5.2)	37 (2.1)	97 (5.4)	80 (12.4)	7 (13.7)
Angioedema*	9 (0.2)	4 (0.2)	3 (0.2)	2 (0.3)	0
Cough	94 (2.2)	33 (1.9)	47 (2.6)	14 (2.2)	0

* Angioedema or an angioedema-like event. Source: Prepared by FDA.

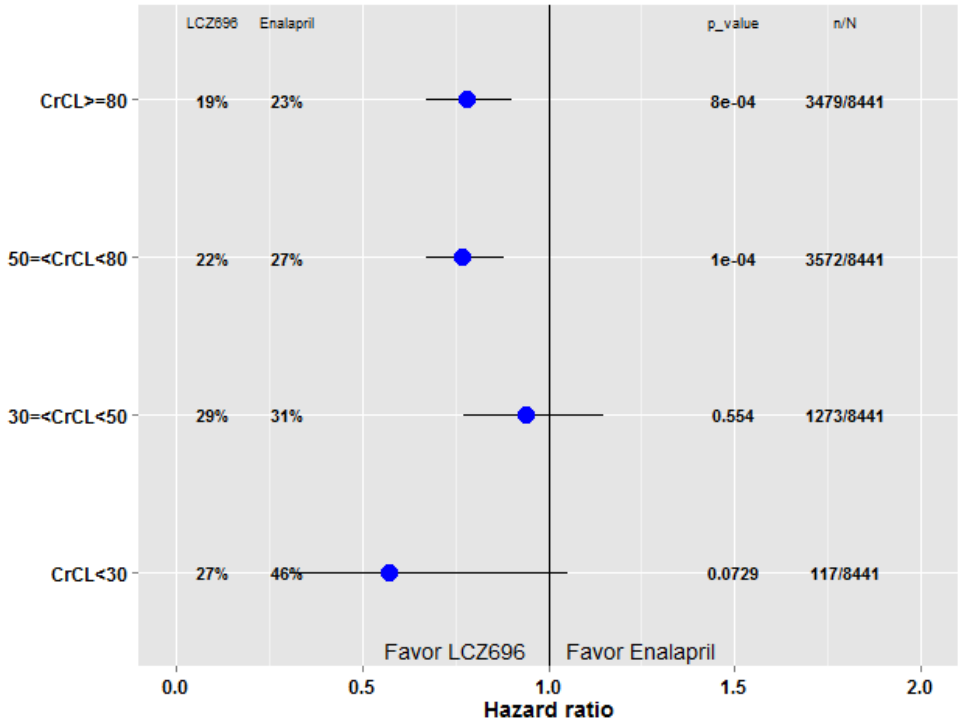

Figure 10 Primary efficacy endpoint by renal function category. Source: Prepared by FDA

LCZ696 is a fixed dose combination of sacubitril (prodrug for LBQ657) and valsartan. Therefore adjusting dose levels for LBQ657 alone without affecting the dose of valsartan is not feasible. The incremental increase in exposure seen in severe renal impairment is 2.7X relative to healthy subjects and is closer to the 2.2X increase seen in moderate renal impairment. There is clinical experience with LCZ696 in patients with moderate renal impairment in Phase III, where no dose adjustments were employed. Since LCZ696 is to be titrated in each patient based on tolerability to the target dose of 200 mg BID, a lower starting dose of 50 mg BID proposed in patients with severe renal impairment.

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2.4.1.3 Hepatic Impairment

Study B2203 evaluated the safety and PK of LCZ696 in subjects with mild and moderate hepatic impairment (Child-Pugh Class A/B) with matched healthy subjects (N=8 per group). No studies were conducted in subjects with severe hepatic impairment (Child-Pugh Class C). The exposures of sacubitril, LBQ657 and valsartan increased by about 53 %, 48 % and 19 %, respectively in mild hepatic impairment relative to healthy subjects. The increase in exposure seen in moderate hepatic impairment was about 245 %, 90 % and 109 % for sacubitril, LBQ657 and valsartan respectively (Figure 9). Sacubitril is an inactive pro-drug and no significant safety issues are reported from toxicology studies (as per PharmTox reviewer). No dose adjustments are proposed for mild hepatic impairment. A lower starting dose of 50 mg BID is recommended in patients with moderate impairment. Use of LCZ696 in patients with severe hepatic impairment is not recommended.

2.4.1.4 What pregnancy and lactation use information is there in the application?

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy can reduce fetal renal function and increase fetal and neonatal morbidity and death. When pregnancy is detected, discontinue LCZ696 as soon as possible. It is not known whether LCZ696 analytes are excreted in human milk. Because of the potential risk to newborns and infants, LCZ696 is not recommended during breast feeding. These recommendations are consistent with the approved label for valsartan.

2.5 Extrinsic Factors

2.5.1 What is the drug-drug interaction (DDI) potential for LCZ696?

The involvement of CYPs for the biotransformation of sacubitril, LBQ657 and valsartan is considered minimal. Therefore, the DDI potential of LCZ696 as a victim with co-administered drugs that may affect CYP system is expected to be low.

2.5.1.1 Is there i*n vitro* basis to suspect drug-drug interactions?

In vitro studies were conducted mainly for the pro-drug sacubitril and the active moiety LBQ657. Sacubitril was relatively high permeable where as LBQ657 was poorly permeable in Caco-2 assays. Sacubitril was considered a low affinity substrate (K_m > 100 uM) for P-gp. Therefore, no significant effects are expected from P-gp inhibitors on the PK of LBQ657.

