24 September 2015
EMA/671279/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Entresto

International non-proprietary name: SACUBITRIL / VALSARTAN

Procedure No. EMEA/H/C/004062/0000

Note

Assessment report as adopted by the CHMP with all information of commercially confidential nature deleted.

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List of abbreviations

Aβ	Amyloid beta
AAS	Atomic absorption spectroscopy
ACE	Angiotensin converting enzyme
ACEi	Angiotensin converting enzyme inhibitors
AD	Alzheimer's disease
ADR	Adverse drug reaction
AE	Adverse event
AHU377	Sacubitril, pro-drug that is metabolized to LBQ657
AGP	Acid glycoprotein
AL(U)	Aluminium
ANP	Atrial natriuretic peptide
API	Active Pharmaceutical Ingredient
APP	Aminopeptidase P
APP	Amyloid beta precursor protein
AR	Assessment Report
ARB	Angiotensin II receptor, type 1 blocker
ARNi	Angiotensin receptor neprilysin inhibitor
AT1R	Angiotensin II receptor, type 1
AUC0-t	Area under the serum concentration-time curve from time zero to time t, using the log-linear trapezoidal rule. Concentrations below the LOQ are set to zero and therefore excluded from the calculation. Actual sample collection times are used. Where 0-t is shown as t this denotes the AUC under a dosing interval
AUC0-∞	Area under the serum concentration-time curve from time zero to infinity. For extrapolation to infinity Clast /λz is used, where Clast is the estimated concentration at the last sample time point above LOQ from linear regression of the terminal elimination phase
AUEC	Area under the effect curve
BID	Bis in die, twice a day
BK	Bradykinin
BMD	Bone mineral density
BNP	B-type natriuretic peptide

BP	Blood pressure
BUN	Blood urea nitrogen
CEC	Clinical Endpoint Adjudication Committee
cGMP	Cyclic guanosine monophosphate
CHF	Chronic heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Cl/F	Clearance for extravascular administration
Cmax	Maximum serum concentration
CNP	C-type natriuretic peptide
CNS	Central nervous system
CPMP	Committee for Proprietary Medicinal Products
CSF	Cerebrospinal fluid
CSF	Clinical Service Form
CV	cardiovascular
CYP	Cytochrome P450
DMC	Data Monitoring committee
DPP-4	Dipeptidyl peptidase-4
DSC	Differential scanning calorimetry
DSS	Dahl Salt Sensitive (strain of rat)
dTGR	Double-transgenic rat overexpressing human renin and angiotensinogen
EAIR	Exposure-adjusted incidence rate
EC	European Commission
EC50	Half maximal effective concentration
ECG	Electrocardiogram
EDQM	European Directorate for the Quality of Medicines
EFD	Embryo-fetal development
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D	EuroQol quality of life questionnaire
ERA	Environmental Risk Assessment

ERPF	Estimated renal plasma flow
EU	European Union
EWP	Efficacy Working Party
FAS	Full analysis set
FDA	Food and Drug Administration
FMI	Final Market Image
GC	Gas chromatography
GCP	Good clinical practice
GFR	Glomerular filtration rate
GLP	Good laboratory practice
GMP	Good manufacturing practice
GPCR	G -protein -coupled receptor
HanWist	Wistar Hannover
HCTZ	Hydrochlorothiazide
hERG	Human ether-a-go-go-related gene
HF	Hart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HPLC	High performance liquid chromatography
HR	Hazard Ratio
IC50	Half maximal inhibitory concentration
ICD	Implantable cardioverter defibrillator
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma
IR	Infrared
IU	International Units
KCCQ	Kansas City Cardiomyopathy Questionnaire
KF	Karl Fischer titration
Ki	Equilibrium dissociation constant for an enzyme inhibitor
KIM-1	Kidney injury molecule-1

LBQ657	ctive metabolite of sacubitril, a neprilysin inhibitor
LC-MS/MS	Liquid chromatography – tandem mass spectrometry
LCZ696	sacubitril/valsartan
LCZ696-ABA	LCZ696 sodium salt hydrate, crystal modification A
LD50	Lethal dose, 50%
LOQ	Limit of quantification
LSM	Least square mean
LVEF	Left-ventricular ejection fraction
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MEB	Medicines Evaluation Board
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Myocardial infarction
MPA	Medical Products Agency
MME	Membrane metallo-endopeptidase (neprilysin)
MMP-2	Matrix metalloprotease-2
MPA	Medical Products Agency
MRA	mineralocorticoid antagonist
MRP	Multi-drug resistance protein
MS	Mass spectrometry
MTD	Maximal tolerated dose
MTP	Multiple testing procedure
NCO	Nonclinical Overview
NEP	Neutral endopeptidase
NEP-2	Neprilysin-2
NLT	Not less than
NMQ	Novartis MedDRA Query
NMT	Not more than
NMR	Nuclear magnetic resonance
NOAEL	No observable adverse effect level

NOEL	No observable effect level
NP	natriuretic peptide
NPR-A	Natriuretic peptide receptor-A
NT-proANP	N-terminal pro-atrial natriuretic peptide
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
OAT	Organic anion transporter
OATP	Organic anion-transporting polypeptide
P-gp	P-glycoprotein
PAR	Proven acceptable range
PD	Pharmacodynamics
PDCO	Paediatric Committee
PDE-5	Phospo-Di-Esterase 5
PDE	Permitted Daily Exposure
PE	Polyethylene
PETP	Polyethyleneterephthalate
Ph. Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PIP	Peadiatric Investigation Plan
PK	Pharmacokinetics
p.o.	Oral
POC	Proof of concept
PopPK	Population pharmacokinetic
pQCT	Peripheral quantitative computed tomography
PRO	Patient-reported outcome
PT	Preferred term
PVC	Poly vinyl chloride
PVdC	Poly vinylidene Chloride
QC	Quality control
QTc	Corrected QT interval
RAAS	Renin-angiotensin-aldosterone system

RAS	Renin-angiotensin system
RH	Relative Humidity
SA	Scientific Advice
Sacubitril	prodrug of LBQ657 (a neprilysin inhibitor), also known as AHU377
SAE	Serious adverse event
SAWP	Scientific Advice Working Party
SBP	Summary of Biopharmaceutic Studies and Associated Analytical Methods
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology Studies
SCS	Summary of Clinical Safety
SHR	Spontaneously hypertensive rat
SHRSP	Stroke-prone spontaneously hypertensive rats
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Query
SNP	Single nucleotide polymorphism
T1/2	Half-life (Elimination half-life)
Tmax	Time to peak concentration
TGA	Thermogravimetric analysis
TIMP-2	Tissue inhibitor of matrix metalloprotease-2
TSE	Transmissible Spongiform Encephalopathy
UACR	Urinary albumin to creatinine ratio
US	United States
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
valsartan	an angiotensin receptor blocker
Vss	volume of distribution at steady state
Vz/F	apparent volume of distribution
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Ltd submitted on 16 December 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Entresto, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 September 2014. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The applicant applied for the following indication:

Entresto is indicated for the treatment of heart failure (NYHA class II-IV) in patients with systolic dysfunction. Entresto has been shown to reduce the rate of cardiovascular death and heart failure hospitalisation compared to angiotensin-converting enzyme (ACE) inhibitor therapy (see section 5.1).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that sacubitril , as part of the fixed dose combination sacubitril/valsartan, was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0106/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0106/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance sacubitril contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 25 June 2009, 24 September 2009, 19 December 2013 and 20 September 2012. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pieter de Graeff Co-Rapporteur: Kristina Dunder

- The application was received by the EMA on 16 December 2014.
- Accelerated Assessment procedure was agreed-upon by CHMP on 20 November 2014.
- The procedure started on 22 January 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 April 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 April 2015. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 7 May 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 18-21 May 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 May 2015. The evaluation procedure was reverted to the standard timetable.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 July 2015
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 01 September 2015.
- During the meeting on 10 September 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 23 September 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Entresto.

2. Scientific discussion

2.1. Introduction

Heart failure (HF) is a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection. It is a major public health problem associated with a high mortality rate, frequent hospitalizations and poor quality of life. HF is a progressive disease characterized by increasing symptoms that lead to repeated hospitalizations and a significantly greater risk of premature death. A total of 1.0 million patients are hospitalized due to HF each year in the US (*Askoxylakis et al 2010*) and in Europe, approximately 5% of all acute hospital admissions are HF-related (*Braunschweig et al 2011*). Approximately 40% of HF patients admitted to the hospital will either die or be readmitted within 1 year and nearly 50% of HF patients die within 4 years of diagnosis (*Dickstein et al 2008*). The overall 5 year survival rate for HF is as poor as or worse than that for advanced cancer or stroke (*Askoxylakis et al 2010, Stewart et al 2010*).

The current standard of care of pharmacologic treatment for HF with reduced ejection fraction (HFrEF) includes angiotensin converting enzyme (ACE) inhibitors (ACEis) as the cornerstone of renin-angiotensin system (RAS)-based therapy in conjunction with β-blockers and/or mineralocorticoid antagonists (MRAs) as tolerated by the patient (*HFSA 2010 Comprehensive Heart Failure Practice Guideline, ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 20122012, 2013 ACCF/AHA Guideline for the Management of Heart Failure*). ACEis reduced the mortality rate by 10-20% compared to placebo in several landmark clinical trials (The CONSENSUS Trial Study Group 1987, The SOLVD Investigators 1991). Evidence for a mortality benefit with angiotensin-receptor blocker (ARB) treatment in HF is inconsistent (*White and Hall 2000*) and considered less robust (*Heran et al 2012*). ACEis are therefore recommended by all major international HF treatment guidelines as the choice of first-line pharmacotherapy for all patients with HFrEF unless they are intolerant, with ARBs as an alternative for those who are unable to tolerate ACEis.

Even with current guideline-recommended HF therapy of RAS blockade, β-blockers and MRAs, mortality and morbidity rates remain high in the HF patient population (*McMurray et al 2012, Sayago Silva et al 2013, Roger 2013, Liu et al 2014*). Therefore, there is a high unmet medical need for new therapies with different mechanisms of action for HF treatment that can provide further reduction in mortality and morbidity and improvement in quality of life as compared to the current standard of care.

Neurohormonal pathways are of critical importance in the pathogenesis and progression of HF. Current HF therapies mainly focus on blocking the detrimental effects of long-term neurohormonal activation (ACEis, ARBs, β-blockers and MRAs) and largely ignore the physiological compensatory effect of the natriuretic peptide system and other endogenous vasodilator systems. Inhibition of neprilysin results in an increase in the activity of natriuretic peptides (NPs) and other vasoactive peptides that potentially exert favorable long-term compensatory effects. However, neprilysin inhibition also leads to an increase of angiotensin II, which is a major mediator of HF development and progression. Therefore, the full compensatory benefit of NEP inhibition can only be leveraged if both the RAS and NEP systems are inhibited simultaneously. Omapatrilat, a dual ACEi/NEPi, was no more effective than an ACEi alone in reducing the risk of death and HF hospitalization in the OVERTURE study of 5,770 HF patients; it was suspected that once-daily dosing of omapatrilat did not provide 24-hour NEP and ACE-inhibition (*Packer et al 2002*). In addition, omapatrilat treatment was associated with an increased incidence of serious angioedema with airway compromise requiring mechanical support (*Kostis et al 2004*).

The LCZ696 HF clinical development program was designed to determine whether treatment with LCZ696 could provide a greater benefit in CV mortality and morbidity reduction compared to an ACEi, in HF patients who have

been well treated with other HF guideline-recommended therapies. The pivotal phase 3 trial CLCZ696B2314 (also known as PARADIGM-HF) was designed to accomplish this purpose.

LCZ696 (sacubitril/valsartan, Entresto) is a novel therapy proposed for treatment of heart failure (HF) (New York Heart Association (NYHA) class II-IV) in patients with systolic dysfunction (reduced ejection fraction, HFrEF). Following oral administration, LCZ696 dissociates into valsartan and the pro-drug sacubitril (also known as AHU377, a new molecular entity), which is further metabolized to the neprilysin inhibitor LBQ657. LCZ696 exhibits the mechanism-of-action of an angiotensin receptor neprilysin inhibitor (ARNI) by simultaneously inhibiting neprilysin (neutral endopeptidase 24.11; NEP) via LBQ657 and blocking the angiotensin II type-1 (AT1) receptor via valsartan, resulting in complementary effects on the cardiovascular (CV) system that are beneficial in HF patients.

LCZ696 is formulated as film-coated tablets and each tablet contains sacubitril and valsartan as sodium salt complex in the following strengths: 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg. The 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg strengths are in some publications/studies referred to as 50, 100 or 200 mg.

The following indication was granted by the CHMP:

Entresto is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

The recommended posology is:

The recommended starting dose of Entresto is one tablet of 49 mg/51 mg twice daily, except in the situations described below. The dose should be doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient.

In addition, in patients not currently taking an ACE inhibitor or an ARB or taking low doses of these medicinal products, a starting dose of 24 mg/26 mg twice daily and slow dose titration (doubling every 3-4 weeks) are recommended. Also, a starting dose of 24 mg/26 mg twice daily should be considered for patients with SBP ≥100 to 110 mmHg. Also patients with other co-morbidities e.g. moderate renal or hepatic impairment are advised to initiate treatment with the lower dose. The CHMP agreed that LCZ696 should not be co-administered with an ACE inhibitor or an ARB. Due to the potential risk of angioedema when used concomitantly with an ACE inhibitor, it must not be started for at least 36 hours after discontinuing ACE inhibitor therapy. Finally, the valsartan contained within LCZ696 is more bioavailable than the valsartan in other marketed tablet formulations.

2.1. Quality aspects

2.1.1. Introduction

Entresto is a fixed-dose combination product presented as film-coated tablets containing sacubitril and valsartan as active substances as a trisodium hemipentahydrate co-crystal. Three strengths are proposed containing 24.3 mg sacubitril and 25.7 mg valsartan (low strength), 48.6 mg sacubitril and 51.4 mg valsartan (middle strength), and 97.2 mg sacubitril and 102.8 mg valsartan (high strength). Initially, the applicant proposed to express the strength of each tablet based on the combined content of both active substances, i.e. 50 mg, 100 mg and 200 mg respectively. However, it was judged by CHMP that since the product is a fixed-dose combination, the content of each active substance should be declared individually.

Other ingredients are:

Tablet core:

Microcrystalline cellulose, low-substituted hydroxypropylcellulose, crospovidone, magnesium stearate, talc and colloidal anhydrous silica.

Film coating:

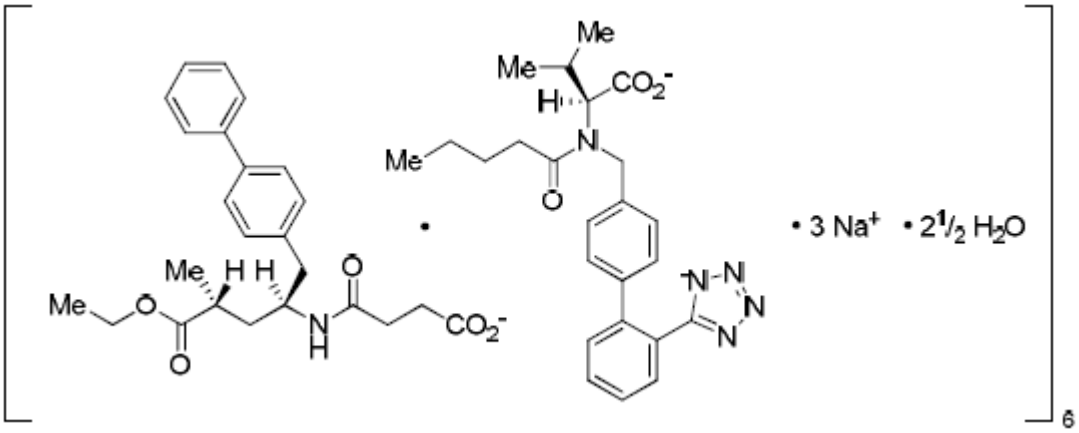
Hypromellose, titanium dioxide (E171), macrogol 4000, talc, iron oxide red (E172), iron oxide black (E172, low and high strength tablets) and iron oxide yellow (E172, middle strength tablets)

The product is available in PVC/PVDC/Aluminium blisters as described in section 6.5 of the SmPC.

2.1.2. Active Substance

General information

The isolated active substance is a co-crystal complex of the sodium salts of two individual active components, sacubitril and valsartan, in hydrated form. The chemical name of the sacubitril-valsartan complex is octadecasodium
hexakis-(4-{[(1*S*,3*R*)-1-([1,1'-biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino}-4-oxobutanoate)
hexakis-(*N*-pentanoyl-*N*-{[2'-(1*H*-tetrazol-1-id-5-yl)[1,1'-biphenyl]-4-yl]methyl}-*L*-valinate)
pentadecahydrate and it has the following structure and properties:



Molecular formula of unit cell: $C_{288}H_{330}N_{36}O_{48}Na_{18}.15H_2O$ - Relative molecular mass: 5747.96 $gmol^{-1}$

The structure of the sacubitril-valsartan complex was inferred from the route of synthesis and confirmed by ^{1}H and ^{13}C NMR spectroscopy (solid and solution state), IR spectroscopy, UV spectroscopy, mass spectrometry, elemental analysis, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), x-ray powder diffraction (XRPD) and x-ray crystallography. The individual active substances were also characterised: the structure of sacubitril was inferred from its route of synthesis and confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, mass spectrometry and chiral HPLC; the structure of valsartan was inferred from its route of synthesis and confirmed chiral HPLC analysis compared to an authentic sample.

The sacubitril-valsartan complex is a white to almost white crystalline powder and is hygroscopic above 60% RH so needs to be protected from water. Solubility was measured for the individual active substances since the

complex dissociates on dissolution which allows the active moieties to act independently *in vivo*. Both active substances exhibit pH dependent solubility in aqueous media, being freely soluble at neutral pH but much less soluble at lower pH. Both are soluble in alcoholic solvents but less so in aprotic organic media.

Sacubitril contains two chiral centres, one of which originates in a starting material, the other being created during the synthetic process and controlled in the subsequent intermediate specification. The single stereocentre in valsartan originates in a starting material. The active substance specification sets limits for all possible stereoisomers of the individual active substances.

Polymorphism has not been observed for the co-crystal complex. The sacubitril-valsartan complex was shown to be stable with respect to changes in polymorphic form in several studies.

Sacubitril is a pro-drug, *in vivo* ester hydrolysis affording the carboxylic acid which is responsible for the therapeutic effect. Both sacubitril and its metabolite can be considered new active substances since neither is structurally related, (as salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives), to any other active substance authorised within a medicinal product in the EU. Valsartan is a known active substance marketed by the applicant in other products within Europe.