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Sacubitril did not inhibit CYP1A2, 2C9, 2D6, 2E1 or 3A4/5 when tested at concentrations up to 100 μM. Sacubitril was a weak inhibitor of CYP2C8 and 2C19 with IC_{50} values of 15 and 20 μM respectively. LBQ657 showed weak inhibition for CYP2C9 with IC50 value of about 40 μM.

Sacubitril did not induce CYP1A2, 2B6, 2C9 or 3A4 in human hepatocytes. Sacubitril was converted to LBQ657 during incubation (50 % by 4h and 100 % by 24h) in these studies and LBQ657 also is not expected to be an inducer in this setting. Studies with valsartan showed no induction of CYP1A2, 2B6, 2C9, or 3A4 activities.

Sacubitril was not expected to inhibit BCRP, P-gp or MRP2. *In vitro* studies suggest that sacubitril inhibits OATP1B1 (IC_{50} ~ 1.9 μM) and OATP1B3 (IC_{50} ~ 3.8 μM) transporters. Sacubitril also inhibits OAT1 and OAT3 transporters. At a concentration of 50 μM or 10 μM the transport activity of OAT1 and OAT3 were inhibited by about 37 % and 91 % respectively. Sacubitril was a weak inhibitor of MATE1 in vitro. Sacubitril may increase the systemic exposure of OATP1B1 and OATP1B3 substrates based on the C_{max} (5.9 μM; unbound Cmax ~0.18 μM) observed in patients at LCZ696 200 mg BID.

LBQ657 was an inhibitor and substrate of OAT3. The IC_{50} value for inhibition was about 15 μM. Active transport by OAPT1B1 (K_m ~174 μM) and OAPTP1B3 (K_m not estimated) may contribute to the systemic clearance of LBQ657. LBQ657 is an inhibitor of OATP1B1 (IC_{50} ~ 126 μM) but not OATP1B3. LBQ657 is a weak inhibitor of MATE1 *in vitro*. Neither sacubitril nor LBQ657 is an inhibitor of OCT1 or OCT2.

In summary, based on in vitro studies LCZ696 has the potential to interact with certain transporters (e.g. OATPs) and may interact with drugs those are substrates to these transporters (e.g. atorvastatin).

2.5.1.2 What is the DDI liability for LCZ696?

A total of twelve clinical pharmacology studies were conducted to evaluate the drug interaction potential with drugs that are likely to be co-administered with LCZ696 in HF patients (Table 3). In all these studies, the effect of co-medications on the pharmacokinetics of LBQ657 and valsartan were also monitored as these are the pharmacologically active components of LCZ696. The forest plots of drug interaction study results are presented as effect of LCZ696 on co-administered medicines (Figure 11) and effect of co-administered medicines on active LCZ696 analytes (Figure 12). Please see Section 2.1.3 for currently available therapies for heart failure that may be co-administered with LCZ696.

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Table 3 Drug-drug interaction studies performed for LCZ696

Co-administered drug	Potential mechanism of interaction
Carvedilol	Beta-blocker / CYP2C9, CYP2D6 and Pgp substrate
Furosemide	Loop diuretic / renally excreted, OAT3 substrate
Nitroglycerine	Vasodilator / increases cGMP levels
Digoxin	Cardiac glycoside / Pgp substrate
Warfarin	Anti-coagulant / CYP2C9 substrate
Atorvastatin	Cholesterol-lowering agent / substrate of OATP1B1 and OATP1B3 transporters and CYP3A4.
Metformin	Antidiabetic / OCT1 substrate
Omeprazole	Proton pump inhibitor / substrate of CYP3A4 and CYP2C19
Hydrochlorothiazide	Thiazide diuretic / renally excreted
Amlodipine	Calcium channel inhibitor / hepatic enzyme metabolism
Sildenafil	PDE inhibitor / cGMP inducer
Combination of levonorgestrel/ethinyl estradiol	Combination oral contraceptive / CYP3A4 substrates

Source: Clinical Pharmacology Summary.

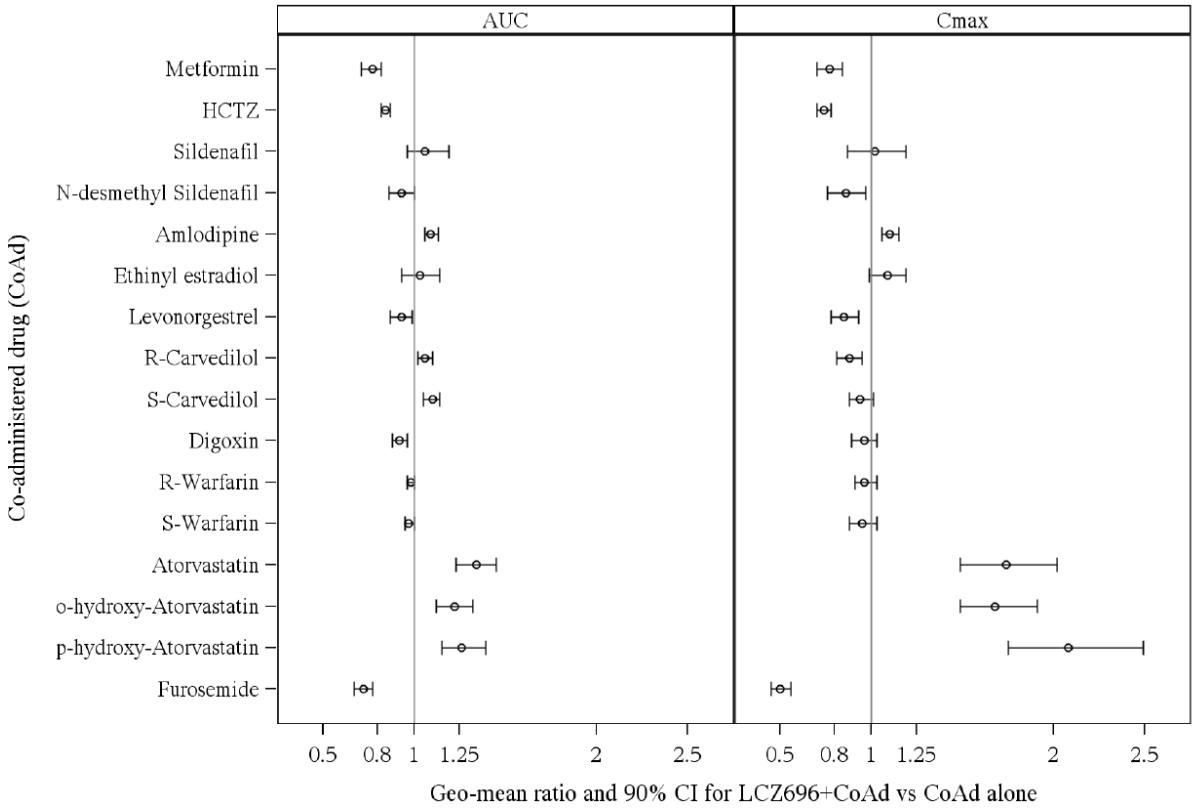

Figure 11 Effect of LCZ696 on pharmacokinetics of co-administered medicines. Source: Clinical Pharmacology Summary.

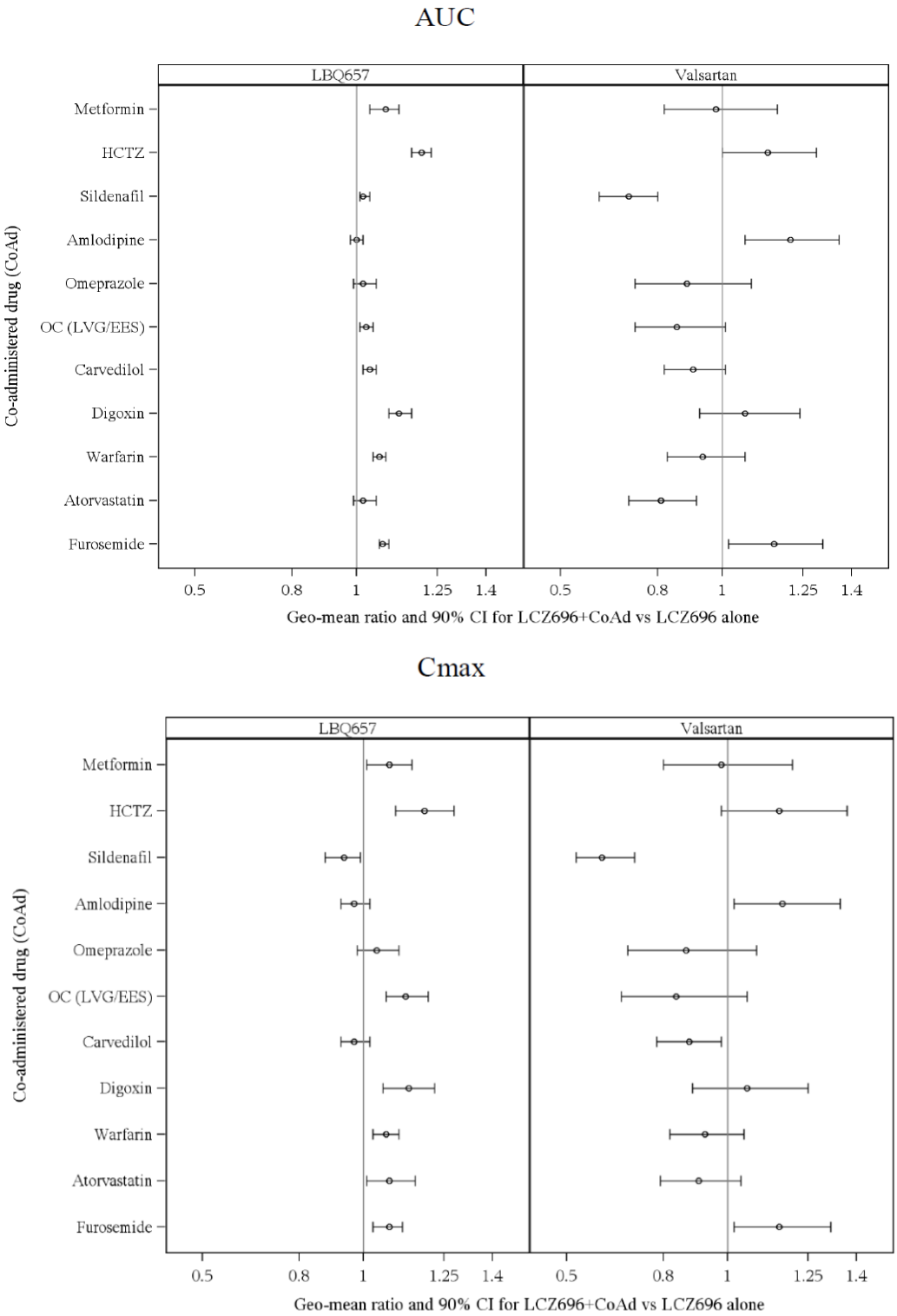

Figure 12 Effect of co-administered medicines on the PK of active LCZ696 analytes. Source: Clinical Pharmacology Summary.