Manufacture, characterisation and process controls

The synthesis of the individual active substances is described, along with their subsequent combination to form the co-crystal complex. Valsartan is a well-known active substance covered by a Ph. Eur. monograph. Declarations were provided that the seven manufacturing sites, route of synthesis and specifications of valsartan, (other than particle size which is not relevant, given that it is dissolved in subsequent processing steps), are identical to valsartan used as the active substance in other EU medicinal products for which the applicant is the MAH. A description of the synthetic route, control of impurities and control methods was also provided. A statement to the effect that valsartan is produced under GMP was also provided along with a declaration that any changes to the manufacturing route of valsartan in the applicant's other products will automatically be applied to Entresto. Therefore, in line with the reflection paper the requirements for selection and justification of starting materials for the manufacture of chemical active substances, valsartan is considered acceptable as a starting material for the production of the co-crystal complex.

Sacubitril is synthesized as in multiple steps by four manufacturers using well-defined starting materials with acceptable specifications. The two active substances are then combined in order to generate the co-crystal complex which is then milled or sieved to ensure the correct particle size distribution.

Potential and actual impurities were well discussed with regards to their origin and characterised. The depletion of heavy metals originating from catalysts was demonstrated. The genotoxicity of alerting materials present in the synthetic process was assessed and limits put in place where necessary. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are aligned across manufacturers. Stereoisomers are limited in each intermediate in order to ensure adequate purge throughout the synthetic sequence. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

The active substance is packaged in polyethylene bags which are sealed with plastic closures, placed in quadruple laminated foil bags (PE/PETP/Alu/PETP) which are sealed. To further protect the material, the bags are stored in a metal container. This packaging configuration has been demonstrated to effectively control moisture uptake by the hygroscopic active substance. The primary polyethylene material complies with Ph. Eur. 3.1.3 and Regulation EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identity (IR, UV, XRPD), assay (HPLC – individual components and co-crystal), sodium content (flame AAS), related substances (HPLC), stereoisomers (chiral HPLC), residual solvents (GC), water content (KF), heavy metals (ICP-MS), calcium (flame AAS), chloride (argentometry), microbial quality (Ph. Eur.) and particle size (laser diffraction).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. One impurity is the active metabolite of sacubitril and its limit is set higher accordingly.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on 23 production scale batches of the active substance manufactured at the proposed commercial site using the commercial manufacturing process are provided. The results are within the specifications and consistent from batch to batch. In addition, supportive batch data on an addition 40 batches of the sacubitril-valsartan complex manufactured during development and used in toxicological and clinical studies. The evolution of the manufacturing route and specifications throughout development has been described.

Stability

Stability data on three commercial scale batches of the co-crystal complex from the proposed manufacturers stored in a container closure system representative of that intended for the market for up to 24 months under long term conditions (30 °C / 75% RH), for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. Other packaging formats were also investigated in order to find the optimum protection from water, and the chosen pack was the best. The following parameters were tested: appearance, identity (by XRPD), assay, related substances, stereoisomers, water content, microbial quality and colour and clarity of solution. The analytical methods used were the same as for release, other than the tests for assay, related substances and clarity and colour of solution and were stability indicating. The current analytical method for assay and related substances will be used from the 24 month time point onwards and have been shown to give equivalent results to the methods used at earlier time-points. Colour and clarity of solution was measured for information only. All tested parameters were well within specification at all time-points and no significant trends were observed.

Photostability testing following the ICH guideline Q1B was performed on one batch and the active substance shown not to be photosensitive.

Solid state stress testing was carried out at a range of temperatures and humidities. The co-crystal complex deliquesces at high humidity, more rapidly at increased temperature, along with a decrease in assay and increase in impurities. Forced degradation was carried out in water, aqueous acid, aqueous base, all at reflux, and in aqueous hydrogen peroxide at ambient temperature. Sacubitril degrades under acidic and basic conditions whilst valsartan is susceptible to oxidative degradation.

Additional studies were carried out at 5 ^{o}C / ambient humidity for up to 24 months in order to assess transport conditions. All parameters were within specifications under these conditions.

The stability results indicate that the active substance made by the proposed manufacturers is sufficiently stable. The stability results justify the proposed retest period of 36 months in the proposed container which has been demonstrated to provide sufficient protection from moisture.

2.1.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The aim of development was to identify an immediate release solid oral dosage form of sacubitril and valsartan. The co-crystal form identified by the applicant renders valsartan more bioavailable than in its standalone formulations and the dose was reduced accordingly. Both active substances are highly soluble in aqueous media above pH 5 and show medium permeability.

Early clinical studies used tablets made by direct compression. However, as development continued, an alternative more robust manufacturing method was employed, in order to accommodate the physicochemical properties of the active substance. This dry-granulation roller compaction process was used to supply later trials and the commercial market. Additionally, a film-coating step was introduced, both for taste masking purposes and to easily distinguish between the different strengths based on their colour.

All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards or in-house methods in the case of the non-compendial film coating mixture. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in section 2.1.1 of this report. Compatibility of the active substance with the excipients was demonstrated by a series of binary stability studies.

In order to develop a robust roller compaction step, multivariate experiments were carried out optimising compression force, screen size and the amounts of talc and magnesium stearate. The middle and high strength tablets are dose proportional and were used in pivotal clinical studies. However, low strength formulation was subsequently changed and is not proportional in terms of components with the higher strength tablets. Therefore, a clinical bioequivalence study was carried out in order to bridge from the clinical formulation to that planned for commercialisation.

The dissolution method has been shown to be discriminatory and suitable limits have been included in the specification. However, the appropriateness of the limits will continue to be monitored as more commercial batches are manufactured and they will be re-evaluated if necessary.

The primary packaging is PVC/PVDC/Aluminium blisters. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of six main steps: blending of intra-granular excipients; roller compaction; blending with extra-granular excipients; compression; film-coating; packaging. The process is considered to be a standard manufacturing process. The roller compaction force is critical to tablet hardness and subsequent dissolution and limits have been set accordingly. Similarly, the outlet temperature following film-coating is carefully controlled so as to maintain the desired appearance of the tablets. A stability study was carried out on bulk film-coated tablets and a bulk storage time up 6 months at 25 ^{o}C / 60% RH has been adequately justified.

Proven acceptable ranges (PARs) have been defined for the following steps of the manufacturing process: roller compaction force; compression force; film coating spray rate; outlet temperature. The available development data, the proposed control strategy and batch analysis data from validation batches fully support the proposed PARs and set-points.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls and PARs are adequate for the production of Entresto film-coated tablets.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance, identification (IR, HPLC), identity of colorants (colour reaction, skip testing), mean mass, dissolution (Ph. Eur.), degradation products (HPLC), chiral purity (chiral HPLC), assay (HPLC), uniformity of dosage units (Ph. Eur.) and microbial enumeration (Ph. Eur., skip testing). The major degradant is also an in vivo metabolite and has been qualified. Thus, its proposed limit is acceptable. The absence of a test for water content has been adequately justified as the slightly increased water content observed during stability studies had no impact on product performance. The individual active substances and the co-crystal complex are readily distinguished by the IR method. This ensures that the superior bioavailability conferred by the complex is maintained in the finished product at release and throughout shelf-life.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for more than ten production scale batches of each strength, manufactured at the proposed commercial site and also at a previous development site, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data was provided on three pilot to production scale batches of each strength. The higher strength batches were manufactured at the proposed commercial site whilst the low strength tablets were manufactured at a development site, all using the proposed commercial manufacturing process. The batches of finished product were stored in the proposed commercial packaging for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH), according to the ICH guidelines. Samples were tested for appearance, identity (IR only), dissolution, degradation products, chiral purity, assay and microbial quality. The analytical procedures used are stability indicating. No significant changes or trends to any parameters were observed under either condition, except for a small increase in degradation products for the low strength tablet under accelerated conditions and a slight increase in water content in all strengths. In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results indicate that Entresto is not photosensitive.

One batch of each strength was also tested under the following conditions: 5 ºC / ambient RH; -20 ºC / ambient RH; 50 ºC / ambient RH; freeze/thaw cycles between -20 ºC and 25 ºC / 60% RH. Results showed no significant trends to any of the measured parameters. This study allowed assessment of acceptable transport conditions.

Based on available stability data, the shelf-life of 30 months protected from moisture, as stated in the SmPC are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used. Magnesium stearate is of vegetable origin.

2.1.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. PARs have been defined for parts of the finished product manufacturing process and the proposed set-points and ranges are deemed acceptable. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.1.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The suitability of the dissolution specification should be re-evaluated once sufficient commercial scale manufacturing experience has been gathered. Limits should be tightened if necessary to ensure it remains discriminatory.

2.2. Non-clinical aspects

2.2.1. Introduction

LCZ696 is a first-in-class angiotensin receptor neprilysin (neutral endopeptidase 24.11; NEP) inhibitor (ARNI) intended as an oral treatment for HF in adult patients with reduced left-ventricular ejection fraction , LVEF. LCZ696 is a salt complex comprising sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5 (ratio of 6:6:18:15 in the asymmetric unit cell of the solid-state crystal). Following oral administration, LCZ696 dissociates into valsartan and the pro-drug AHU377 (sacubitril), which is further metabolized to the NEP inhibitor LBQ657. LCZ696 exhibits the novel mechanism of action of an ARNI by simultaneously inhibiting NEP via LBQ657and by blocking the angiotensin II type-1 (AT1) receptor via valsartan. The resulting increase in natriuretic peptide (NP) activity due to NEP inhibition and reninangiotensin-aldosterone system (RAAS) inhibition through AT1 receptor blockade have complementary cardiovascular and renal effects that are considered beneficial in HF.

Neprilysin

NEP exists as an ectoenzyme of the M13 zinc metalloproteinase family, preferentially hydrolyzing extracellular oligopeptides (<5 kDa) on the amino side of hydrophobic residues. NEP cleaves a variety of physiologically

relevant substrates, including enkephalins, tachykinins, chemotactic peptide, adrenomedullin, and the NPs such as atrial natriuretic peptide (ANP), C-type NP (CNP) and to a lesser degree B-type NP (BNP). In mammals, NEP is widely expressed in kidney, lung, endothelial cells, vascular smooth muscle cells, cardiac myocytes, fibroblasts, neutrophils, adipocytes, testes, and brain, with the highest expression in the renal proximal tubule. NEP plays an important role in terminating peptide signalling events at the cell surface and NEP activity has been shown to contribute to ANP's short half-life (2-3 minutes). Inhibition of NEP increases circulating levels of NPs, with the potential to enhance their cardiovascular and renal actions, including reduction of blood pressure, vasodilation, natriuresis and diuresis, increased glomerular filtration and renal blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity, and anti-hypertrophic and anti-fibrotic effects.

Angiotensin II type-1 receptor

AT1 receptors are primarily found in the brain, adrenal glands, heart, vasculature and kidney, and regulate blood pressure and electrolyte balance in response to angiotensin II binding. Competitive blockade of the AT1 receptor by valsartan inhibits the vasoconstrictive actions of angiotensin II, inhibits aldosterone release, reduces sodium and water retention, and inhibits cardiovascular hypertrophy and remodelling.

Concomitant modulation of both systems provides greater suppression of renin and aldosterone release, with the effect of further improving renal function through augmenting natriuresis and diuresis, reducing blood pressure, and inhibiting cardiovascular hypertrophy and vascular remodeling more than is achieved with single-agent therapy.

The non-clinical studies with LCZ696, AHU377 and LBQ657 provided were assessed in the current application. These studies and new studies with valsartan have been assessed and summarised in this AR. In addition, studies on valsartan were provided that were assessed previously at the time of MAA for valsartan. Previously performed preclinical studies with valsartan supported approval of valsartan in the EU from 1996 onwards in indications such as hypertension and post myocardial infarction. Moreover, there is now extensive clinical experience with valsartan. Only new studies with valsartan have been assessed and summarised in the current AR.

The pharmacologic targets of LCZ696 (AT1 receptor and NEP) are evolutionarily conserved across mammalian species. Additionally, although there are some species differences in the rate of hydrolysis of AHU377 to LBQ657, all species are exposed to the same major compounds delivered by LCZ696. LCZ696 has been tested in a range of species including mice, rats, rabbits, and cynomolgus monkeys. The cynomolgus monkey was chosen as the principal nonrodent species for toxicity assessment of LCZ696 based on homology of NEP and NEP substrates to human, but AHU377 has also been evaluated in dogs and marmosets. Toxicology studies in the marmoset with AHU377 provided a basis for comparison to previous valsartan marmoset studies and helped define the specific toxicologic effects of these two LCZ696 components.

The nonclinical **pharmacodynamic (PD)** activity and selectivity of LCZ696 have been characterized in vitro and in vivo pharmacological studies conducted with LCZ696, AHU377, LBQ657, or valsartan. The animal studies were conducted in cardio-renal disease models and demonstrate the effect of the dual-acting LCZ696 on cardiac, renal, and vascular function and organ protection. In addition to these efficacy studies, safety pharmacology studies were conducted with both LCZ696 and AHU377 to assess the effects on the cardiovascular, respiratory, and central nervous systems.

The program of nonclinical **pharmacokinetics (PK)** for LCZ696 included radiolabeled ADME studies in the species used for chronic toxicity or carcinogenicity testing (mouse, rat and cynomolgus monkeys). Both oral and intravenous dosing routes were evaluated in all species to allow estimation of absorption and oral bioavailability. Additional information obtained from the ADME studies included PK parameters of the compounds delivered by

LCZ696 and total radioactivity, routes and rates of excretion, metabolic pathways, mass balance, tissue distribution, placental transfer, and milk excretion. *In vitro* studies with LCZ696 or AHU377, LBQ657, and valsartan detected *in vivo* were performed to assess blood-plasma distribution, plasma-protein binding, enzyme inhibition and induction, and drug transporters.

Studies to profile the **toxicity** of LCZ696 and support its chronic clinical administration have been performed with LCZ696 itself as well as with AHU377 and valsartan. Studies performed with LCZ696, AHU377 and valsartan included repeated-dose toxicity studies, embryo-fetal development studies, fertility studies, and genotoxicity studies. One *in vitro* genotoxicity study was also performed with LBQ657. Where the toxicity related to AT1-receptor blockade was dose limiting, some assessments were not performed with LCZ696 but were performed with AHU377, to ensure adequate exposure to LBQ657, and separately with valsartan. Pre- and post-natal development studies, juvenile toxicity studies, and carcinogenicity studies were performed with AHU377, complemented with the studies previously conducted with valsartan, but were not performed with LCZ696. In addition, local subcutaneous tolerability studies were performed with LCZ696; contact hypersensitivity studies and irritancy studies were performed with AHU377 and valsartan. Additional studies were performed with either LCZ696 or AHU377 to investigate theoretical concerns of inhibiting degradation of other NEP substrates (e.g., potential effects of increased C-type natriuretic peptide (CNP) in bone and increased amyloid beta (Aβ) in the CNS). LCZ696, AHU377, LBQ657, and valsartan do not absorb light between 290 and 700 nm, so phototoxicity testing was not performed. No specific immunotoxicity or drug-dependence studies were performed.

2.2.2. Pharmacology

Primary pharmacodynamic studies

The *in vitro* binding and inhibitor potencies of sacubitril (AHU377), LBQ657, and valsartan were evaluated for the NEP enzyme and AT1 receptor. LCZ696 was not tested in vitro because it readily dissociates into sacubitril and valsartan in aqueous media.

LBQ657 is a potent inhibitor of the human NEP enzyme activity with an IC_{50} of 2.3 nM. Similar IC50 values were found for NEP in rat and human renal cortex microsomes (IC50 1.4 and 7.3 nM respectively). However, in human plasma, the IC_{50} increased to 2.5 µM because of the high protein binding. Binding to NEP-2, a related enzyme of the M13 zinc metalloproteinase family, with a high degree of sequence identity, but other physiological roles, is negligible.

Neither sacubitril (AHU377) nor LBQ657 inhibited the human AT1 receptor and valsartan did not inhibit NEP at relevant concentrations, so they seem specific for their mechanistic pathways.

Concomitant inhibition of NEP by LBQ657 in the presence of AT1-receptor blockade by valsartan provided greater reductions of angiotensin II-stimulated rat cardiac fibroblast collagen synthesis than the reduction by each compound administered alone. At the lowest tested valsartan concentration the reduction by the combined treatment appears larger than would be expected from the additive effects of NEP inhibition and AT1-receptor blockade alone. Concomitant inhibition of NEP in the presence of AT1-receptor blockade a reduction of angiotensin II-stimulated rat cardiomyocyte hypertrophy which at the highest tested valsartan concentration exceeded that of either agent alone. The effect of 10 µM LBQ657 alone was similar to that of 1 µM valsartan alone (50-60% reduction of cardiomyocyte hypertrophy).

Oral administration in rats of sacubitril inhibited NEP-activity in renal cortex microsomes up to 84%. The NEP-inhibition by LCZ696 was shown by single dose administration to rats infused with atrial natriuretic peptide

(ANP), a substrate for NEP. A dose dependent increase of plasma ANP was shown, up to 132% at 60 mg/kg. In rats and dogs, administration of sacubitril up to 30 mg/kg increased ANP 80% to 101%, respectively. In cynomolgus monkeys, at 10 and 30 mg/kg p.o. sacubitril, 79 to 85% inhibition of plasma NEP activity was achieved and lasted up to 5 hours at the highest dose. The IC_{50} value for LBQ657 in plasma was 0.5 µM.

Effects of LCZ696 on diuresis and natriuresis were measured in Dahl Salt-Sensitive (DSS) rats and compared with losartan (angiotensin II receptor antagonist) and hydrochlorothiazide (HCTZ, diuretic). Treatment of 4 weeks significantly reduced the mean arterial pressure, LCZ696 as much as the combination losartan/HCTZ. Sacubitril (30 mg/kg) caused a 14-times increase of urinary sodium excretion in male rats, infused with saline. LBQ657 (10 mg/kg) increased urinary sodium excretion and urinary volume significantly in male dogs, infused with saline. LCZ696 prevented salt-induced decrease of glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) in Dahl Salt-Sensitive (DSS) rats in a similar way as the combination of losartan and HCTZ. LCZ696 reduced high-salt diet increased blood urea nitrogen (BUN) to normal level. LCZ696 reduced the renal injury markers KIM-1, NGAL and osteopontin significantly, but not as strong as the losartan/HCTZ combination.

Four weeks of treatment with 68 mg/kg/day LCZ696 significantly reduced left ventricular weight in DSS rats fed a high-salt diet for 7 weeks. This cardioprotection was similar to the losartan/HCTZ combination. LCZ696 68 mg/kg/day (p.o.) for 4 weeks reduced cardiac hypertrophy in rats with induced myocardial infarction. Valsartan showed also cardioprotection by preventing left-venticular hypertrophy in DSS rats with high-salt diet.