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No clinically relevant interaction was observed when LCZ696 was co-administered with carvedilol, furosemide, nitroglycerine, digoxin, warfarin, metformin, omeprazole, hydrochlorothiazide, amlodipine, and oral contraceptives. Administration of a proton pump inhibitor (omeprazole) did not alter the systemic exposure of any of the LCZ696 analytes, suggesting gastric pH may not affect its absorption.

Co-administration of LCZ696 increased the C_{max} of atorvastatin and its metabolites by up to 2X and AUC by 1.3X. These effects may potentially be due to the OATP1B1 and OATP1B3 inhibitory effects of sacubitril. Atorvastatin was used as a co-medication in the Phase III study for LCZ696 (~ 31 % each in LCZ696 and enalapril treatment arms used atorvastatin or atorvastatin calcium in the safety set) and no significant adverse events related to statins were reported in patients in the LCZ696 treatment group. No dose adjustments are proposed for atorvastatin when co-administered with LCZ696.

Although there was no indication of a PK interaction, co-administration of sildenafil and LCZ696 resulted in additive effect in blood pressure (BP) reduction, due to additive pharmacodynamic effects. A PK/PD study in patients with mild to moderate hypertension (N~27) evaluated single dose of sildenafil 50 mg (period 1), followed by LCZ696 400 mg once daily for 5 days (period 2) and a combination of single dose of 40 mg sildenafil and 400 mg LCZ696 (period 3). Ambulatory blood pressure monitoring (ABPM) was used for BP measurements. The BP results are shown in Table 4 below. Patients should be advised about possible adverse effects associated with BP reduction when sildenafil or any other phosphodiesterase-5 inhibitors are used while receiving treatment with LCZ696.

Table 4 Reduction in BP with LCZ696 administered alone and in combination with sildenafil.

Time Interval	Treatment	Mean change from baseline in ABPM (mmHg)	
		SBP	DBP
During the day	LCZ696	-15.4	-7.1
	LCZ696 + sildenafil	-21.8	-11.4
24- hour	LCZ696	-16.9	-8.0
	LCZ696 + sildenafil	-22.3	-11.8

Source: Adapted from Clinical study report CLCZ696B2225

2.5.1.3 Food effect

Food intake did not alter the bioavailability of sacubitril or LBQ657, but exposure of valsartan decreased by about 40 % from LCZ696. This observation is in agreement with the food effect reported for commercially available valsartan formulations. However, this change is not

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considered clinically significant and LCZ696 can be taken with or without food, as done in the pivotal efficacy study.

2.6 Other relevant issues

2.6.1 What are the common reasons for dose reduction during the double blind period in the Phase III study?

The target dose of LCZ696 was 200 mg BID. Patients were to be titrated based on tolerability to the target dose, starting with 50 mg or 100 mg BID, with dose doubling every 2-4 weeks. The target dose of enalapril was 10 mg BID. The majority of patients in both the LCZ696 and enalapril treatment groups maintained study drug at the target dose level throughout the study duration (58.2% vs. 57.5%, respectively). Similar proportions of patients in the LCZ696 and enalapril groups had a dose reduction at least once during the trial (41.8% vs. 42.5%, respectively) as shown in Table 5 below.

Table 5 Reasons for study drug dose reduction during double-blind period by treatment group

	LCZ696 (N=4203) n (%)	Enalapril (N=4229) n (%)	Total (N=8432) n (%)
Patients at target dose throughout study duration	2445 (58.17)	2433 (57.53)	4878 (57.85)
Patients with at least one dose reduction	1758 (41.83)	1796 (42.47)	3554 (42.15)
Dose reduction due to adverse event[1]	1388 (33.02)	1409 (33.32)	2797 (33.17)
Hyperkalemia	139 (3.31)	156 (3.69)	295 (3.50)
Hypotension	412 (9.80)	297 (7.02)	709 (8.41)
Renal dysfunction	179 (4.26)	219 (5.18)	398 (4.72)
Angioedema or an angioedema-like event	13 (0.31)	9 (0.21)	22 (0.26)
Cough	40 (0.95)	93 (2.20)	133 (1.58)

(1) – A patient may have multiple reductions with the same reason. This reason only counts once for each patient.

Source: Clinical safety summary report, Page 76, Table 2-8

The number of patients who had dose reductions due to AEs was similar between the LCZ696 and enalapril groups (33.0% vs. 33.3%, respectively), and the most common AEs causing dose reductions were hypotension, renal dysfunction, and hyperkalemia. Fewer patients had dose interruption of study treatment due to cough, renal dysfunction or hyperkalemia in the LCZ696 group compared to the enalapril group (0.95% vs. 2.2%; 4.3% vs. 5.2%; 3.3% vs. 3.7%; respectively).

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2.6.2 What percentage of patients stayed on the target dose during the double-blind period?

The percent of patients on target dose for LCZ696 is analyzed by visit as shown in Figure 13 below. The majority of the patients were on target dose for each visit. The percent of patients off target dose was slightly increased over time. However, it should be noted that the patients who died during double-blind period were excluded from the calculation for each visit, resulting in the total number of patients decreasing over time.

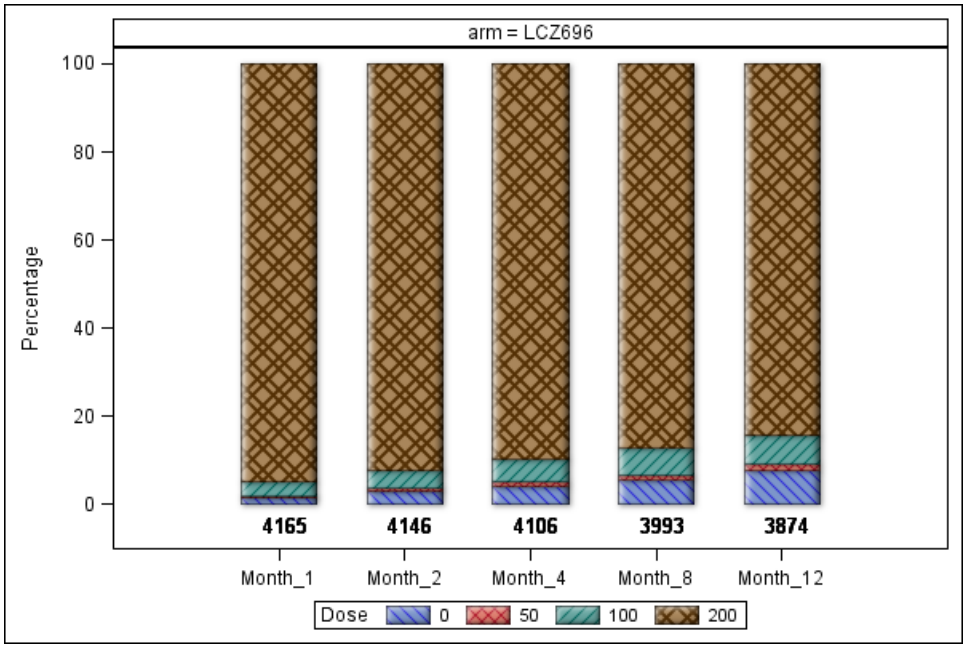

Figure 13 Percent of patients on different dose levels per visit (months 1, 2, 4, 8 and 12) during the double-blind period by treatment. The dose of "0 mg" represents a scenario that the patient discontinued the study medication but was still in the trial and had follow-up visits. Source: Prepared by FDA

2.6.3 How long were patients off the target dose when they had a dose reduction?

To address this question, the study population was separated into two groups: patients who completed treatment and patients who discontinued treatment. Within each group, patients were further separated to those who were alive or who died during the double-blind period. The percentage of time on the target dose for each patient was calculated for the four groups within each treatment arm (completed/alive, completed/died, discontinued/alive, discontinued/died) and are summarized in Table 6. The number of days that the patients were on the target dose was used as the numerator and the number of days that patients stayed in

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the trial was used as the denominator. Around 58 % of the patients completed the trial and were on the target dose throughout the entire study (See Section 2.6.1). Of these, 51.7 % were alive and 6.1 % died while on treatment. Of the patients who completed the study, 8.4 % were on the target dose for < 50% of the time (7.4 % alive and 1.0 % died). These patients probably had a dose reduction and did not return to the target dose for an extended period of time, if at all. For the group of patients who discontinued treatment, as expected, almost half of the patients were off the target dose for more than 50 % time.

Table 6 Percent of patients on the target dose during double-blind period by treatment group

	LCZ696 (n=4201)				Enalapril (n=4228)			
% time on target dose	Completed		Discontinued		Completed		Discontinued	
	Alive	Died	Alive	Died	Alive	Died	Alive	Died
100 %	51.7	6.1	1.2	0.6	50.0	7.6	1.2	0.5
90-100 %	7.5	1.9	0.8	2.1	6.8	1.7	0.9	2.3
50-90 %	5.7	1.0	3.3	2.2	5.7	1.1	3.2	2.8
<50 %	7.4	1.0	5.6	2.1	5.7	1.5	6.8	2.2
Total	72.2	10.0	10.9	7.0	68.2	11.9	12.1	7.8

Source: Prepared by FDA

2.6.4 What is the impact of dose reductions in the efficacy of LCZ696?

The survival rates of patients on the target dose throughout the study or with at least one dose reduction were compared using Kaplan-Meier plot as shown below (Figure 14). The baseline demographic characteristics of the two groups are summarized in Table 7.