At 60 mg/kg LCZ696 an antihypertensive effect was still observed for more than 24 hours in the double-transgenic rat (dTGR), a model of high-renin activity that develops fulminant hypertension with premature morbidity and mortality. LCZ696 was more effective than valsartan as an antihypertensive in male Dahl Salt-Sensitive (DSS) rats. LCZ696 and valsartan were similar effective antihypertensive agents in a normal-renin, salt-insensitive rat model of hypertension.

LCZ696 did not alter the elevated cGMP in salt-overloaded DSS rats exhibiting increased ANP levels. In contrast, administration of losartan, HCTZ or the combination losartan/HCTZ all significantly reduced urinary cGMP excretion. In dogs, valsartan and LCZ696 (45 mg/kg) significantly increased plasma renin activity and angiotensin I levels, demonstrating that LCZ696 blocked angiotensin II signalling through the AT1 receptor. While sacubitril had no effect on plasma renin activity or angiotensin I levels, there was a significant increase of angiotensin II levels, consistent with LBQ657 being an inhibitor of NEP, which also degrades angiotensin II. sacubitril reduced plasma aldosterone modestly. In contrast, LCZ696 15 mg/kg, LCZ696 45 mg/kg and valsartan all significantly decreased plasma aldosterone levels. LCZ696 at 45 mg/kg increased plasma cGMP by ca. 180%.

In stroke-prone spontaneously hypertensive rats (SHRSP) treated for 10 weeks, valsartan (10 mg/kg/day) in combination with sacubitril (100 mg/kg/day) significantly decreased diastolic blood pressure, cardiac arteriole media to lumen ratio and collagen density and tissue inhibitor of metalloproteinases-2 (TIMP-2) activity, increased vascular matrix metalloproteinase-2 (MMP-2) activity and decreased macrophage infiltration, whereas the tested doses of valsartan or sacubitril alone exerted no smaller and/or statistically non-significant effects.

Secondary pharmacodynamic studies

LBQ657 only marginally inhibited ACE at high doses, making it unlikely that LBQ657 will cause angioedema at therapeutic concentrations. sacubitril and LBQ657 did not inhibit the enzyme activity of the metalloproteases ACE-1, ECE-1, IDE, APN, APP, APP-2, Meprin-α, Meprin-β, or serine protease DPP-4. LBQ657 weakly inhibited the enzyme activity of NEP-2 and ECE-2, whereas sacubitril did not. Valsartan did not inhibit any of the tested enzymes.

Off-target activity of sacubitril, LBQ657 and valsartan was assessed on 57 (sacubitril), 129 (LBQ657) and 81 (Valsartan) G-protein-coupled receptors (GPCRs), transporters, ion channels, nuclear receptors and enzymes, 62 kinases (LBQ657 and sacubitril) and 13 neurotransmitters (valsartan). Due to the lack of inhibition or inhibition at concentrations higher than pharmacologically expected in vivo, no side effects induced by sacubitril, LBQ657 or valsartan related to the tested targets are expected.

Increased bradykinin (BK, also a substrate for NEP) is associated with angioedema and may be an important causative factor in clinical angioedema induced by ACE inhibitors and which was observed with omapatrilat. In two rat models of angioedema (BK-induced rat paw edema or blood pressure lowering), sacubitril in the presence of valsartan did not potentiate BK action, whereas ACE inhibitors or omapatrilat did, suggesting that LCL696 has a low potential for inducing angioedema in humans. However, the Applicant also states that in PARADIGM-HF, the LCZ696 cohort exhibited a numerically but statistically insignificantly higher incidence of angioedema relative to the enalapril cohort. Together, these clinical results suggest that NEP inhibition introduces a similar angioedema risk as ACE inhibition, which makes the predictive ability of these animal models for clinical angioedema uncertain.

In animal studies no signs were found for confirming a theoretical risk associated with elevation in NPs relating to stimulation of lipolysis in human adipocytes and lipid mobilization in humans.

Safety pharmacology programme

LCZ696 and sacubitril did not inhibit hERG channel in human kidney HEK293 cells modified with hERG channel expression, at 3000 µM and 1000 µM, respectively. These concentrations were approximately 2700x and 150x higher than the human C_{max} at 200 mg single dose, for the LCZ696 and sacubitril hERG channel tests, respectively. However, cells were not exposed to the active metabolite LBQ657, therefore it was recommended the Applicant perform the hERG-channel test with LBQ657 under GLP in a concentration-response study (REC), because an *in vivo* cardiovascular study is insufficient (*ICH Guideline S7B*).

LCZ696 did not affect electrocardiographic parameters measured by telemetry in cynomolgus monkeys after oral administration of up to 100 mg/kg. Mean arterial, systolic and diastolic blood pressure were marginally decreased 6 hours after exposure to LCZ696, which indicates the pharmacological effect of LCZ696.

Sacubitril up to a dose of 250 mg/kg (estimated exposure about 3 x human exposure at 200 mg BID) by oral gavage in Beagle dogs did not have any adverse effect on heart rate, blood pressure, body temperature or electrocardiographic parameters.

Respiratory effects of 200 and 600 mg/kg LCZ696 and 250, 1000 and 2000 mg/kg sacubitril were evaluated in male Wistar Hannover rats. No adverse effects on tidal volume, respiratory rate and derived minute volume were observed for either compound. C_{max} values at 600 mg/kg compared to human exposure at 200 mg BID LCZ696 were 1.2 times for valsartan, 0.24 times for sacubitril and 2.4 times for LBQ657. At 2000 mg/kg, exposure unbound LBQ657 C_{max} was 8-fold higher than LBQ657 exposure at LCZ696 200 mg BID in human.

Effects of LCZ696 on the central nervous system (CNS) were tested in male Wistar Hannover rats at doses of 200 and 600 mg/kg. The only effect observed was a decrease in fecal excretions at 600 mg/kg. C_{max} values at 600 mg/kg compared to human exposure at 200 mg BID LCZ696 were 1.2 times for valsartan, 0.24 times for sacubitril and 2.4 times for LBQ657.

Effects of sacubitril on the CNS were assessed in male CD-1 mice. No effects on CNS parameters, clinical signs or body temperature were observed with a treatment of 2000 mg/kg sacubitril. LBQ657 Cmax at this 2000 mg/kg sacubitril was estimated to be about 36-fold higher than human at an LCZ696 dose of 200 mg BID.

For both CNS studies, too limited information on measured study parameters was provided for adequate assessment. The Applicant was asked to provide these data for both studies. Within the procedure, the Applicant provided the raw data of these studies, which confirmed the conclusions in the original study reports, resolving this issue.

Pharmacodynamic drug interactions

No studies were performed with LCZ696 to evaluate PD drug interactions other than valsartan, which was agreed.

2.2.3. Pharmacokinetics

Analytical methods

LC-MS/MS methods were used for the toxicokinetic analysis of mouse, rat, rabbit and monkey plasma. All toxicokinetic studies contained satisfactory description of the method as used in the study and satisfactory calibration and quality control data. Most of the studies were done before the *Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009)* came into force. In addition similar LC-MS/MS methods for the quantitation of sacubitril, LBQ657 and valsartan, fully validated in accordance with the *Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009)* were provided. Overall, the package of validation data is acceptable.

Absorption

The absorption of orally administered LCZ696 or sacubitril (suspension and capsule) was relatively rapid in both onset and rate in all species. In general, tmax of sacubitril, LBQ657 and valsartan drug-related radioactivity after oral dosing of LCZ696 or sacubitril was 0.25 to 2 h. Absorption of sacubitril was high in mouse, rat and dog (70 – 90%) and lower in monkey (40%).

Plasma pharmacokinetics

Oral bioavailability of LBQ657 was high in mouse, rat and dog (70 – 100%) and lower in monkey (41%). In dogs treated with equal molar amounts of either LCZ696 or valsartan + sacubitril, systemic exposure to valsartan was more than twice as high after treatment with LCZ696.

Vss was relatively low in monkey (0.280 L/kg) and larger than total body water in mouse, rat and dog (1.32, 2.0 and 2.5 L/kg respectively). After IV administration of LBQ657 (mice, dogs, monkeys) or sacubitril (rats), t1/2el of LBQ657 was short in mice (0.17 h), rats (2.0 h) and dogs (2.5 h) and longer in monkeys (14.1 h). Compared to hepatic blood flow, clearance in mice (7.8 L/h/kg), rats (4.3 L/h/kg) and dogs (2.9 L/h/kg) was relatively high, whereas it was moderate to low in monkeys (0.2 L/h/kg). After oral administration of LCZ696 t1/2el of LBQ657 in monkeys (5.9 h) was shorter than that in humans. In IV treated rats, clearance of sacubitril (t1/2el = 0.1 h and Cl = 108 L/h/kg) was very high, indicating fast conversion.

Repeated dose plasma pharmacokinetic studies were not performed. Toxicokinetic studies show that exposure to LBQ657 and valsartan increased approximately dose-proportional in rats and dogs. Conversion of sacubitril was fast and nearly complete in rats, but not fast and/or not complete in monkeys. In Cynomolgus monkeys and marmosets, there was no evidence of accumulation or induction of LBQ657 or a gender effect. In rats, in some studies, exposure to LBQ657 seemed higher in males than in females. Conversion of sacubitril into LBQ657 may be faster in male rats than in females. Exposure to valsartan increased approximately dose-proportional in rats

and monkeys. No clear evidence of accumulation or induction was observed for valsartan. No gender effect was observed for valsartan.

Distribution

Plasma protein binding of LBQ657 was 90%, 80%, 93% and 97% in rat, dog, monkey and human, respectively, independent of concentration in the tested range (0.02-100 µg/mL). Therefore, interspecies extrapolation from animal models to man without correction for plasma protein binding results in worst case estimates of exposure ratios. Correction for plasma protein binding would result in about 3.3 fold (rat), 6.7 fold (dog), 2.3 fold (monkey) increase of the ratio of exposure in the animal species vs humans. No estimate is available for the mouse.

Blood to plasma ratios of sacubitril or LBQ657 ranged from 0.5 to 0.6, independent of concentration in the tested range (0.02-100 µg/mL). These results indicate absence of significant distribution to the red blood cells.

In single dose oral tissue distribution studies in pigmented and non-pigmented rats, the highest tissue concentrations were found in bile, stomach, small and large intestine, kidney and liver. High concentrations in the gastrointestinal tract were likely related to the routes of administration c.q. excretion (in the rat the major part is excreted via the faeces). The gastrointestinal tract is also target for toxicity (gastritis) in rats and monkeys. The kidney is a major organ for excretion in monkeys and humans, but only to a small extent in rats. The high levels in rat kidney may be related to the high expression of neprilysin in kidney. The lowest concentrations were found in brain, eye, seminal vesicles and testis and spinal cord. Radioactivity in skin and uveal tract was low. In pigmented rats, drug-related radioactivity had low affinity for pigmented skin and uveal tract. At 24 – 168 h still radioactivity was present in large intestine, kidney and stomach, indicating a potential for accumulation in these organs.

Following oral administration of [14C]LCZ696 to pregnant rats, radioactivity distributed moderately to the fetus. In rabbits, fetal exposure to [14C]LCZ696-related activity was low. LBQ657 was excreted into rat milk.

Metabolism

The main biotransformation reaction, in the toxicological species and humans, consists of hydrolysis of sacubitril to LBQ657.

In vitro studies: sacubitril was metabolised to LBQ657, by hydrolysis of the ethyl ester, in rat, dog and human liver slices and in human liver microsomes and S9. Rate of metabolism in rat liver slices was faster than in dog and human liver slices. Conversion of sacubitril to LBQ657 by human liver microsomes was inhibited by the esterase inhibitor KF. sacubitril and LBQ657 were not significantly further metabolized.

In vivo studies: The rate of conversion from sacubitril to LBQ657 was high in mouse and rat. LBQ657 was the major circulating component in mouse plasma (~73% of AUC) and in rat blood (~80% AUC). However, in dog and monkey conversion rate was moderate. Both sacubitril and LBQ657 were prominent components in dog blood (sacubitril: LBQ657 = ~34%:~46% of AUC) and monkey plasma (sacubitril: LBQ657 = ~37%:~62% of AUC). In human (n=4), the conversion rate was high and the major circulating component was LBQ657 (sacubitril: LBQ657 = ~2-6% :~93-98% of AUC). In addition, several minor metabolites (hydroxylated and conjugated) were identified in plasma/blood from various species. In the rabbit sacubitril was also quickly hydrolysed to LBQ657.

LBQ657 was the major component detected in urine or faeces. In addition, small amounts of unchanged sacubitril and several minor metabolites were identified in faeces and/or urine.

Excretion

Sacubitril related radioactivity was predominantly excreted in faeces in mice, rats and dogs (~74-98% of the radioactive dose), whereas urinary excretion was minor. In monkeys and humans, sacubitril- or LCZ696 related radioactivity was excreted to a higher extent in urine (~42-65% of the dose). Biliary excretion was not investigated in the mass balance studies. In the rat distribution studies, high radioactivity was found in bile. However, based on plasma pharmacokinetics, there is no evidence of enterohepatic recycling. Excretion was complete within 7 days.

2.2.4. Toxicology

Single dose toxicity

Single dose toxicity studies with sacubitril were performed in mice and rats. Sacubitril was well tolerated in mice and rats with lethal dose after oral administration > 2000 mg/kg and >500 mg/kg after intraperitoneal administration.

Repeat dose toxicity

Repeated dose toxicity studies were performed with LCZ696 in mice up to 13 weeks, in rats up to 26 weeks and cynomolgus monkeys up to 39 weeks and with sacubitril in rats up to 26 weeks and in marmosets up to 52 weeks.

A theoretical risk associated with NEP inhibition relates to effects on Aβ metabolism and the potential accumulation of Aβ in the brain. Alzheimer's disease is associated with the presence of Aβ plaques in the brain. In a 2-week study in which Aβ was measured in cerebral spinal fluid (CSF) in cynomolgus monkeys, LCZ696 was found to reduce the proteolytic clearance of Aβ in the CNS (Aβtotal as well as isoforms 37, 38, 40 and 42), with no effect on total amyloid content in the brain. No evidence was found of LCZ696-related amyloid plaques in the brain sections of cynomolgus monkeys in the 39-week study. The presence or absence of amyloid or plaque material was determined qualitatively based on immuno-histochemical staining, but amyloid content was not quantified. In a clinical study in which Aβ was measured in CSF of human volunteers for two weeks, Aβ38 was found to be increased but not Aβ40 and Aβ42.

Effects on the gastro-intestinal tract were observed following both LCZ696 and sacubitril treatments. In rat and mouse studies with LCZ696, mixed cell inflammation in the stomach was observed, with stomach erosion in the 26-week rat study. In studies with sacubitril, glandular dilatation in stomach and duodenum was observed in marmosets, hyperplasia and/or hyperkeratosis in the stomach were observed in marmosets and rats and stomach ulceration at high dose in one rat study. Both LCZ696 and sacubitril induced diarrhoea and emesis in monkeys and abdominal distention in rats and mice. In several rodents, labored respiration was observed which seemed to correlate with abdominal distention. Gastro-intestinal irritation may be an effect of NEP inhibition, but it is likely that also local irritation by LCZ696 plays a role. Potential gastrointestinal adverse effects are covered in the clinical AR.

Decreases in heart weight were observed in all animal species. This is considered due to decreased blood pressure and a resulting decreased cardiac work load, i.e. related to the pharmacological effect.

CNS-related clinical signs
In mice and rats treated with LCZ696, some clinical signs related to possible effects on the central nervous system (CNS) were observed. These comprised decreased or increased locomotor activity, aggression, hypersensitivity to touch, twitches and impaired righting reflex. Generally, these findings occurred at exposure levels below the clinical target exposure, both in terms of AUC and C_{max}. However, the clinical relevance of the

CNS findings in rats and mice were dismissed by the Applicant based on lack of findings in the safety pharmacology studies as well as the lack of imbalance of CNS events in the pivotal PARADIGM HF study in patients. It is agreed that no clinical CNS signals so far have been identified. The concern regarding amyloid build-up and possible effects on cognition has been raised by the PRAC in the RMP D80 Assessment report, and the Applicant has been requested to add 'Cognitive impairment' as an important potential risk. No further risk minimisation as regards CNS effects is considered necessary at the moment.

Thyroid gland

In the 52-week marmoset study with sacubitril, moderately lower thyroid weights were observed in males at ≥ 25 mg/kg. This organ weight change was correlated with microscopic findings of slight to moderate reduction in colloid. Females displayed similar microscopic findings, although the weight of the thyroids showed an increase as compared with controls. Additional histopathological changes (follicular hyperplasia, follicular atrophy) were observed in individual animals. Findings of decreased thyroid weight and reduction in colloid were not reversible in high dose (200 mg/kg) males. Based on the absence of similar findings in other species, the Applicant argues that the thyroid effects observed in male marmosets are probably incidental in nature. Since AHU377 did not demonstrate off-target binding potential, any treatment-related effect would likely be due to inhibition of neprilysin. AHU377, however, is a much weaker inhibitor of neprilysin as compared with LBQ657. Thus the higher exposure to AHU377 relative to LBQ657 in marmosets is not considered to be of any toxicological importance. The Applicant also emphasizes the lack of imbalance between LCZ696 and enalapril-treated patients with regard to TSH levels and other PTs related to thyroid events.

In view of the clear dose response relationship of thyroid findings in males, it is difficult to dismiss these effects as incidental. On the other hand, the dose groups were rather small (5 animals per group) and in females the incidence of reduced colloid was similar between controls and drug-treated animals. Thus it appears that the observed effect represents an enhancement of an already existing background pathology phenomenon. It is possible that male marmosets may be more sensitive to this effect. On balance, it is agreed with the Applicant that the absence of thyroid findings in other non-clinical species, and the lack of signal in the clinic, support the notion that the thyroid effects in male marmosets administered AHU377 are not likely to be relevant to the clinical situation.

Thymus lymphoid depletion / involution was observed in rats and monkeys treated with LCZ696 and in one rat study with sacubitril. Otherwise, no effects affecting the immune system were observed.

Known effects of valsartan in the repeated dose studies were juxtaglomerular cell hypertrophy / hyperplasia in the kidney, increased BUN and reductions in red blood cell parameters.

Genotoxicity

No evidence of genotoxicity was found in an extensive package of tests in which both LCZ696 and sacubitril were tested (Ames tests, in vitro chromosomal aberration tests and in vivo rat micronucleus tests).

Carcinogenicity

Two-year carcinogenicity studies were performed with sacubitril in rats and mice. No evidence of carcinogenic potential was found.

Reproduction Toxicity

Fertility studies were performed with LCZ696 and sacubitril in rats. No effects were found on male and female fertility. Estimated exposure (based on AUC from repeated dose studies) was below the human exposure in the study with LCZ696 and up to about 1.5 times human exposure in the study with sacubitril.

Embryofoetal development (EFD) studies were performed with LCZ696 and sacubitril. LCZ696 was embryotoxic in rats at > 100 mg/kg and in rabbits at > 10 mg/kg.. In the LCZ696 EFD rabbit study, decreased foetal body weight, late resorptions, decreased viable foetuses, abortions, premature birth, incomplete ossification, hydrocephaly (most likely an effect of valsartan) and absent gall bladders (incidence 3 out of 3 litters; incidence control group is 0) were observed, in the presence of maternal toxicity. In addition, 3 fetuses at 3 mg LCZ696/kg (from 3 different litters) showed multiple visceral malformations mainly affecting the heart. The historical control data provided by the Applicant cannot convincingly substantiate the position that these findings were incidental in nature. Therefore the Applicant is requested to discuss the cardiovascular findings in rabbits in context with what is known about the pharmacological targets of valsartan and sacubitril, especially their roles in embryofetal heart development. It was not possible to fully conclude on the teratogenic potential of LCZ696. From subsequent discussion with the Applicant it can be concluded that it has not been convincingly shown that the cardiovascular findings in the LCZ696 rabbit study are not related to the pharmacology of the compound, particularly the valsartan component. Based on limited published data, a role for sacubitril seems less likely.

EFD studies on sacubitril alone showed embryofetal toxicity and skeletal malformations in rabbits at maternally toxic doses (500 mg/kg). No evidence of embryofetal toxicity or teratogenicity was observed in rats treated with sacubitril.

A pre- and postnatal development study was performed with sacubitril in rats. Apart from a slightly reduced weight in F1 pups in the high dose group, sacubitril did not affect pre- and postnatal development. Maximum exposure was 2 times the human exposure based on AUC.

Juvenile toxicity studies were performed with sacubitril and valsartan in rats. Treatment of juvenile rats with sacubitril induced decreased bone size, bone density and bone strength. Effects on bone started at exposures below human exposure, compared to adult human AUC. The possible mechanism behind this effect was not clarified. In a 13-week bone study in adult rats, there was one observation of a decrease in the gain in bone mineral content in lumbar spine. Absolute values of bone size and bone mineral content and bone mineral density were not affected in adult rats. Pharmacological effects of valsartan on the kidney leading primarily to juxtaglomerular cell hypertrophy / hyperplasia in adult animals, seem to be exaggerated in juvenile animals leading to tubular nephropathy, sometimes accompanied by tubular epithelial necrosis, which was not reversible. This occurred at exposures below human exposure based on adult AUC of valsartan.AHU377

Local Tolerance

Sacubitril was not irritating to rabbit skin. Sacubitril was irritating to rabbit eyes. Sacubitril was a weak sensitizer in the local lymph node assay in mice.

Other toxicity studies

Neither LCZ696, sacubitril, LBQ657 nor valsartan absorb light within the UV-A and visible and within the UV-B range a slight increase of absorption is only detectable below 300 nm. Therefore no phototoxicity studies were performed.

No immunotoxicity studies were performed. Except for thymus depletion in some studies, which may have been secondary to toxicity, there were no significant indications for immunotoxicity. Also pharmacologically there does not seem to be an indication for immunotoxicity.

2.2.5. Ecotoxicity / environmental risk assessment

LBQ657 is not a PBT, nor vPvB substance. Considering the data, LBQ657 is not expected to pose a risk to the STP, surface water and groundwater compartment. For LBQ657 risk to the sediment compartment seems unlikely, but the applicant was recommended to use the geometric mean K_{OC} value for the PEC sediment calculation and it was agreed to address this post-authorisation (REC).

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of LBQ657 to the environment. The ERA for valsartan was based on the earlier assessment of the compound in procedures EMEA/H/C/1068, EMEA/H/C/1159, EMEA/H/C/1160, EMEA/H/C/1161 and post-authorisation measures to these procedures. Valsartan is not a PBT, nor vPvB substance. A risk of valsartan for the STP, surface water, sediment, soil and groundwater compartments from the prescribed use of the product was not anticipated.

Summary of main study results

Substance (INN / Invented Name): LBQ657			
CAS-number (if available): 149709-44-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log D_{ow} (= log K_{ow}) = 2.9 at pH 2, for fully neutral species	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.9	not B
Persistence	ready biodegradability	not readily biodegradable	
	$DegT50_{system}$ water/sediment	23 d at 12 °C 23 d at 12°C	not P
Toxicity	NOEC algae NOEC crustacea NOEC fish	≥ 100 mg/L 46 mg/L ≥ 10 mg/L	not T based on aquatic toxicity data
	CMR	not investigated	potentially T
PBT-statement :	LBQ657 is considered not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$, default F_{pen}	0.97	µg/L	> 0.01 threshold
Other concerns (e.g. chemical class)	not investigated		

Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 22.6; 45.0 L/kg (sludge) K_{oc} = 367 L/kg (non-sterilized soil); 39.2 and 40.6 L/kg (sterilized soil)			2 sludge types 3 soil types
Ready Biodegradability Test	OECD 301B	not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DissT_{50,\ water}$ = 6.0 and 6.5 d $DegT_{50,\ system}$ = 11 and 11 d % shifting to sediment: 36% and 56% at day 14, increasing thereafter			Values determined at 20°C
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *P. subcapitata*	OECD 201	NOEC	≥ 100	mg/L	growth rate
Daphnia magna, reproduction Test	OECD 211	NOEC	46	mg/L	reproduction and growth
Fish, Early Life Stage Toxicity Test/ *P. Promelas*	OECD 210	NOEC	≥ 10	mg/L	survival, growth
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC EC10	≥ 1000 756	mg/L	respiration
Phase IIb Studies					
Sediment dwelling organism/*C. riparius*	OECD 218	NOEC	≥ 1867	mg/kg	emergence, development; normalised to 10% o.c.

2.2.6. Discussion on non-clinical aspects

Pharmacology

Sacubitril (AHU377) showed a potent and selective NEP inhibition *in vitro* and *in vivo* by way of its metabolite LBQ657. No important secondary pharmacology effects, e.g. related to NEP-inhibition, were found.

The applicant argued that the potential for LBQ657 to prolong QTc has been sufficiently assessed in *in vivo* safety pharmacology studies and in clinical trials. This was not agreed, as according to ICH guideline S7B *"In vitro and in vivo assays are complementary approaches; therefore, according to current understanding, both assay types should be conducted."* Therefore, the applicant committed to conduct a hERG channel test with LBQ657 under GLP in a concentration-response study. Because in clinical studies a concern regarding QT

prolongation was not raised, it was agreed that the hERG channel test can be performed post-authorisation (as recommendation; [REC]).

No respiratory effects of LCZ696 were seen in rats. Also no effects on the central nervous system were seen in rats and mice.

Pharmacokinetics

In general, sufficient data were provided regarding plasma pharmacokinetics and toxicokinetics, distribution, metabolism and excretion. The PK data support the choice of animal species for the pivotal toxicity studies: rats and cynomolgus monkeys or marmosets.

Toxicology

In repeated dose toxicity studies, LCZ696 and sacubitril were fairly well tolerated, apart from effects on **heart weight, red blood cell parameters and kidneys** known to be related to the pharmacological action (compensatory physiological and exaggerated pharmacological effects) and only **gastrointestinal irritation** considered as target organ toxicity. Specific studies revealed however some relevant issues, as discussed below.

It was noted from the pharmacological action of LCZ696 and from the results of the 2-week monkey study that LCZ696 is capable of **decreasing amyloid degradation**, including Aβ40 and Aβ42. No effect was found on total amyloid content in the brain. The study duration was however only two weeks and a significant effect on total amyloid content would not be expected in this period of time. In the 39-week study in monkey, no evidence was found of treatment-related plaques in the brain. However, since no quantitative comparison of amyloid content at the start vs the end of the study was made, it was not possible to exclude a small increase in amyloid content. It was considered impossible to get more certainty regarding this issue with more non-clinical data. Further assessment of the cognitive function was agreed to be included as part of the pharmacovigilance plan and included in the RMP.

Assessment of paediatric data on non-clinical aspects

The following nonclinical studies included in the P/0106/2014 were submitted and assessed within current application: **Mechanistic** in-vitro study (1170517); 4-week dose range-finding juvenile **rabbit bone** toxicity study (1170514); 4-week investigative **bone** study in juvenile **rats** (1170516) included in the EMA Decision P/0106/2014.

An mechanistic *in-vitro* **study 1170517** was performed to determine the effect of CNP (C-type natriuretic peptide) and neprilysin inhibition, via AHU377 or LBQ657 treatment, on mineralization in an *in vitro* rat osteoblast cell model, the UMR-106 osteosarcoma cell line. The results of this study suggests that the bone effects observed in juvenile rats do not appear to be related to direct effects of AHU377 or LBQ657 on the CNP system.

In juvenile toxicity studies, sacubitril caused effects on bone and valsartan affected the kidney, more severely than the pharmacological effects that are known from valsartan in adults. In juvenile **rats** treated with sacubitril (postnatal days 7 to 70), there was a reduction in age-related bone mass development and bone elongation. A study in adult **rats** showed only a minimal transient inhibitory effect on bone mineral density but not on any other parameters relevant for bone growth, suggesting no relevant effect of sacubitril on bone in adult patient populations under normal conditions. However, a mild transient interference of sacubitril with the early phase of fracture healing in adults cannot be excluded. Currently, LCZ696 is not intended for paediatric patients. In case of a future application for a paediatric indication, the clinical relevance of the effects on bone for the growth of

children and the clinical relevance of the kidney effects should be discussed and the observations were included in section 5.3 of the SmPC.

Effects on bone were also studied in **adult rats**. The observation of a decrease in the gain in bone mineral content was considered most likely specific to rats, in which some growth continues throughout life. Since not any effects were observed on absolute values of bone size, bone mineral content and bone mineral density, there is no strong evidence that a relevant effect of sacubitril on bone could be expected in human adults under normal conditions. Although evidence for effects on bone in adult animals was weak, a potential to inhibit e.g. recovery of bone damage in adults could not be excluded.

Also in **rabbit study 1170514**, biomarkers were analysed (formation marker osteocalcin in serum and resorption marker Cross-Linked-N-Telopeptides of Type I Collagen in urine) and bone densitometry (in vivo and ex vivo, by DXA and pQCT), radiography and biomechanical testing were performed. In this study, no effect on bone parameters was found.

2.2.7. Conclusion on the non-clinical aspects

With regard to toxicity, potential safety issues were identified. A potential **risk of decreasing amyloid degradation**, including Aβ40 and Aβ42, could not be excluded on the basis of the non-clinical data. Further evaluation of the cognitive function was agreed to be included as part of the pharmacovigilance plan and included in the RMP.

Cardiovascular abnormalities (mainly **cardiomegaly**) were observed in rabbit foetuses at a maternally non-toxic dose. A slight increase in two foetal skeletal variations (misshapen sternebra, sternebra bipartite ossification) was observed in rabbits at an LCZ696 dose of 4.9 mg sacubitril/5.1 mg valsartan/kg/day.

In addition, potential risks of **adverse effects on bone and kidney** in case of paediatric use were identified. In juvenile rats treated with sacubitril (postnatal days 7 to 70), there was a reduction in age-related bone mass development and bone elongation. A study in adult rats showed only a minimal transient inhibitory effect on bone mineral density but not on any other parameter relevant for bone growth. This suggested no relevant effect of sacubitril on bone in adult patients under normal conditions. However, a mild transient interference of sacubitril with the early phase of fracture healing in adults could not be excluded. Although these risks were not relevant for the current indication, they could become relevant in case of a future application for paediatric indication. Evidence for effects on bone in adult animals was weak; however a potential adverse effect in case of e.g. recovery of bone damage in adult animals could not be excluded.

Concerning the Environmental Risk Assessment, for LBQ657 risk to the sediment compartment seems unlikely, but the applicant was recommended to use the geometric mean K_{OC} value for the PEC sediment calculation and it was agreed to address this post-authorisation as a recommendation (REC).

In conclusion, the nonclinical data (including studies with sacubitril and valsartan components and/or LCZ696) based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and fertility support the safe and effective use of LCZ696 in humans.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Following routine GCP inspections of 2 of the sites where the pivotal study was conducted, several critical and major findings were observed. Further analysis showed that the findings did not affect the measurement of the primary endpoint; this was confirmed by several sensitivity analyses. In addition the applicant demonstrated that the measurement of AEs was sufficiently accurate to support benefit-risk assessment.

- Tabular overview of clinical studies

• Study	Study purpose	Posology	Formulation	Population (n)
List of LCZ696 (sacubitril/valsartan) clinical pharmacology studies				
Pharmacokinetics in healthy subjects				
A2101	Single ascending dose study to assess PK, safety and tolerability of LCZ696 compared to valsartan	Single doses of LCZ696 5, 20, 80 mg; single dose of valsartan 40 mg	LCZ696 5 and 50 mg CSF tablets and matching placebo Valsartan 40 mg tablets and matching placebo	Healthy subjects (25)
A2103	Relative bioavailability of valsartan from LCZ696 compared to valsartan tablets	Single doses of LCZ696 400 mg, single doses of valsartan 320 mg	LCZ696 50 mg and 300 mg CSF tablets Valsartan 160 mg filmcoated tablets	Healthy subjects (53)
B2107	Effect of food on the PK of LCZ696	Single dose of LCZ696 400 mg	LCZ696 400 mg FMI tablets	Healthy subjects (36)
B2114	Bioequivalence of LCZ696 50 mg FMI compared to CSF tablet	Single doses of LCZ696 50 mg	LCZ696 50 mg FMI and CSF2 tablets	Healthy subjects (85)
B2126	Relative bioavailability of LCZ696 minitablets and effect of food on the PK of LCZ696 minitablets	Single doses of LCZ696 200 mg FMI and minitablets	LCZ696 200 mg FMI tablets and LCZ696 minitablets (200 mg given as appropriate number of mini tablets)	Healthy subjects (40)
Safety and pharmacokinetics in heart failure patients				
A2117	Multiple dose study to assess safety, tolerability, PK and PD of LCZ696	LCZ696 7-day dose titration with 100 mg bid followed by 200 mg bid for 14 days (optional start of dose titration with LCZ696 50 mg was not utilized)	LCZ696 100, 200 mg FMI tablets	Patients with stable chronic heart failure (NYHA II-IV) (30)
Absorption, distribution, metabolism and excretion in healthy subjects				
B2105	Absorption, distribution, metabolism and elimination of LCZ696	Single dose of [14C]-LCZ696 200 mg	100 mg radiolabelled [14C]-LCZ696 in hard gelatin capsules	Healthy subjects (4)
Drug interactions in healthy subjects				

Study	Study purpose	Posology	Formulation	Population (n)
B2125	PK interaction with carvedilol	Multiple doses of LCZ696 400 mg once daily and carvedilol 12.5 and 25 mg (titration) twice daily	LCZ696 400 mg FMI tablets Carvedilol Immediate Release 12.5 and 25 mg tablets	Healthy subjects (28)
B2116	PK and PD interaction with furosemide	Multiple doses of LCZ696 200 mg twice daily and single dose of furosemide 40 mg	LCZ696 200 mg FMI tablets Furosemide 40 mg tablets	Healthy subjects (28)
B2128	PD interaction with intravenous nitroglycerin	Multiple doses of LCZ696 200 mg twice daily and nitroglycerin infusion up to 40 µg/min and matching placebo	LCZ696 200 mg FMI tablets LCZ696 matching placebo tablets Nitroglycerin infusion and matching placebo	Healthy subjects (39)
B2111	PK interaction with digoxin	Multiple doses of LCZ696 200 mg twice daily and digoxin 0.25 mg once daily	LCZ696 200 mg FMI tablets Digoxin 0.25 mg tablets	Healthy subjects (24)
B2112	PK and PD interactions with warfarin	Multiple doses of LCZ696 200 mg twice daily and single dose warfarin sodium 25 mg	LCZ696 200 mg FMI tablet and matching placebo Warfarin sodium 5 mg	Healthy subjects (25)
B2115	Single ascending dose study of LCZ696 and PK interaction study with atorvastatin	Single doses of LCZ696 50, 100, 200, 400 mg; Multiple doses of LCZ696 200 mg twice daily and atorvastatin 80 mg once daily	LCZ696 50 mg CSF, 100 and 200 mg FMI tablets Atorvastatin 20 mg tablets	Healthy Chinese subjects (68)
B2122	PK interaction with metformin	Multiple doses of LCZ696 400 mg and metformin 1000 mg once daily	LCZ696 200 mg FMI tablets Metformin 500 mg tablets	Healthy Japanese subjects (26)
B2113	PK interaction with omeprazole	Multiple doses of LCZ696 400 mg and omeprazole 40 mg once daily	LCZ696 400 mg FMI tablets Omeprazole 40 mg delayed-release capsules	Healthy subjects (28)
A2120	PK interaction with hydrochlorothiazide (HCTZ)	Multiple doses of LCZ696 400 mg and HCTZ 25 mg once daily	LCZ696 400 mg FMI tablets HCTZ 25 mg tablets	Healthy subjects (28)
A2119	PK interaction with amlodipine	Multiple doses of LCZ696 400 mg and amlodipine 10 mg once daily	LCZ696 400 mg FMI tablets Amlodipine 10 mg tablets	Healthy subjects (28)
A2124	PK interaction with combination oral contraceptive (COC)	Multiple doses of LCZ696 400 mg once daily and single dose of COC	LCZ696 400 mg FMI tablets COC tablets (levonorgestrel 150 µg; ethinylestradiol 30 µg)	Healthy subjects (24)
Drug interactions in patients				
B2225	PK interaction with sildenafil	Multiple doses of LCZ696 400 mg once daily and single dose of sildenafil 50 mg	LCZ696 400 mg FMI tablets Sildenafil 50 mg tablets	Patients with mild/ moderate hypertension (28)