Table 7 Baseline patient characteristics

		LCZ696 (N=4203)		Enalapril (N=4229)	
		Target dose (N=2445)	Reduced dose (N=1758)	Target dose (N=2433)	Reduced dose (N=1796)
Age at screening (years) (Median)		63	66	63	65
Age≥65 years (%)		44.7	56.4	44.7	53.8
Gender, male (%)		78.5	79.5	77.3	77.4
LVEF> 35% at screening		9.8	13.3	10.2	13.5
NYHA class at randomization	Class I	4.8	4.1	5.8	4.2
	Class II	72.9	69.8	69.9	68.7
	Class III	21.4	26.3	24.0	26.5
	Class IV	1.1	0.8	0.8	0.7
eGFR≥60mL/min/1.73m^2 at randomization		69.3	54.7	70.5	54.8
Hypertension status at screening		70.1	71.7	70.6	70.7

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Diabetic status at randomization	32.5	37.7	32.5	37.4
Atrial fibrillation at randomization	25.6	26.5	25.5	26.2
Prior HF hospitalization	61.6	63.1	62.9	63.9
Prior use of ACEi	78.1	77.7	78.6	76.1
Prior use of ARB	21.9	22.8	21.9	24.3
Diuretic use at randomization	79.1	82.0	78.7	82.1
Beta blocker use at randomization	93.7	92.4	94.0	91.4
ICD	11.8	19.1	12.3	17.9
CRT	5.2	9.4	5.6	8.2

Source: Prepared by FDA

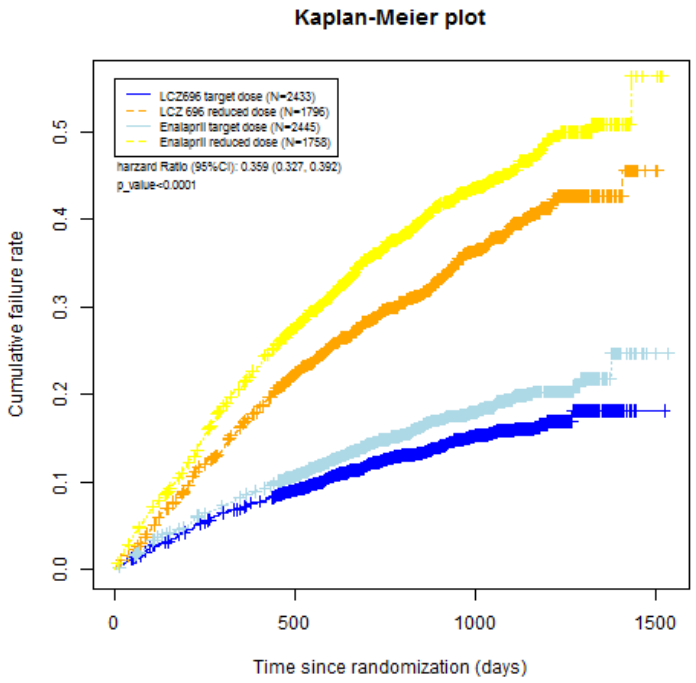

Figure 14 Kaplan-Meier plot for patients on the target dose or with dose reduction. Source: Prepared by FDA

Although the patients on the target dose during the double-blind period have an overall better survival rate compared to those with at least one dose reduction for both LCZ696 and enalapril treatment groups, the baseline demographic features showed that the patients with dose reduction are relatively sicker (based on Age, LVEF,NYHA, GFR, ICD and CRT use). However, if we compared patients with dose reduction between treatment arms, we observed that these patients had similar baseline demographics but the patients in the LCZ696 treatment arm had a

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numerically better survival rate. The similar finding could also be identified in patients on the target dose throughout the study. Although the dose reduction may have occurred due to AEs during the double-blind period, LCZ696 still retained clinical benefits compared to enalapril.

2.6.4 Does LCZ696 increase Amyloid-β levels in the brain or CSF?

Amyloid-β is generated in the brain through sequential cleavage of amyloid precursor protein by β- and γ-secretases. Amyloid-β is removed from the brain my multiple process, including transport in cerebrospinal fluid (CSF) and plasma and by degradation[11]. *In vitro* and non-clinical studies suggested neprilysin as one of the enzymes involved in the degradation of amyloid-β. Amyloid-β deposition is brain is thought to increase the risk for Alzheimer's disease. Since LCZ696 can cross blood brain barrier there is a possibility that neprilysin inhibition by LCZ696 may affect the clearance of amyloids.

To evaluate this possibility, a placebo controlled study in healthy subjects with 400 mg once daily LCZ696 dose for 14 days was conducted (Study A2126, N~39). Peak CSF and plasma levels of LBQ657 were seen by 8 h and 2 h post dose, respectively. Average C_{max} at steady state in CSF and plasma were approximately 19 ng/mL and 14100 ng/mL, respectively. The change from baseline of CSF amyloid-β 1-40 $AUEC_{0\text{-}36h}$ and $AUEC_{0\text{-}24h}$ on Day 14 was not different between LCZ696 and placebo. There was about 50 % increase in plasma amyloid-β ($AUEC_{0\text{-}36h}$) 1-40 with LCZ696 relative to placebo. There was no significant difference with LCZ696 for amyloid-β 1-42 in CSF. However, CSF amyloid-β 1-38 $AUEC_{0\text{-}36h}$ increased from baseline with LCZ696by about 42% relative to placebo. In the Phase III study, incidence of adverse events in both narrow and broad dementia Standardized MedDRA Query (SMQ) was similar between LCZ696 and enalapril groups (0.29 % vs 0.35 % and 2.1 % vs 2.0 %)[12]. Clinical significance of these findings is not known.

2.7 Biopharmaceutics

2.7.1 What are the characteristics of the bioanalytical method(s) used in the clinical pharmacology studies?

Validated LC-MS/MS methods were used for the quantification of sacubitril, LBQ657 and valsartan in plasma and urine. Validation parameters included specificity, matrix effect, recovery, carry over, accuracy, precision and stability and were within acceptable limits (Table 8).