• Study	Study purpose	Posology	Formulation	Population (n)
Special populations				
A2204	Effect of mild and moderate renal impairment on LCZ696 PK	Multiple oral doses of LCZ696 400 mg once daily	LCZ696 400 mg FMI tablet	Subjects with mild and moderate renal impairment and healthy subjects (32)
A2205	Effect of severe renal impairment on LCZ696 PK	Multiple oral doses of LCZ696 400 mg once daily	LCZ696 400 mg FMI tablet	Subjects with severe renal impairment and matched healthy subjects (12)
B2109	Effect of age and gender on LCZ696 PK	Single doses of LCZ696 400 mg	LCZ696 400 mg FMI tablet	Healthy Subjects (36)
B2203	Effect of hepatic impairment on LCZ696 PK	Single dose LCZ696 200 mg	LCZ696 200 mg FMI tablet	Subjects with mild or moderate hepatic impairment and matched healthy subjects (32)
Pharmacodynamics in healthy subjects and patients				
A2126	Effect of LCZ696 on amyloid-β concentrations in cerebrospinal fluid	Multiple doses of LCZ696 400 mg once daily for 14 days	LCZ696 200 mg FMI tablets and matching placebo tablets	Healthy Subjects (26)
A2222	Effect of LCZ696 compared to valsartan on natriuresis in Asian patients with saltsensitive hypertension	LCZ696 400 mg and valsartan 320 mg once daily for 4 weeks in a cross-over design	LCZ696 400 mg FMI tablets and matching placebo Valsartan 320 mg filmcoated tablet and matching placebo	Asian patients with saltsensitive hypertension (SSH) (72)
B2207	Metabolic effects of LCZ696 compared to amlodipine in obese hypertensive patients	Multiple doses of LCZ696 400 mg or amlodipine 10 mg once daily for 8 weeks	LCZ696 400 mg FMI tablets and matching placebo Amlodipine 5 mg tablets and matching placebo	Obese patients with mild to moderate essential hypertension (50)
B2223	Effect of LCZ696 compared to valsartan on natriuresis in patients with heart failure and hypertension	LCZ696 400 mg and valsartan 320 mg once daily for 1 week in a cross-over design	LCZ696 200 and 400 mg FMI and matching placebo Valsartan 160 and 320 mg film-coated tablets and matching placebo	Patient with stable chronic heart failure (16) Patients with Hypertension (16)
Studies conducted within the LCZ696 development program that provide results relevant to the Summary of Clinical Pharmacology				
B2214	Efficacy, safety and tolerability of LCZ696 compared to valsartan in patients with HF and preserved left ventricular ejection fraction (HFpEF); “PARAMOUNT” trial	LCZ696 50 mg, 100 mg and 200 mg twice daily for 36 weeks Valsartan 40 mg, 80 mg and 160 mg twice daily for 36 weeks	LCZ696, 100 mg and 200 mg FMI tablets. 50 mg CSF tablets and matching placebo Valsartan 40 mg, 80 mg and 160 mg tablets and matching placebo	Patients with HFpEF (149)

• Study	Study purpose	Posology	Formulation	Population (n)
B2314	Efficacy and safety of LCZ696 compared to enalapril in patients with chronic heart failure and reduced ejection fraction (HFrEF); "PARADIGM-HF" trial	LCZ696 50 mg, 100 mg and 200 mg twice daily Enalapril 2.5 , mg, 5, mg and 10 mg twice daily	LCZ696 100, 200 mg FMI tablets, 50 mg CSF tablets and matching placebo tablets Enalapril 2.5, 5, 10 mg tablets and matching placebo	Patients with HFrEF (4209)
A1304	Safety, tolerability and efficacy of LCZ696 in Japanese hypertensive patients with renal dysfunction	LCZ696 100 mg, 200 mg and 400 mg once daily; placebo	LCZ696 100 and 200 mg FMI tablets and matching placebo (to LCZ696 100 mg tablets)	Japanese hypertensive patients with renal dysfunction (32)
A1306	Efficacy and safety of LCZ696 compared to olmesartan in Japanese patients with essential hypertension	LCZ696 200 mg once daily for 1 week, uptitrated to LCZ696 400 mg once daily for 7 weeks; placebo Olmesartan 20 mg once daily for 8 weeks; placebo	LCZ696 200 mg FMI tablet and matching placebo Olmesartan 20 mg hardd gelatin capsule and matching placebo	Japanese patients with mild to moderate essential hypertension (387)
A2201	Dose ranging study of LCZ696 compared to valsartan and to compare sacubitril to placebo	LCZ69: 100 mg, 200 mg and 400 mg* once daily for 8 weeks (*one week treatment with 200 mg LCZ696 followed by 7 weeks treatment with 400 mg LCZ696); placebo Valsartan 80 mg, 160 mg and 320 mg** once daily for 8 weeks (**one week treatment with 160 mg valsartan followed by 7 weeks treatment with 320 mg valsartan); placebo Sacubitril 200 mg; placebo	LCZ696 100 mg, 200 mg, 400 mg CSF tablets and matching placebo Valsartan 80 and 160 mg tablets and matching placebo Sacubitril 100 mg CSF tablets and matching placebo	Patients with mild-to moderate essential hypertension (497)
A2219	Dose-ranging study of LCZ696 in Patients with mild-to moderate essential hypertension	LCZ696 100 mg, 200 mg and 400 mg* twice daily for 8 weeks (*one week treatment with 200 mg LCZ696 followed by 7 weeks treatment with 400 mg LCZ696); placebo	LCZ696 100 and 200 mg FMI tablets and matching placebo	Patients with mild-to moderate essential hypertension (297)
List of sacubitril clinical pharmacology studies				

• Study	Study purpose	Posology	Formulation	Population (n)
CVNP489A2102CVNP489 A2102	Single ascending dose study of sacubitril to assess pharmacokinetics, safety, tolerability and PD / food effect	Single doses of sacubitril 10, 30, 100, 200 mg; matching placebo; Nesiritide1.5 mg iv	Sacubitril 5 mg capsules (size 1) Sacubitril 25 mg capsules (size 1) Sacubitril 100 mg capsules (size 0) Placebo capsules,size 1 to 5mg and 25 mg sacubitril Placebo capsules,size 0 to 100 mg sacubitril Nesiritide 1.5 mg vials	Patients with mild hypertension (60)
CVNP489A2103CVNP489 A2103	Multiple ascending dose study to assess safety, tolerability and mode of action of sacubitril administered alone and in combination with valsartan; assess the pharmacokinetic interaction with valsartan	Single doses sacubitril 400 mg, 600 mg; Multiple ascending doses sacubitril 10 mg, 30 mg, 100 mg, 200 mg, 400 mg and 600 mg and 320 mg valsartan, matching placebo once daily for 14 days	Sacubitril 5 mg capsules (size 1), Sacubitril 25 mg capsules (size 1) Sacubitril 100 mg capsules (size 0) Placebo capsules, size1 to 5mg and 25 mg sacubitril and valsartan 160mg Placebo capsules, size 0 to 100 mg sacubitril Valsartan 160 mg capsule size 1	Healthy Subjects (56)
Summary of biopharmaceutical studies of LCZ696				
CLCZ696A2103CLCZ696 A2103	Relative bioavailability	400 mg (1 x 300 mg+2x50 mg) 320 mg(2 x 160 mg) valsartan	LCZ696 CSF tablet Valsartan registered tablet	HV (54)
CLCZ696A1101CLCZ696 A1101	Food effect	Single dose 200 mg	CSF tablet	HV (8)
CLCZ696B2114CLCZ696 B2114	Bioequivalence	50 mg	CSF2, FMI	HV (124)
CLCZ696B2126CLCZ696 B2126	Relative bioavailability	200 mg (as minitablets) 200mg	Mini tablets, FMI 200 mg	HV (40)

CSF; Clinical Service Formulation, FMI; Final Market Image

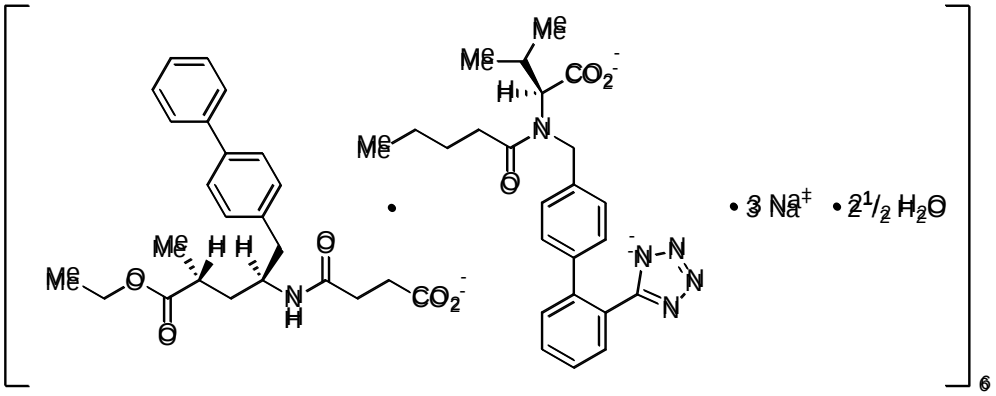
2.3.2. Pharmacokinetics

The majority of the pharmacokinetic studies have been performed in healthy subjects. The proposed target dose of LCZ696 is 97 mg/103 mg twice daily, as tolerated by the patient.

LCZ696 is formulated as film-coated tablets and each tablet contains sacubitril and valsartan as sodium salt complex in the following strengths: 24 mg of sacubitril / 26 mg of valsartan (50 mg), 49 mg of sacubitril / 51 mg of valsartan (100 mg), 97 mg of sacubitril / 103 mg of valsartan (200mg).

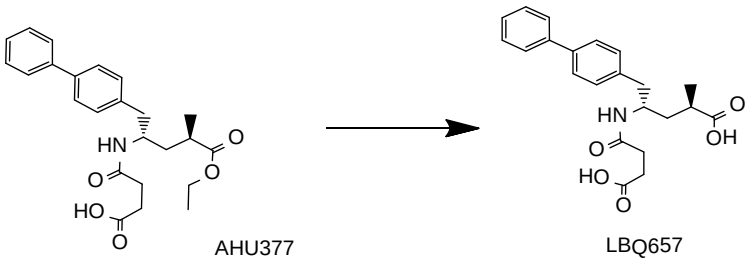
LCZ696 is a salt complex comprising the anionic molecular moieties of sacubitril and valsartan, sodium cations and water molecules in the molar ratio of 1:1:3:2.5, respectively. The schematic two-dimensional structure of LCZ696 representing the stoichiometry between the individual moieties is displayed below.

Figure 1: Schematic 2-D structure of LCZ696-ABA Sacubitril (left) and valsartan (right)



Following oral administration, LCZ696 dissociates into valsartan and the pro-drug sacubitril (also known as AHU377) upon dissolution. Sacubitril is subsequently metabolised to the neprilysin inhibitor LBQ657.

Figure 2: Conversion of sacubitril (AHU377) to LBQ657



Methods

The bioanalytical methods (LC-MS/MS) for the simultaneous determination of sacubitril, valsartan and LBQ657 were sufficiently validated, both for the urine and plasma methods. Cross validation was performed for the methods in use at the different analytical sites. For all methods a high degree of carry-over was observed, however during the analysis of the clinical study samples sufficient measures (extra blank sample injections, low concentrations clustered) were taken to reduce the risk for carry-over problems. No general problems regarding the bioanalytical methods were observed. The applied methods for pharmacokinetic and statistical data analysis were adequate.

Population pharmacokinetics

The applicant developed a Population pharmacokinetic (PPK) method to describe the pharmacokinetics of the LCZ696 analytes valsartan, sacubitril and LBQ657. The pharmacokinetics of these analytes were described by a 2-compartment PPK model with 1st order absorption and elimination. A parent-metabolite model was successfully developed via sequential PK fitting to describe the prodrug conversion of sacubitril to the active metabolite LBQ657.

The population model was appropriately validated. No important systematic deviations or major bias in of the goodness of fit plots were observed and the predictive performance of the model was appropriately assessed using bootstrap and VPC techniques.

With this model, the influence of demographic factors and laboratory findings were tested as potential model covariates. The PPK model identified several statistically significant covariates for PK parameters of the analytes of LCZ696:

- Age, eGFR, levels of aspartate aminotransferase, total bilirubin and NYHA stage were relevant covariates for the clearance of valsartan. Age and NYHA stage were relevant covariates for the absorption of valsartan. Body weight affected the volume of distribution.
- Age, eGFR, total bilirubin and NYHA stage were relevant covariates for the clearance of LBQ657; body weight affected the volume of distribution.

No relevant covariates were identified for sacubitril.

Absorption

Following oral administration, LCZ696 dissociates into valsartan and the prodrug sacubitril. Sacubitril is further metabolised to the active metabolite LBQ657. These reach peak plasma concentrations in 2 hours, 1 hour, and 2 hours, respectively. Following twice daily dosing of LCZ696, steady state levels of sacubitril, LBQ657 and valsartan are reached in three days. At steady state, sacubitril and valsartan do not accumulate significantly, while LBQ657 accumulates 1.6 fold.

An absolute bioavailability study was not conducted with LCZ696 because no IV formulation was available. Based on recovery in urine following oral administration of [14C]-labelled LCZ696 in study LCZ696B2105, the estimated oral absorption of sacubitril was more than 60%. In vitro studies characterized sacubitril as a moderately high permeable drug substance.

The absolute bioavailability of valsartan following administration of LCZ696 was not estimated, valsartan bioavailability for LCZ696 was found to be higher relative to marketed valsartan. From study LCZ696A2101 it was estimated that valsartan delivered from LCZ696 with a mean relative bioavailability of 161% as compared to Diovan tablets, in the dose range of 5 to 80 mg. In study LCZ696A2103 comparable bioavailability of valsartan following administration of 400 mg LCZ696 (corresponding to 206 mg valsartan) and 320 mg Diovan was concluded.

Bioequivalence

Most of the (pharmacology) studies throughout the development of LCZ696 were performed using the Final Market Image (FMI) tablet formulation. Most importantly, the pivotal phase 3 study, study LCZ696B2314 (PARADIGM HF), was performed using the 100 and 200 mg FMI formulations. For this and other studies, a Clinical Service Form 2 (CSF2) of the 50 mg was used. In study LCZ696B2114, bioavailability of the CSF2 and FMI 50 mg formulations were compared. The C_{max} and AUC of LCZ696 analytes following administration of 50 mg FMI tablets proposed for commercialization are bioequivalent to 50 mg tablets administered in the pivotal Phase III trial. Study LCZ696B2126 results indicate that the rate and extent of absorption of LCZ696 analytes are similar between a paediatric formulation of mini-tablets (not further used) and FMI formulation.

Influence of food

Sacubitril C_{max} decreased by 48% and 56% following LCZ696 administration with food (low fat and high fat meals respectively) compared to fasting state. The t_{max} was delayed in the presence of food from 1 to 3 hours after a high fat meal. The extent of exposure AUC was slightly reduced upon administration with a low fat meal and appeared to be unchanged after administration of a high fat meal, as compared to fasting state.

The LBQ657 C_{max} decreased by 19% and 28% in the low fat and high fat treatment arms, respectively. The t_{max} was delayed from 2 to 6 hours with a high fat diet. The extent of exposure of LBQ657 was unchanged upon administration with food, as compared to fasting state. The valsartan C_{max} decreased by 40% in the low fat and high fat meals treatment arms, as compared to the fasting treatment arm. The t_{max} was delayed from 1.75 to 4 hrs in the presence of high fat meal.

Valsartan AUC decreased by 30% upon administration with low fat food, as compared to the fasting treatment arm and only to a minor extent following administration with a high fat meal.

During the pivotal phase III study, LCZ696 was administered regardless of food intake. This is acceptable. The most pronounced food effect was found for valsartan, which was deemed clinically not relevant (see the SmPC of Diovan). Active metabolite LBQ657 only demonstrated a slight reduction of the C_{max}, but not AUC. This was acceptable and the proposed SmPC text of the food effect was supported.

In conclusion, administration of LCZ696 with food has no clinically significant impact on the systemic exposures of sacubitril, LBQ657 and valsartan. LCZ696 can be administered with or without food.

Further, no interaction due to changes in gastric pH is expected as no effect on LCZ696 analytes was seen in an interaction study with omeprazole.

Distribution

The apparent volumes of distribution (Vz/F) of sacubitril and valsartan were 157.4 L and 107.8 L following administration of LCZ696, suggesting distribution to tissues. LCZ696 analytes were highly bound to plasma proteins. The plasma protein binding for sacubitril, LBQ657 and valsartan was 97%, 97% and 94% respectively. Both sacubitril and LBQ657 were highly bound to human serum albumin protein (99%) and less extensively to α1-acid glycoprotein (AGP). The protein binding of LBQ657 and valsartan was similar between subjects with mild hepatic impairment and matched healthy subjects. The free fractions of LBQ657 in moderate hepatic impairment subjects were slightly higher than those of matched healthy subjects. Data from a mass balance study suggested that the drug-related radioactivity was not significantly distributed to red blood cells. Based on the comparison of plasma and CSF exposures, LBQ657 crosses the blood brain barrier to a limited extent (0.28%).

Elimination

About 52 - 68 % of the sacubitril dose from LCZ696 was excreted in urine and about 37 – 48 % of dose was excreted in the faeces. The conversion to LBQ657 was almost complete, metabolite LBQ657 was the main constituent of the excreta. Renal clearance of LBQ657 was higher than the estimated filtration (fu*GFR) and, thus, the renal excretion likely involved active secretion. *In vitro* data indicated that this may be mediated by OAT3. The smaller route, hepatic/biliary excretion, may involve hepatic uptake by OATP1B1 and 1B3.

Valsartan is primarily eliminated in faeces (about 86% of dose) and urine (about 13% of dose), mainly as unchanged drug.

Metabolism

Following oral administration, LCZ696 dissociates into valsartan and into the pro-drug sacubitril. Sacubitril is systemically readily converted to LBQ657 by ester hydrolysis with an estimated terminal half-life of about 1.5 hours following oral administration of LCZ696 and possibly also by esterase activity in the gastrointestinal tract. *In vitro* data indicated that carboxylesterase(CES)1b and CES1c similarly contributed to converting sacubitril to LBQ657, but CES2 did not. Exposure to other metabolites is considered not clinically relevant due to the very low concentrations. The metabolic profile is similar to the profile observed for other species. LBQ657 is the major

circulating metabolite of sacubitril in the plasma. In vitro permeability values classify LBQ657 as a poorly permeable substance. It can be concluded that sacubitril and LBQ657 do not undergo significant metabolism by cytochrome P450 (CYP450) isozymes.

As LBQ657 is the predominant metabolite in both the plasma and the excreta, it can be concluded that LBQ657 does not undergo significant metabolism. The half-life of LBQ657 was determined to be about 11.5 hours, concentrations were high compared to sacubitril (4-fold). The mean peak concentration following administration of 200 mg was about 8000 ng/ml. The maximum concentrations were reached between 1.5 and 2 hour.

Valsartan is not significantly metabolized, it is CYP2C9 mediated metabolized to valeryl-4hydroxy-valsartan which contributes to less than 10% of total administered dose.

Dose proportionality and time dependencies

The exposure of sacubitril, LBQ657 and valsartan increased approximately dose linear in the pooled analysis study CLCZ696B; with a 2-fold increase in LCZ696 dose, the exposure of sacubitril increased proportionally and LBQ657 and valsartan exposure increased by 1.87-fold and 1.69-fold, respectively.

Following BID administration of 200 mg LCZ696 for 5 days, sacubitril, LBQ657 and valsartan were slightly accumulated with Racc 1.10, 1.61 and 1.30. The t_{max} of the three analytes was not altered. Half-life values of 1.4h (sacubitril), 11.5h (LBQ657) and 9.9h (valsartan) were found in the pooled analysis. The accumulation as estimated in both analyses is expected considering these half-life values. These ratios of accumulation were confirmed in the pooled analysis and are expected to be higher in the patient populations, based on the PopPK.

Intra- and inter-individual variability

With pooled analysis of pharmacokinetic data, the inter-subject variability of LBQ657 was found up to 26% for C_{max} and 33% for the AUC.

Pharmacokinetics in target population

Approximately 2-fold increase in plasma exposure (AUC) of LBQ657 and valsartan was observed in patients compared to healthy volunteers and the $C_{max,ss}$ values were also more than 50% higher. A higher ratio of accumulation upon multiple dose administration of up to 3.5-fold for LBQ657 and 1.9-fold for valsartan was estimated. The absorption rate in patients with HFrEF appeared to be slightly reduced. The observed higher exposure in heart failure patients is probably the result of the combined effect of several covariates.

Special populations

Impaired renal function

The exposure of LBQ657 increased by 1.27-fold, 2.29-fold and 2.90-fold in subjects with mild, moderate and severe renal impairment, respectively compared to healthy volunteers. No significant impact of mild to moderate renal impairment was observed on the exposure of both sacubitril and valsartan. While severe renal impairment has no impact on sacubitril exposure, the valsartan exposure increased by 1.58-fold. No studies have been performed in patients undergoing dialysis.

In the population PK analysis there was ~2-fold increase in exposure of LBQ657 for patients with moderate renal impairment compared to subjects with normal renal function.

Consequently, advice was given in section 4.2 of the SmPC on the starting dose in moderate renal impairment and the usage in severe renal impairment.

Impaired hepatic function

The total concentration exposures of sacubitril increased by 1.5- and 3.4- fold, LBQ657 increased by 1.5- and 1.9-fold and valsartan increased by 1.2-fold and 2.1-fold, in patients with mild and moderate hepatic impairment, respectively, compared to matching healthy subjects. No studies have been conducted in patients with severe hepatic impairment (Child-Pugh C classification).

In the population PK analysis total bilirubin (TBIL), a marker of hepatic impairment, was identified as possibly relevant covariate. When comparing patients with high (>9 µmol/L) vs low (≤ 9 µmol/L) TBIL levels suggests ~30% increase of the AUC_{ss} for valsartan but minimal increase for LBQ657.

Gender and race

There is no effect of gender on the pharmacokinetics of LCZ696, the pharmacokinetics of LBQ657 and valsartan are similar between male and female subjects. Furthermore, no significant impact of the race/ ethnicity of the patients on the pharmacokinetics of LCZ696 analytes is observed.

Weight

The pharmacokinetic analyses indicate that there is no clinically relevant difference in exposure of sacubitril, valsartan and LBQ657 in subjects weighing more than 99 kg compared to less than 75 kg. In the population PK analysis weight increased exposure of LBQ657 ($p<0.05$) with ~15% for lighter weight (≤65kg versus >65kg).

Elderly

Patients over 65 years of age are expected to have higher exposures of 22, 39 and 24% for sacubitril, LBQ657 and valsartan respectively. This may be associated with the decreased renal function in the elderly subjects.

Table Representation of older subjects/patients receiving LCZ696 in the LCZ696 program

	All ages n	Age 65-74 n (%)	Age 75-84 n (%)	Age 85+ n (%)
PK/PD Trials	1117	57 (5.1%)	16 (1.4%)	0 (0%)
Controlled Trials				
Hypertension[1]	4639	1345 (29.0%)	311 (6.7%)	9 (0.2%)
Heart failure[2]	4849	1507 (31.1%)	856 (17.7%)	81 (1.7%)
Study B2314 run-in	9419	2894 (30.7%)	1625 (17.3%)	150 (1.6%)
Non-controlled Trials[3]	408	55 (13.5%)	6 (1.5%)	1 (0.2%)

[1] Controlled HTN trials: CLCZ696A1306, CLCZ696A2316, CLCZ696A2319, CLCZ696A2201, CLCZ696A2219 and CLCZ696A2223 (hypertension pooled Group B [SCS Table 1-2] – Randomized set/Full analysis set)

[2] Controlled HF trials: double-blind period of studies CLCZ696B2214, CLCZ696B2228 and CLCZ696B2314 (Safety set)

[3] Non-controlled hypertension studies: CLCZ696A1304 (Safety set), CLCZ696A1305 (Safety set) and CLCZ696A2219E1 (Treated set)

The number of older subjects included in PK/PD trials was low (16 subjects 75-84yrs) or non-existent (subjects >85 yrs). However, older patients were included in controlled and non-controlled trails and safety and efficacy was established for the older age groups. The percentage of older patients included in the phase-3 trial was in line with other HF trials and was considered sufficient for evaluating LCZ696 in a target population with many older patients. In all age groups, efficacy on the primary endpoint and it's components was better for LCZ696 compared to enalapril, although both absolute and relative benefits were smaller than in younger age groups. AEs and SAEs increase with age, but as in younger subjects, less (S)AEs occurred with LCZ696 compared to enalapril.

With regard to PK/PD: exposure of valsartan and LBQ657 was assessed in a subpopulation of HF patients who participated in PARADIGM-HF. The steady state AUC values for both LBQ657 and valsartan tend to be higher for elderly patient, but only to a minor extent. Therefore, CHMP agreed that no dose adjustment is necessary and it is sufficient to emphasise the importance of dosing in accordance with the renal function for the elderly population, which is now included in section 4.2 of the SmPC.

Paediatric population

The pharmacokinetics, pharmacodynamics, safety and efficacy have not yet been evaluated in the clinical development program in children with HF condition either for LCZ696 (sacubitril/valsartan) or sacubitril alone or valsartan alone. LCZ696is indicated in adults and there is currently no indication in children (<18 years old).

Pharmacokinetic interaction studies

Other drugs affecting the pharmacokinetics of sacubitril, LBQ657 or valsartan

The company evaluated the potential for interactions of sacubitril (AHU377), the active metabolite LBQ657 and valsartan in vitro and in vivo. Sacubitril is extensively metabolised by systemic esterase activity and possibly also by esterase activity in the gastrointestinal tract. Therefore, DDIs could occur with other drugs that inhibit the esterase.

Sacubitril and its active metabolite LBQ657 do not undergo CYP-mediated metabolism. Valsartan is metabolized to a limited extent (about 10%) by CYP2C9, which is the enzyme responsible for the formation of 4-hydroxyvaleryl metabolite of valsartan in human microsomes. Therefore no interactions with inhibitors of inducers of the cytochrome P450 enzymes are expected.

In *in vitro* trials was found that sacubitril is a substrate for P-gp, however its Km value associated with the sacubitril interaction with P-gp was >100 µM, which is higher than the expected maximum gastrointestinal concentration of sacubitril. Therefore P-gp is not expected to be a clinically relevant transporter.

LBQ657 is found to be a substrate for OAT3, OATP1B1 and OATP1B3. Valsartan is reported to be a substrate for the hepatic uptake transporters OATP1B1/OATP1B3 and of the hepatic efflux transporter MRP2. The interaction risk has not been studied *in vivo*, but a warning against inhibitors of these transporters is given in the SmPC.

The effect of sacubitril, LBQ657 or valsartan on other drugs

Sacubitril is a weak inhibitor for CYP2B6, CYP2C8 and CYP2C19, but not at clinically relevant concentrations. LBQ657 is a weak inhibitor for CYP2C9 which may be clinically relevant. Using pooled HLM, no time dependent inhibition was observed for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5. Valsartan is not a clinical significant inhibitor of CYPs. Sacubitril and valsartan are not CYP inducers. Although in vitro data indicated LBQ657 and valsartan are both weak inhibitors for CYP2C9 no relevant interaction was observed with the CYP2C9 substrate warfarin in study LCZ696B2112.

The transport in vitro interaction studies are summarised in Table 3.

Table 1. Summary table of in vitro transporter interaction data for sacubitril, LBQ657 and valsartan

Substance	Transporter	Substrate	Inhibitor		*In vivo* study available	Mentioned in SmPC
			IC50 (µM)	*In vivo* relevant		
Sacubitril	Pgp	Yes	>100	no		Substrate: No
	BCRP	n.d.	>100	no		
	MRP2	No	>50	Unknown		
	OATP1B1	n.d.	1.9	Yes	Atorvastatin (confirmed inhibition)	Yes
	OATP1B3	n.d.	3.8	Yes	Atorvastatin (confirmed inhibition)	Yes
	OAT1	n.d.	>50	No	Yes	No
	OAT3	n.d.	0.8	No	Yes	No
	OCT1	n.d.	>50	No		
	OCT2	n.d.	>50	No		
	MATE1	n.d.	>50	No		
	MATE2-K	n.d.	>50	No		
	BSEP	n.d.	>11.4	No		
LBQ657	Pgp	No	>50	No		
	BCRP	n.d.	>50	No		
	MRP2	No	n.d.			
	OATP1B1	Yes	126	No		Yes
	OATB1B3	Yes	>250	No		Yes
	OAT1	Yes	>50	No	Yes	Substrate: Yes, Inhibition: No
	OAT3	Yes	15.2	No	Yes	Substrate: Yes Inhibition: No
	OCT1	n.d.	>500	No		
	OCT2	n.d.	>500	No		
	MATE1	n.d.	>250	No		
	MATE2-K	n.d.	>250	No		
	BSEP	n.d.	>100	No		
Valsartan	Pgp	n.d.	n.d.			

Substance	Transporter	Substrate	Inhibitor		*In vivo* study available	Mentioned in SmPC
			IC50 (µM)	*In vivo* relevant		
	BCRP	n.d.	n.d.			
	MRP2	Yes	n.d.			Yes
	OATP1B1	Yes	n.d			Yes
	OATP1B3	Yes	n.d			Yes
	OAT1	inconclusive	14.8	No	Yes	Substrate: Yes Inhibition: No
	OAT3	Yes	1.1	No	Yes	Substrate: Yes Inhibition: No
	OCT1	n.d.	>100	No		
	OCT2	n.d.	>100	No		
	MATE1	n.d.	>100	No		
	MATE2-K	n.d.	>100	No		
	BSEP	n.d.	>50	No		

n.d. = not determined (not studied)

Sacubitril is an inhibitor of the transporters OATP1B1, OATP1B3 and OAT3 transporter. Furthermore, valsartan is an inhibitor of OAT3 and OAT1. LCZ696 may increase the systemic exposure of OATP1B1 and OATP1B3 substrates such as statins. In a clinical study LCZ696B2115 co-administration of LCZ696 with atorvastatin confirmed that co-administration of both drugs increased the C_{max} of atorvastatin and its metabolites by up to 2 fold and AUC by up to 1.3 fold.

Study LCZ696B2116 was conducted to evaluate the interaction with the OAT3 substrates. Co-administration of furosemide 40 mg (single dose) and LCZ696 200 mg bid (steady state) compared with furosemide 40 mg (single dose) alone resulted in a decreased furosemide exposure, the C_{max} and AUC were decreased by 50% and 28%, respectively. The urinary excretion of furosemide was also reduced by 26%. In this study also potential pharmacodynamic interaction of furosemide and LCZ696 was evaluated by comparing the urine volume and the excretion of sodium, potassium and creatinine after single-dose administration of furosemide with the concomitant administration of furosemide and LCZ696 (steady state). Compared with furosemide alone, the co-administration of LCZ696 reduced the mean urinary excretion of sodium within the first 4 hours after drug intake by 36.7 mmol and led to a small decrease of 1.5 mmol during the following 4 hours. The excretion of potassium and creatinine was not affected and also a minor reduction in the urinary volume was observed.

Transporter function of the other tested transporter P-gp, was not affected by sacubitril or LCZ696. Several studies with substrates digoxine (study LCZ696B2111) and carvedilol (study LCZ696B2125) confirmed that P-gp transporter function was not affected by LCZ696.

In study CLCZ696B2113 the effect of omeprazole on pharmacokinetics of LCZ696 analytes was evaluated to identify the effect of gastric pH on the absorption of LCZ696. No interaction was observed in this study.

In study LCZ696B2122 the drug interaction potential between LCZ696 and the OCT1 substrate metformin was evaluated. LCZ696 steady state pharmacokinetics did not change when administered in combination with metformin however the C_{max} and AUC of metformin were decreased by 23% when co-administered with LCZ696.

No clinically relevant interactions were observed when LCZ696 was co-administered with amlodipine, hydrochlorothiazide.

As LBQ657 has shown teratogenic effects in non-clinical studies, an *in vivo* pharmacokinetic interaction study with LCZ696 and a combined oral contraceptive was performed, as required in the EMA Interactions guideline for teratogenic substances, regardless of the results of *in vitro* induction studies. The study included 7 days of dosing with LCZ696. Small but statistically significant decreases in levonorgestrel AUC and Cmax were seen (7% and 15%, respectively) while there were no statistically significant effects on ethinyl estradiol.

In study LCZ696B2225 addition of a single dose of sildenafil to LCZ696 at steady state in patients with hypertension was associated with a significantly greater blood pressure reduction compared to administration of LCZ696 alone. The observed additional reduction of the blood pressure was mainly observed in the first few hours after administration of sildenafil.

In study LCZ696B2128 the pharmacodynamic interaction potential between LCZ696 and intravenously administered nitroglycerine was evaluated. No pharmacodynamic interaction was observed between nitroglycerin and LCZ696 with respect to blood pressure reduction. However an increase of the pulse rate was observed when nitroglycerin was administered with LCZ696.

2.3.3. Pharmacodynamics

The beneficial effects of LCZ696 in patients with heart failure are likely to result from enhancement of protective endogenous systems such as the natriuretic peptide system and other vasoactive neprilysin substrates and the simultaneous inhibition of organ injury, driven by activation of the RAAS.

This section summarizes pharmacodynamic results from studies with LCZ696, sacubitril and valsartan (table PD1). Due to limited PD results from studies with sacubitril and valsartan alone, PD results are not separated by LCZ696, sacubitril and valsartan. Results generated with sacubitril and valsartan alone are highlighted as appropriate.

Table PD1: Most important studies providing PD data

A2102	LCZ696A2102 was a randomized, double-blind, placebo controlled, time-lagged, parallel group, interwoven single- and multiple-ascending dose study to assess safety, tolerability and pharmacokinetics of LCZ696 in healthy subjects. Doses in the multiple dose part ranged from 0 (placebo) to 900 mg once daily. At each of two study days data from N=7-9 subjects were available for analysis. The changes from baseline in the plasma cGMP area under the effect curves (AUEC) were the endpoints in the analysis.
A2103	An open-label, randomized, two-treatment, two period crossover, single-dose study to determine the relative bioavailability of valsartan following administration of 400 mg LCZ696 compared to 320 mg Diovan in healthy volunteers.
A2117	An open label, non-randomized study to explore safety/tolerability, pharmacokinetics and

	pharmacodynamics of LCZ696 in patients with stable heart failure.
A2126	A randomized, double-blind, placebo-controlled study to explore the effect of LCZ696 on amyloid-β concentrations in cerebrospinal fluid (CSF) in healthy subjects This was a non-confirmatory, double-blind, randomized, placebo-controlled, multiple dose and parallel-group study investigating the effect of LCZ696 on CSF amyloid-β concentrations in healthy subjects.
A2201	The purpose of this study was to evaluate the efficacy and safety of LCZ696 (100 mg, 200 mg and 400 mg qd) in comparison to valsartan (80, 160, 320 mg qd) or sacubitril (200 mg qd) alone and was conducted in Caucasian patients with essential hypertension. This was a multi-center, randomized, double-blind, active- and placebo-controlled, 8 week treatment, dose-ranging study in patients with hypertension.
B2123	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. The study was a randomized, positive and placebo controlled, partially blinded, single dose, twelve sequence crossover study in healthy male subjects. The study comprised of a screening period of up to 21 days, four baseline (1 day each) and four treatment periods (2 days each) separated by three wash-out periods of at least 4 days and a final study completion evaluation approximately 4 to 10 days after last treatment. The total duration of study participation per subject was approximately 8 weeks.
B2207	A randomized, double-blind, parallel group study to evaluate metabolic effects of LCZ696 and amlodipine in obese hypertensive subjects. This was an exploratory, multi-centre, randomized, double-blind, double-dummy, parallel group study to evaluate metabolic effects of LCZ696 and amlodipine in obese hypertensive patients. The study started with a screening period (up to 4 weeks), followed by a washout period (Day -28 to Day 1) and a double-blind treatment period (Day 1 to Day 57) and concluded with an end of study visit.
B2223	LCZ696B2223 was a randomized, double-blind, two-way cross-over study. Following screening, 16 patients with HF were randomized to receive LCZ696 200 mg bid and valsartan 160 mg bid for 7 days in two cross-over treatment periods, while remaining on stable valsartan 160 mg bid treatment during the 7-day run-in and washout periods. The purpose of this study was to evaluate the effect of LCZ696 and valsartan on sodium excretion in patients with stable chronic heart failure (EF $\leq$ 40% and plasma BNP concentrations $\geq$ 100 pg/mL) and in patients with mild to moderate hypertension.
B2314 PARADIGM-HF	Paradigm-HF was the pivotal trial in this dossier and is described extensively under efficacy.

Mechanism of action and primary pharmacology

Pharmacodynamic data obtained in the clinical pharmacology and clinical development programs demonstrate that LCZ696 exhibits the novel mechanism of action of an angiotensin receptor neprilysin inhibitor (ARNI) by simultaneously inhibiting neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril and by blocking the angiotensin II type-1 (AT1) receptor via valsartan. The cardiovascular effects of LCZ696 in heart failure patients were attributed to the enhancement of peptides that are degraded by

neprilysin such as natriuretic peptides (NP) by LBQ657 and the simultaneous inhibition of the deleterious effects of angiotensin II by valsartan.

NPs exert their effects by activating membrane-bound guanylyl cyclase-coupled receptors (NPR-A and -B), resulting in increased concentrations of the second messenger cyclic guanosine monophosphate (cGMP) which was therefore used as one of multiple biomarkers indicative of neprilysin inhibition. NPs have been associated with beneficial cardiovascular and renal effects, including reduction of BP, vasodilation, natriuresis and diuresis, increased glomerular filtration and renal blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity and anti-hypertrophic and anti-fibrotic effects.

In a 7-day valsartan-controlled study (B2223) in patients with HFrEF, administration of LCZ696 resulted in an initial increase in natriuresis, increased urine cGMP and decreased plasma MR-proANP and NT-proBNP compared to valsartan.