[11] Clinical study report CLCZ696A2126
[12] Clinical study report CLCZ696B2314

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Table 8 Snap shot of validation parameters for LCZ696 analytes

Analytes/Parameters	Sacubitril	LBQ657	Valsartan
Range	1-1000 ng/mL (plasma) and 10-10000 ng/mL (urine)		
Accuracy (intra-day)*	-3.7 – 7.0 %	-8.8 - -1.8 %	-1.2 – 4.0 %
Precision (intra-day)*	5.2 – 6.7 %	5.9 - 8.7 %	2.9 – 5.8 %
Accuracy (inter-day)**	1 %	-4.5 %	1 %
Precision (inter-day)**	7.2 %	7.6 %	4.5 %
Stability – in plasma extracts at 10C	96 h		
Stability – in plasma QC samples at -20C	~ 5 months and stable for 3 freeze-thaw cycles		
Average recovery	66 %	63 %	61 %

*For plasma, at LLOQ. Accuracy and precision values at other levels were within acceptable limits.

** Average value, for plasma, Validation parameters in urine was also within acceptable limits.

Source: Reports DMPK-R0600891, DMPK-R0700990

2.7.2 How is the final marketing image formulation bridged to the Phase III formulation?

The pivotal efficacy study PRADIGM-HF used 50 mg, 100 mg and 200 mg dose strengths of LCZ696. The 100 mg and 200 mg tablets were the final marketing image (FMI) formulations. The 50 mg tablet used in phase III was a clinical service form (CSF) tablet. The applicant performed a pivotal bioequivalence (BE) study for the 50 mg CSF and FMI tablets (Study A2114). This was a randomized, open-label, single-dose, two-treatment, two-sequence, three-period, replicate, cross-over study in healthy subjects (N=84). The reported geometric mean ratio and 90 % CI for AUC_{last}, AUC_{inf} and C_{max} for LCZ696 analytes (sacubitril, LBQ657 and valsartan) were within the BE acceptance criteria. OND-QA Biopharmaceutics team is currently reviewing this study.

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/s/

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05/14/2015

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05/15/2015

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

The applicant is seeking approval for LCZ696 for the treatment of heart failure (NYHA class II-IV) [redacted] (b) (4). LCZ696 is a [redacted] (b) (4) and upon oral administration dissociates into valsartan and a prodrug called sacubitril. Sacubitril further metabolizes to LBQ657. LBQ657 is an angiotensin receptor neprilysin inhibitor. Valsartan is an angiotensin receptor blocker. Simultaneous effects of valsartan and LBQ657 on the cardiovascular system is hypothesized to be beneficial in patients with heart failure (HF). The proposed target dose of LCZ696 is 200 mg (97 mg sacubitril/103 mg valsartan) twice daily. The single pivotal efficacy trial called PARADIGM-HF demonstrated a relative risk reduction of 20 % ($p<0.0001$) compared to enalapril 10 mg twice daily for the primary efficacy endpoint (cardiovascular death and hospitalization for worsening HF). LCZ696 also demonstrated a 20 % relative risk reduction in CV mortality relative to enalapril. The NDA includes 44 *in vivo* studies, 18 *in vitro* study reports, a pop-PK analysis report, PK/PD reports and 12 bioanalytical reports.

	Information		Information
NDA Number:	**207620**	**Brand Name:**	**TBD**
OCP Division (I, II, III, IV, V):	**I**	**Generic Name:**	**LCZ696 (sacubitril/valsartan)**
Medical Division:	**DCRP**	**Drug Class:**	**Neprilysin inhibitor & angiotensin receptor blocker**
OCP Reviewer:	**Sreedharan Sabarinath**	**Indication:**	**Heart Failure** [redacted] (b) (4)
OCP Team Leader:	**Rajanikanth Madabushi**	**Dosage Form:**	**Immediate release tablets**
Pharmacometrics Reviewer: Team Leader:	**Luning Zhuang Jeffry Florian**	**Dosing Regimen:**	**Starting dose of 100 mg twice daily (or 50 in some cases), with doubling the dose every 2-4 weeks to the target dose of 200 mg twice daily**
Date of Submission:	**December 17, 2014**	**Route of Administration:**	**Oral**
Estimated Due Date of OCP Review:	**May 15, 2015**	**Sponsor:**	**Novartis**
Medical Division Due Date:	**May 15, 2015**	**Priority Classification:**	**Priority**
PDUFA Due Date:	**August 16, 2015**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies/reports submitted	Number of studies reviewed	Critical Comments, if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	12		12 bioanalytical reports