In a 21-day, open label, non-controlled study in HFrEF patients (A2117), LCZ696 increased urine ANP and cGMP and plasma cGMP and decreased plasma NT-proBNP, aldosterone and endothelin-1 compared to baseline. LCZ696 also blocked the AT1-receptor as evidenced by increased plasma renin activity and plasma renin concentrations.

Treatment with sacubitril alone resulted in increased plasma angiotensin II concentrations [A2103]. Since LCZ696 administration also results in increased angiotensin II levels due to AT1-receptor blockade and subsequent inhibition of the negative feedback on angiotensin II, the individual contribution of sacubitril and valsartan to angiotensin II increase following administration of LCZ696 cannot be discerned.

AT1-receptor blockade

Biomarker data (increased plasma renin activity, plasma renin concentration and angiotensin II) demonstrate that LCZ696 provides AT1-receptor blockade comparable to valsartan in patients with heart failure. LCZ696 also resulted in a reduction of aldosterone in patients with HFrEF [A2117: -21% after 21 days, PARADIGM-HF: -15.1% after 8 months].

Renal effects

Since natriuretic peptides inhibit sodium reabsorption resulting in natriuretic and diuretic effects and are increased as a result of neprilysin inhibition, both natriuresis and diuresis were studied within the LCZ696 clinical pharmacology program.

On the first day of use, LCZ696 resulted in more natriuresis (+11%) and diuresis (+11%) in patients with HF than valsartan (B2223). Cumulative data over one week show small decreases of these parameters (-8% and -6% respectively). The data were non-conclusive with regards to measured GFR and renal blood flow (RBF).

Secondary pharmacology

Effects on blood pressure

LCZ696 was associated with BP reductions in healthy subjects, patients with HF and patients with hypertension in the absence of consistent increases in heart rate. The largest study from the hypertension program so far was LCZ696A2201. This study also contributed to the description of PD, the characterization of the components of LCZ696 and dose selection. The purpose of this study was to evaluate the efficacy and safety of LCZ696 (100 mg, 200 mg and 400 mg qd) in comparison to valsartan (80, 160, 320 mg qd) or sacubitril (200 mg qd) alone and was conducted in Caucasian patients with essential hypertension. This was a multi-center,

randomized, double-blind, active- and placebo-controlled, 8 week treatment, dose-ranging study in patients with hypertension. Main study results are included in table PD2.

Table PD2: Within treatment comparison for change from baseline in mean sitting diastolic blood pressure (msDBP) at Week 8 endpoint (Intent-to-treat population): Change from baseline between baseline and week 8 endpoint

Treatment group	N	Baseline Mean (SE)	Week 8 Mean (SE)	Change Mean (SE)
LCZ696 100 mg	154	99.97 (0.28)	89.77 (0.70)	-10.20 (0.69)
LCZ696 200 mg	168	99.97 (0.31)	87.00 (0.72)	-12.97 (0.72)
LCZ696 400 mg	170	100.41 (0.31)	86.38 (0.71)	-14.04 (0.72)
Valsartan 80 mg	163	99.47 (0.32)	90.48 (0.71)	-9.00 (0.68)
Valsartan 160 mg	163	100.02 (0.32)	90.05 (0.76)	-9.97 (0.77)
Valsartan 320 mg	163	99.50 (0.28)	88.63 (0.73)	-10.87 (0.73)
sacubitril 200 mg	164	100.16 (0.30)	90.29 (0.71)	-9.87 (0.70)
Placebo	172	99.02 (0.29)	92.61 (0.74)	-6.40 (0.77)

Source A2201, Table 14.2-1.1a

Lipolysis

Angiotensin II and ANP have been implicated in the regulation of glucose and free fatty acid metabolism, including increased adipose tissue lipolysis by ANP. Since an increase in lipolysis may result in impaired insulin sensitivity, the metabolic effects of LCZ696 have been investigated within the clinical pharmacology program.

In trial B2207, the effects of treatment of obese hypertensive patients for 8 weeks with LCZ696 (400 mg qd) or amlodipine (10 mg qd) on the insulin sensitivity index (SI) were compared. SI improved both after amlodipine (+3.8%) and LCZ696 (+11.9%). The treatment contrast was not statistically significant.

Amyloid-β

In vitro and non-clinical studies have shown that neprilysin is one of multiple enzymes involved in the proteolytic degradation of amyloid-β (Aβ). To investigate the risk of Aβ accumulation in the brain, CSF levels of Aβ were investigated in healthy volunteers after 2 weeks treatment with LCZ696 or placebo.

In study LCZ696A2126, administration of LCZ696 400 mg once daily for 14 days did not result in changes in cerebrospinal fluid concentrations of amyloidogenic Aβ subtypes 1-40 and 1-42, despite having measurable concentrations of LBQ657 in the cerebrospinal fluid sufficient to inhibit neprilysin. For Aβ 1-38 in CSF, increases were found both after treatment with LCZ696 (58%) and placebo (11%). The treatment effect (42%, 95% CI: 5%, 91%) was statistically significant (p=0.023). There was also an increase in plasma Aβ 1-40 with LCZ696 treatment (baseline: 2287.0 pg/mL*hr, change 1143.9 (+50.0%)).

Cardiac conduction and repolarization

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 2005* and subsequent *Q&A documents issued by the ICH E14 Implementation Working Group* as a definitive evaluation to determine whether therapeutic (400 mg) and supra-therapeutic (1200 mg) doses of LCZ696 have the potential to delay cardiac repolarization as detected by a prolongation of the QT/QTc interval by more than 10 ms at the two-sided upper 90% confidence limit. LCZ696 had no significant effect on QT/QTc as demonstrated in fig PD1, tables PD3 and PD4.

Figure PD1: Estimated mean difference and 90 percent CI for placebo-corrected change from baseline in QTcF (ΔΔQTcF) for LCZ696 400 mg and 1200 mg and moxifloxacin 400 mg

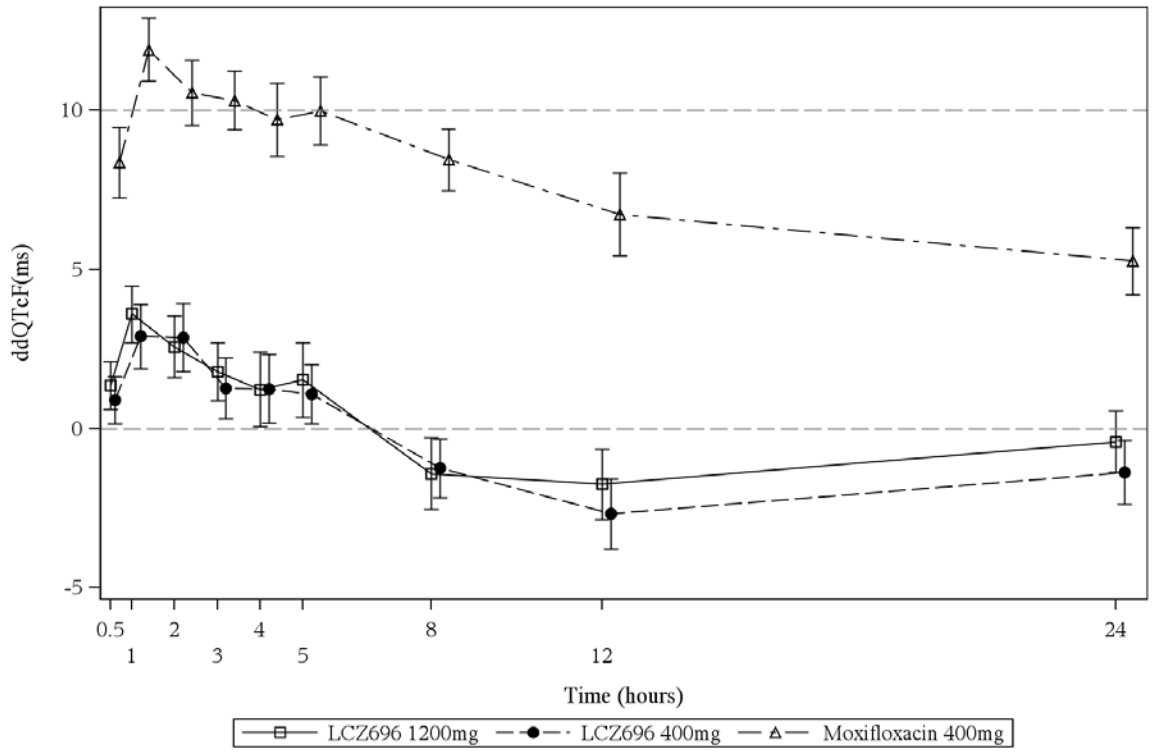


Table PD 3: Treatment comparisons for placebo-corrected change from mean baseline in QTc (ΔΔQTc) by time and LCZ696 dose (Pharmacodynamic analysis set)

		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)

Table PD 4: Treatment comparisons of placebo-corrected change from mean baseline in QTc (ΔΔQTc) by time for moxifloxacin (Pharmacodynamic analysis set)

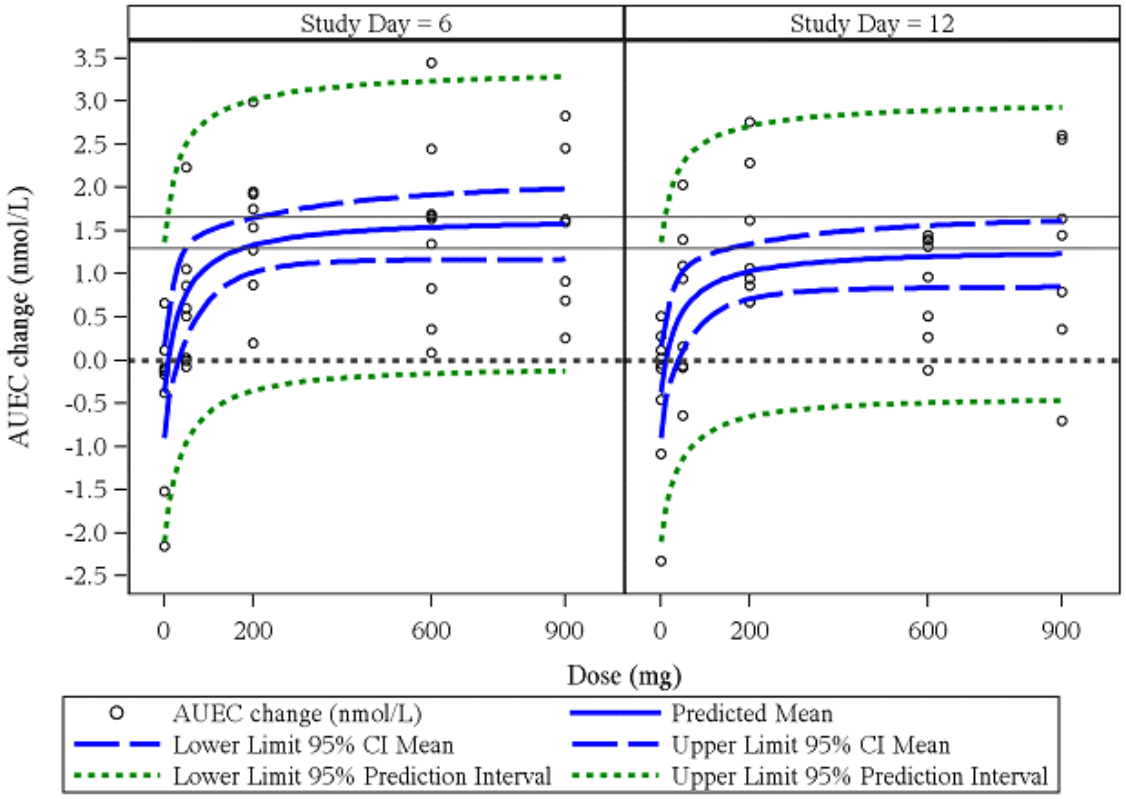
		Moxifloxacin 400mg- Placebo			
Parameter	Hours post dose (hh:mm)	Estimated difference	SE	90% CI	p-value
QTcF (ms)	0:30	8.360	0.661	(7.26, 9.46)	<.001
	1:00	11.903	0.602	(10.91, 12.90)	<.001
	2:00	10.555	0.608	(9.54, 11.57)	<.001
	3:00	10.311	0.551	(9.39, 11.23)	<.001
	4:00	9.703	0.691	(8.55, 10.85)	<.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

Relationship between plasma concentration and effect

To assess the dose-response relationship of LCZ696 with respect to biomarker response, a dose response analysis was performed for cyclic guanosine monophosphate (cGMP) following multiple ascending doses of LCZ696 in healthy subjects [Study LCZ696A2102]. As described earlier, cGMP is a biomarker of neprilysin inhibition. Exposure-response modeling was not performed as plasma concentrations of LCZ696 were not measured at the times at which the biomarker samples were collected.

An Emax model was used to describe cGMP AUEC changes from baseline. Changes from baseline in cGMP AUEC in the dose range of 0 to 900 mg LCZ696 were well described by an Emax model with a steep dose response at the lower doses (up to approximately 100 mg LCZ696) and a saturation of the effect at the higher doses (at and above 200 mg). Model predicted means overlaid to individual cGMP AUEC change from baseline data from are shown in Figure PD2. The maximum change from baseline (Emax) in cGMP AUEC was estimated to be 2.03 and 1.67 nmol/L for Day 6 and Day 12, respectively. The cGMP (95% CI) simulation relative to this maximum was estimated to be 56% (21%, 92%), 72% (43%, 100%), 84% (64%, 100%) and 91% (80%, 100%) with LCZ696 50, 100, 200 and 400 mg once daily, respectively.

Figure PD2: Model predicted means overlaid to individual cGMP AUEC change from baseline data [Study LCZ696A2102]



The cGMP dose response curves estimated from study LCZ696A2102 suggest that in terms of biomarker response a dose of 200 mg once daily is superior over 100 mg and 50 mg once daily because it produces the largest cGMP increase. Furthermore, the cGMP dose-response curve is initially steep and flattens at a dose of 200 mg and above, resulting in only small further increases in cGMP response when escalating the dose above 200 mg. Therefore, the dose of LCZ696 200 mg provides close to maximal neprilysin inhibition. No additional benefit with respect to neprilysin inhibition is expected when further increasing the dose.

2.3.4. Discussion on clinical pharmacology

Bioavailability

Valsartan contained in LCZ696 has a higher bioavailability than valsartan in other marketed tablet formulations. Uncertainties were observed regarding the formulations used during the comparative studies. Valsartan given as Diovan 160 mg capsule, which was administered during study LCZ696A2103, was not the marketed formulation, but a capsule formulation based on the EU commercial capsule blend. Furthermore, the 5 mg and 50 mg tablets that were used in comparative bioavailability studies LCZ696A2101 and LCZ696A2103 have been manufactured using a direct compression (DC) technique instead of the finalized roller compaction (RC) method. More rapid dissolution for the DC tablets was observed. However, a cross-study comparison of exposure data for 5 and 50 mg DC and RC studies did not indicate major differences. Furthermore, the 50 mg tablets used in study LCZ696A2103 were only a small part of the dose. Overall, it was concluded that the estimation of the extent of suprabioavailability might not be accurate. However, no major deviations were expected that would impact on the proposed dosing or dosing recommendations of LCZ696.

The most prominent *in vivo* metabolic pathway of sacubitril involved the **ester hydrolysis of sacubitril** to yield LBQ657, the active metabolite. The applicant performed an investigation *in vitro* using recombinant human carboxylesterase 1b, 1c and 2. It was demonstrated that CES1b and CES1c similarly contributed to converting sacubitril to LBQ657, CES2 did not. The applicant did not investigate all possibly relevant carboxyl esterases (e.g. CES3) that might be involved in the ester hydrolysis of sacubitril to LBQ657. However, the low sequence homology and lower reported catalytic activity indicate that the potential of a relevant contribution of CES3, CES4, or CES5 can be considered unlikely.

With respect to **dose proportionality**, only sacubitril increases proportionally to the dose. The exposure to LBQ657 was nearly dose proportional for the extent of absorption but not in C_{max}. For valsartan dose proportionality was not established. Only a crude estimation was provided to substantiate the claim for dose proportionality and dose linearity. However, it was agreed to state approximate linearity for the pharmacokinetics of sacubitril, LBQ657 and valsartan, but only over the approved dose range.

The justification for applicability of the **dose finding studies** performed in healthy volunteers to the actual patient population was limited. Based on the dose finding studies a LCZ696 dosing regimen of a 200 mg BID was selected for further development and LCZ696 has only been studied in a 200 mg BID posology. However the target population has a reduced clearance of the LCZ696 analytes compared to healthy subjects. Still, the results of the PARADIGM-HF study have shown that the proposed dose was effective and reasonably safe. Using a higher dose in a once daily regimen might be associated with adverse effects, especially more hypotension, that can be mitigated by twice daily dosing. Therefore, the dose was considered acceptable.

Regarding the **food effect** the following was discussed. Compared to fasted state, low fat and high fat food reduced valsartan exposure by 34% and 9%; and Cmax by 39% and 40%, respectively. The applicant put forward arguments where results from a Diovan PD food effect study were referred to. In the study, the effect of a high fat meal on BP response in 102 hypertensive patients was not found to be clinically or statistically significant. This argumentation was not shared with the applicant as the conditions tested in the PD study were with high fat food, while the most problematic scenario is administration with low fat food, and further, it was not obvious that BP response were a suitable PD marker under the current circumstances. Consequently, the information from dedicated studies regarding the potential impact of ingestion with concomitant low fat meals was not available. However, as pivotal PARADIGM-HF study included a large number of patients and allowed administration irrespective of food intake, the CHMP accepted the recommendations stated in the SmPC where no restrictions regarding the food intake were included.

Special populations

While severe **renal impairment (RI)** has no impact on sacubitril exposure, the valsartan exposure increased by 1.58-fold. The exposure of LBQ657 increased by 1.27-fold, 2.29-fold and 2.90-fold in subjects with mild, moderate and severe RI, respectively. The applicant considered the increased exposure of metabolite LBQ657 up to a factor of 2 for subjects with moderate RI as not clinically relevant, as LCZ696 was safe and well tolerated in RI studies and in patients with RI enrolled in the pivotal PARADIGM-HF study. In PARADIGM-HF the mean GFR was 68 ml/min/1.73 m2, with about 1/3 of patients with a GFR <60 ml/min/1.73 m2. Thus, the “typical” patient in the phase III study had mild RI, and the exposure in the mild RI in the PK study was therefore considered the most relevant target exposure. Compared with mild RI, the mean increase in LBQ657 exposure was 1.4-fold and 2.2-fold in moderate and severe RI, respectively. There was no increase in valsartan exposure in moderate or severe RI as compared with mild RI. Given the safety concerns for patients with moderate and severe RI, and as the dose may be up-titrated if tolerated, it was proposed halving the starting dose in moderate RI as well as severe RI, which is reflected as a recommendation in section 4.2 of the SmPC. Regarding the PK for severe RI, based on an assumed linear relationship between GFR and apparent clearance of LBQ657, the applicant had

estimated that there may be about 1.6-fold difference in exposure depending on whether a patient has a GFR of 30 ml/min or 11 ml/min. However, data were limited and it was not considered possible to refine dose recommendations for severe renal impairment any further. As reflected in section 4.2 of the SmPC the use of LCZ696 should not be recommended to patients with end-stage renal disease (ESRD) as there is no experience in such patients.