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I. Clinical Pharmacology				
Mass balance:	x	1		CLCZ696B2105
Isozyme characterization:	x			Section 4 2 2.4 metabolism ADME-US-R0300251 ADME-US-R0300249
Blood/plasma ratio:	x			
Plasma protein binding:	x			DMPK R0300065
Pharmacokinetics (e.g., Phase I) -	x			
Healthy Volunteers-				
single dose:	x	2		CLCZ696A1101-SAD Japanese, 20-600 mg LCZ696A2101 – SAD 5-80 mg
multiple dose:	x	3		LCZ696A2102 – MAD 200-900 mg CLCZ696B2115 – Chinese Atorvastatin/SAD/MAD (b) (4) – sacubitril/valsartan
Patients-				
single dose:				
multiple dose:	x	12		CLCZ696B2223 – Na excretion in HF and hypertension CLCZ696B2207 Metabolic effects, obese hypertensive LCZ696A2222 – Salt sensitive hypertension CLCZ696A2201-Hypertension CLCZ696A2219 – Hypertension CLCZ696A2219E1 – Hypertension, extension study CLCZ696A2223 – Systolic hypertension LCZ696A1306 – Hypertension LCZ696A2316 – Hypertension LCZ696A2319 – Hypertension LCZ696A1305 – Japanese hypertensive with renal dysfunction (b) (4) – Hypertension – sacubitril
Dose proportionality -				
fasting / non-fasting single dose:	x			
fasting / non-fasting multiple dose:	x			
Drug-drug interaction studies -				
In-vivo:	x	12		CLCZ696B2115 – Atorvastatin CLCZ696B2122 – Japanese Metformin CLCZ696A2119 – Amlodipine CLCZ696A2120 – HCTZ CLCZ696B2111 – Digoxin CLCZ696B2112 – Warfarin CLCZ696B2113 – Omeprazole CLCZ696B2125 – Carvedilol CLCZ696B2116 – Furosemide CLCZ696B2128 – NTG CLCZ696A2124 – Oral contraceptive CLCZ696B2225 – Sildenafil
In-vitro:	x	17		Section 4 2 2.6 17 study reports for inhibition/induction for CYPs and transporters for LBQ657/sacubitril/valsartan
Subpopulation studies -				
ethnicity:	x			
gender:	x	1		CLCZ696B2109 – Age/gender
pediatrics:				
geriatrics:				

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renal impairment:	x	3		CLCZ696A2204 – Mild/moderate RI CLCZ696A2205 – Severe RI *LCZ696A1305 – Japanese hypertensive with renal dysfunction*
hepatic impairment:	x	1		CLCZ696B2203 – Mild/moderate HI
PD -				
Phase 1	x	2		CLCZ696A2126 –Beta amyloid CLCZ696B2123 TQT study
Phase 2:	x	3		CLCZ696A2117 – Tolerability HF CLCZ696B2214 – HF preserved EF vs valsartan CLCZ696B2228 – TITRATION
Phase 3:	x			CLCZ696B2314 – P3
PK/PD -				
Phase 1 and/or 2, proof of concept:	x			*CLCZ696A2117 – tolerability HF* PK/PD reports from multiple studies
Phase 3 clinical trial:	x			
Population Analyses -				
Data rich:				
Data sparse:	x	1		Pop-PK report
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	2		CLCZ696A2103 – LCZ696 400 mg vs Diovan 320 mg CLCZ696B2126 – (b) (4) mg vs FMI 200 mg
Bioequivalence studies -				
traditional design; single / multi dose:	x	1		CLCZ6962114 for 50 mg FMI vs 50 mg P3 CSF – Pivotal BE Study
replicate design; single / multi dose:				
Food-drug interaction studies	x	1		CLCZ696B2107 – LCZ696 400 mg
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	x			A waiver request was submitted with iPSP agreed on 06/13/2014
Literature References				
Total Number of Studies		**44***		

**in vivo* clinical studies only, does not include *in vitro* studies/Pop-PK/PK-PD reports/bioanalytical reports

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	**Content Parameter**	**Yes**	**No**	**n/a**	**Comment**
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			For FMI 50 mg vs P3 CSF 50 mg. P3 CSF 100 & 200 mg strengths are same as FMI.
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	x			Information submitted
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	x			PK characterized
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			x	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	x			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	x			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	x			Datasets are available as PDF for clinical pharmacology studies. IR sent requesting datasets in .xpt format.
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	x			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	x			
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	x			

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	Content Parameter	Yes	No	n/a	Comment
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	Datasets are available as PDF for clinical pharmacology studies. IR sent requesting datasets in .xpt format.
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
3	Is the appropriate pharmacokinetic information submitted?	x			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			Titration based on tolerability is the strategy.
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		x		Limited PK data collected in P3
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		x		See comments to Q5
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Waiver request submitted with agreed iPSP (06/13/2014)
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	See comments to Q7.
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			Information adequate for describing the PK in the label. ER analyses not conducted; see comments to Q5.
	General				
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

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IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes, the application is fileable.

The following information request was sent to the applicant on 01/26/2014.

(1) Please provide concentration-time data for the following studies in analysis ready .xpt format, along with a define file explaining the variables. You should also provide a PK dataset in .xpt format with individual PK parameters for these studies.
- Renal Impairment Studies LCZ696A2204 and LCZ696A2205
- Hepatic Impairment Study LCZ696B2203
- Extrinsic factor studies LCZ696A2119, A2120, A2124, B2107, B2111, B2112, B2113, B2116, B2122, B2125, and B2128
- Study LCZ696A2102

(2) Please provide analysis-ready PK/PD datasets, define files, control streams and output files for biomarkers (such cGMP, ANP, NT-pro-BNP) used for dose selection for the phase 3 study PARADIGM-HF.

Sreedharan Sabarinath Reviewing Clinical Pharmacologist	01/26/2014 Date
Rajanikanth Madabushi Team Leader/Supervisor	01/26/2014 Date

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

/s/

SREEDHARAN N SABARINATH
01/27/2015

RAJANIKANTH MADABUSHI
01/27/2015