The total concentration exposures of sacubitril increased by 1.5- and 3.4- fold, LBQ657 increased by 1.5- and 1.9-fold and valsartan increased by 1.2-fold and 2.1-fold, in patients with mild and **moderate hepatic impairment (HI)**, respectively, compared to matching healthy subjects. For sacubitril the 3.4-fold increase was not considered relevant as sacubitril is an inactive pro-drug. Protein binding for LBQ657 was reduced with moderate HI. The unbound fraction was increased by about 60% (from 0.0169 ± 0.004 to 0.0278 ± 0.008). Since the precise effect of this was unclear, the ratio of the unbound PK parameters should be used as a 'worst-case' scenario. Thus, the exposure of LBQ657 increased by 3.0-fold in patients with moderate HI compared to matching healthy subjects. LCZ696 was safe and well tolerated in the HI study. It was agreed that LCZ696 should be used with caution in patients with moderate hepatic impairment and the recommended starting dose in patients with moderate HI (Child-Pugh B classification) is 24 mg/26 mg twice daily. LCZ696 is contraindicated in patients with severe HI, biliary cirrhosis or cholestasis (Child Pugh C classification).

PKs results indicate that there is no clinically relevant difference in exposure of sacubitril, valsartan and LBQ657 in subjects **weighing more than 65 kg** compared to less than 65 kg. The applicant specified population PK parameters per body weight quartile. It was indeed agreed with the applicant that exposure differences were not of clinical relevance. It was concluded that body weight did not influence exposure of sacubitril, LBQ657 and valsartan to a significant extent.

Patients **over 65 years of age** were expected to have higher exposures of 22, 39 and 24% for sacubitril, LBQ657 and valsartan respectively. This may be associated with the decreased renal function in the elderly subjects. The number of subjects included in PK/PD trials was low (16 subjects 75-84yrs) or non existent (subjects >85 yrs), but the percentage of older patients included in the phase III trial was similar to other HF trials. The increased exposures of LBQ657 and valsartan in elderly subjects were still associated with a positive benefit-risk profile for LCZ696 in heart failure patients ≥75 years and ≥85 years old. Therefore no dosage adjustment was considered necessary based on the patient's age. As renal function declines with age, the dose should be in line with the renal function of the elderly patient, which is also advised in section 4.2 of the SmPC.

Results of the study LCZ696B2126 [A bioavailability study in healthy adult subjects (CLCZ696 B2126) **included in the agreed PIP**] indicate that the rate and extent of absorption of LCZ696 analytes are similar between a paediatric formulation of mini-tablets (not further used) and FMI formulation.

Interactions

In vitro metabolism studies and available literature indicated that potential for **CYP450 based drug interactions** was low since there was limited metabolism of sacubitril, its active metabolite and LCZ696 and valsartan via CYP450 enzymes. No time dependent inhibition was observed for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5.

Sacubitril inhibited **OATP1B1 and 1B3** *in vitro*. This was confirmed *in vivo* as the AUC for atorvastatin and its metabolites was increased when co-administered with LCZ696. However, the increase in AUC was relatively small (about 20-35%) and the applicant agreed that simvastatin may be a more sensitive OATP substrate than atorvastatin. However, large effects of sacubitril on more sensitive OATP substrates than atorvastatin were not expected, as sacubitril concentrations were rapidly decreasing after administration of LCZ696. It was agreed that a relevantly greater effect on simvastatin might not be expected, since in a study by *Niemi et al* the

difference between effects on a genetic variant of OATP1B1 on simvastatin and atorvastatin was not marked. Further, the applicant referred to co-administration of simvastatin with LCZ696 in the PARADIGM study, but these data were difficult to interpret. Nonetheless, it was agreed to add a general warning of caution when co-administering LCZ696 with statins and describing the effect of LCZ696 on atorvastatin. The applicant was performing a new interaction study primarily to elucidate whether staggered dosing of LCZ696 and a statin could minimize the effects of OATP inhibition. The applicant committed to provide the final CSR of the drug interaction study between LCZ696 and simvastatin and this was reflected in the agreed version of the RMP.

LBQ657 and sacubitril inhibited OAT3 *in vitro* and valsartan inhibited OAT1 and OAT3 *in vitro,* with IC50 below the concentration cut-off for possible clinical relevance. No increases in furosemide or hydrochlorothiazide, reported to be **OAT1 and OAT3 substrates**, were observed in *in vivo* interaction studies with multiple-dose LCZ696. Based on *in vitro* data it could be concluded that LBQ657 may be a substrate for OAT1 and OAT3 and also OATP1B1 and OATP1B3 had some transporter activity. Valsartan was reported to be a substrate for the hepatic uptake transporters OATP1B1/OATP1B3 and of the hepatic efflux transporter MRP2. Therefore interactions with inhibitors of OATP1B1, OATP1B3, OAT1, OAT3 and MPR2 may be expected and this was reflected in the SmPC.

Sacubitril showed no signs of **Pgp or BCRP inhibition** *in vitro*. The concentrations in the experiment (50 µM) were too low to exclude an effect on intestinal Pgp (cutoff value 94 µM). A new *in vitro* study was performed with higher concentrations (100 µM) and it could be concluded that no interaction between sacubutril and P-gp, BCRP or MRP2 were expected at the intestinal level.

In a clinical interaction study with **metformin** the C_{max} and AUC of metformin were slightly decreased when co-administered with LCZ696. Although the mechanism of the observed interaction was not understood and the *in vitro* studies did not predict a clinical relevant interaction with OCT1 substrates, it was agreed to mention the interaction with metformin in the SmPC.

In the PD study with **sildenafil** coadministered with LCZ696 a significantly greater BP reduction was observed, compared to administration of LCZ696 alone. The additional reduction of the BP was mainly observed in the first few hours after administration of sildenafil, which is in line with the short sildenafil half-life of about 4 hours. The company has not investigated the clinical relevant dosing regimen of LCZ696 200mg BID in combination with sildenafil administration in the evening. It could be expected that sildenafil would have a similar effect on the BP during the night, however on top of the physiological decrease of BP at night. Thus potentially the absolute BP may be lower when LCZ696 200mg BID is co-administered with sildenafil in the evening. Therefore, it was agreed to recommend a caution in the SmPC when sildenafil or another PDE 5 inhibitor treatment is initiated.

In the PD interaction study with intravenously administered **nitroglycerin** an increase of the pulse rate was observed when nitroglycerin was administered with LCZ696. This could be considered clinically manageable irrelevant for IV nitroglycerin as it is administered under medical supervision, however the interaction may be clinically relevant when nitrates are administered without medical supervision, via oral, transdermal, or nasal routes of administration, therefore it was agreed to describe the interaction in the SmPC.

The interaction study with **oral contraceptives** was required according to the *EMA Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**)*, as LBQ657 had showed teratogenic effects in non-clinical studies. The study included 7 days of dosing with LCZ696. There were still conflicting results concerning CYP3A4 enzyme half-life in scientific literature, and therefore a duration of 10-14 days was recommended (*Questions & Answers: positions on specific questions addressed to the Pharmacokinetics Working Party (PKWP) EMA/618604/2008 Rev. 12*) to evaluate the full induction effect for a perpetrator that does not accumulate during multiple-dose conditions. If only the enzyme turnover time was used for

extrapolating data from the performed study, the 7 % decrease in levonorgestrel AUC observed in the study may approximate 10 % at a true steady state. Some accumulation of LBQ657 (1.6- fold) was also observed in the study and a marginally larger decrease in levonorgestrel AUC may in worst case be seen at a true steady state. Nevertheless, given the predicted small decrease in levonorgestrel AUC, even in a worst case situation, no specific recommendations regarding concomitant administration with oral contraceptives were considered needed.

Primary pharmacology

LCZ696 provides a novel approach to treatment of HF, by combining neprilysin inhibition with AT1 receptor blockade. The PD trial data consistently showed that LCZ696 has the properties of a NEP inhibitor, increasing the concentrations of its substrates BNP and angiotensin II. Also the levels of **BNP's second messenger cGMP** were increased. The increase in cGMP was considered favourable in HF. The increase in angiotensin II was considered unfavourable and supported the rationale to block its effects by combining NEP inhibition with AT1-recteptor blockade. AT1 receptor blockade is an established therapeutic modality in HF.

LCZ696 indeed shows AT1 receptor blockade, which manifests itself in increased renin and angiotensin II levels. Downstream in the pathway, AT1 receptor blockade could result in **reduction of aldosterone**. In PARADIGM-HF, the reduction of aldosterone was 15.1% after 8 months compared to pre-run-in values. Based on study A2117, the reduction of aldosterone levels was not yet reached after 1 week of treatment, suggesting that other mechanisms beside AT1 receptor blockade were involved. In hypertension trial A2201, aldosterone levels slightly increased. This further supported the hypothesis that other mechanisms beside AT1 receptor blockade determine the effect of LCZ696 on aldosterone. The reduction of aldosterone as caused by LCZ696 could theoretically make treatment with a mineralocorticoid antagonist (MRA) less effective. It was not considered justified to use the PARADIGM-HF to investigate this, because MRA use was promoted in the trial and use of MRAs was thus likely based on patient characteristics (confounding by indication). Still, efficacy was shown in subgroups with and without MRA use at baseline, suggesting that 15% reduction in aldosterone levels does not make co-administration of MRAs irrelevant.

Renal effects were investigated in study B2223. The interpretation of the results of B2223 was difficult as they were confounded by study procedures. Sodium excretion and urine volume with LCZ696 were increased on the first day of its use compared to valsartan, but this outcome was reversed in the cumulative results after one week. It was considered unlikely that natriuretic or diuretic effects are important for the efficacy of LCZ696. Similarly, the results for GFR and RBF were inconclusive. In PARADIGM-HF, treatment with LCZ696 resulted in a larger decrease in NT-pro-BNP than enalapril, consistent with reduced ventricular wall stress. As discussed before, BNP levels were higher with LCZ696 as BNP is a NEP substrate and cannot be used to monitor wall stress in LCZ696 users. A statement was included in the SmPC that in the PARADIGM HF study, LCZ696 **decreased plasma NT - proBNP** and **increased plasma BNP** and urine cGMP compared with enalapril and that BNP is not a suitable biomarker of heart failure in patients treated with LCZ696 because BNP is a neprilysin substrate. NT - proBNP is not a neprilysin substrate and is therefore a more suitable biomarker.

Secondary pharmacology

LCZ696 has been also developed for the treatment of **hypertension** and investigated in a number of clinical trials. Data from this development program have been summarised with respect to safety. Clinical development in HF was the focus of the current application, although LCZ696 seems to be also efficacious in hypertension.

Theoretically ANP and angiotensin II could adversely affect **insulin sensitivity**. In contrast, AT1 receptor blockade is known to improve insulin sensitivity. Thus, the net effect of LCZ696 on insulin sensitivity could not be predicted. To address this, the applicant conducted hyperinsulinaemic glucose clamps in 95 obese,

hypertensive patients. The results showed an improvement in insulin sensitivity in the LCZ696 group, which did not occur in the amlodipine group. However, the treatment contrast was not statistically significant. This may be different in HF, but the results available so far indicate no adverse effect on insulin sensitivity. Also in HFrEF trial A2117, insulin levels decreased over time during treatment with LCZ696, further suggesting that insulin sensitivity is not adversely affected.

Amyloid-β (Aβ) is a NEP substrate. Preclinical data showed that pharmacological NEP inhibition in cerebrospinal fluid (CSF) occurs, thus potentially increasing Aβ in the brain. Trial A2126 was executed to investigate this, using CSF sampling in healthy volunteers. The trial confirmed that treatment with LCZ696 indeed inhibits NEP also in CSF. This caused a 42% increase of Aβ subtype 1-38, but not subtypes 1-40 and 1-42. The clinical relevance of this increase in Aβ 1-38 was not known. Also in plasma, a 50% increase of Aβ 1-40 was observed. This was not considered to be clinically relevant, as Aβ 1-40 has not been implicated in systemic (amyloid) diseases. Cognitive impairment has been identified as an important potential risk in the RMP and further and further evaluation of the effect of LCZ696 on the cognitive function is planned post-authorsation as part of the pharmacovigilance plan of the agreed RMP.

The Applicant provided the results of a **thorough QTc study** consistent with ICH-E14. In this trial, therapeutic and supra-therapeutic doses of LCZ696 (400 mg and 1200 mg) had no effect on QTcF.

Dose selection

Biomarker data from trial A2102 have been used to determine the amount of inhibition of neprilysin provided by LCZ696. In healthy volunteers, the inhibition (95% CI) of neprilysin relative to its maximum was estimated to be 56% (21%, 92%), 72% (43%, 100%), 84% (64%, 100%) and 91% (80%, 100%) with LCZ696 50, 100, 200 and 400 mg once daily, respectively. Based on this, a dose of 200 mg was selected, as higher doses would not provide additional neprilysin inhibition. This generally supports the choice of the sacubitril dose component.

Data from A2201 (dose finding study in hypertension) supported that also in hypertension, most (93%) of the change in blood pressure (as achieved by LCZ696 400 mg) was reached by the 200 mg (once daily) dose of LCZ696. In HF, concentrations of LCZ696 and its components may be higher than in healthy volunteers. This observation suggested that a slightly higher NEP inhibition may occur in HF patients, but this was not considered clinically relevant. The data from A2102 showed a decrease in mean cGMP levels from Day 6 to Day 12 from 2.03 to 1.67 nmol/L (-18%) suggesting adaptation in the body over time.

LCZ696 200 mg bid delivered valsartan exposures that were similar to the valsartan exposures delivered by the globally marketed formulation of valsartan 160 mg bid, which was the approved target dose of valsartan for the treatment of HF. Because neprilysin inhibition causes an increase of angiotensin-II, adequate blockade of the AT1-receptor was especially important. Based on PARADIGM-HF, the blockade of the AT1-receptor was sufficient, although no data were provided regarding even higher doses of valsartan. Trial A2102 also showed that none of the doses tested could provide 24h NEP inhibition (as none of the doses increased cGMP after 24 hours) in healthy volunteers. Thus, the choice of **twice daily dosing** was accepted. In summary, the dose of **LCZ696 200 mg bid** for treatment of HF was supported. As the body adapts to the effects of LCZ696, titration over a period of several weeks is required and the relevant wording was included in section 4.2 of the SmPC.

2.3.5. Conclusions on clinical pharmacology

Following oral administration, LCZ696 dissociated into valsartan and into the pro-drug sacubitril (also known as AHU377, a new molecular entity). Bioavailability of valsartan was found to be about 160% relative to valsartan marketed as Diovan. Sacubitril is readily converted to the active metabolite (neprilysin inhibitor) LBQ657, by

both carboxylesterase 1b and 1c. LBQ657 is the predominant metabolite in both the plasma and the excreta and it does not undergo significant metabolism. Valsartan undergoes CYP-mediated metabolism by CYP2C9, but only to a minor extent. LCZ696 analytes demonstrate approximately linear PK over the approved dose range.

Regarding special populations, higher exposures were observed for patients with renal and hepatic impairment. A starting dose of 24 mg/26 mg twice daily should be considered in patients with moderate renal impairment and caution is recommended (and a reduced starting dose) when using LCZ696 in patients with severe renal impairment. The use of LCZ696 is not recommended in patients with end-stage renal disease. No dose adjustment is required when administering LCZ696 to patients with mild hepatic impairment; it should be however used with caution in patients with moderate hepatic impairment and a starting dose should be 24 mg/26 mg twice daily in these patients. LCZ696 is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis. These recommendations and contraindications are reflected in sections 4.2 and 4.3 of the SmPC. No influence was seen from gender or race/ ethnicity. No large differences in exposures were observed related to weight or age.

The company evaluated the potential for interactions of sacubitril, LBQ657 and valsartan *in vitro* and *in vivo*. Interactions could occur with drugs that inhibit the esterase involved in the hydrolysis, but none are known at this moment. Potential interactions with OAT1B1 and OATP1B3 substrates, e.g. statins; PDE5 inhibitors including sildenafil, potassium, non steroidal anti inflammatory agents (NSAIDs), including selective cyclooxygenase 2 (COX 2) inhibitors, lithium, furosemide and nitroglycerine, metformin are reflected in the SmPC.

LCZ696 exhibits the characteristics of neprilysin inhibition and AT1 receptor blockade. Theoretical and pre-clinical concerns link NEP inhibition also to potential worsening of insulin resistance and accumulation of Amyloid-β. These issues may not be clinically relevant as suggested by the results of the PD trials and are further discussed in the safety section of this AR. LCZ696 does not prolong QTcF as per results of a thorough QTc study consistent with ICH-E14.

The proposed dose for LCZ696 for the use in HF is based on a PD dose-effect model according to which higher doses were not associated with greater efficacy in NEP inhibition. Twice daily dosing is required to achieve 24-hours of NEP inhibition. This dose provided the same AT1 receptor blockade as the approved dose for valsartan in HF indication.

Overall, the clinical pharmacology program was considered by the CHMP to be adequate.

2.4. Clinical efficacy

The applicant presented the following data pertaining to LCZ696 and its components:

Sacubitril

A clinical development program to evaluate the effect of sacubitril alone was not conducted and the following justification was provided by the applicant: (1) sacubitril could not be added to background ACEI therapy based upon previous experience with omapatrilat (a dual NEP inhibitor/ACEI); concomitant administration of a NEP inhibitor with an ACEI was anticipated to increase the risk of angioedema (including serious life-threatening cases) (*Coats 2002*, *Kostis et al 2004*), (2) for ethical reasons, sacubitril could not be studied alone in HFrEF patients since withdrawal of an ACEI, the guideline-recommended first-line therapy for HFrEF patients, would have been required, (3) neprilysin also affects angiotensin II degradation. NEP inhibition alone would therefore

increase angiotensin II concentrations, leading to additional activation of the RAS, potentially resulting in deleterious effects on the development and progression of HF.

Formally, as a component of an FDC, efficacy of sacubitril should have been separately documented. The applicant justified the lack of such clinical studies and the justification was accepted by the CHMP.

Valsartan

Valsartan has been approved in the EU for HF and post MI since 2005. ARBs are primarily recommended for patients who are ACEI intolerant largely due to inconsistent evidence for their mortality reduction in the treatment of HFrEF. The pivotal efficacy studies intended to demonstrate the efficacy of valsartan in HF patients include: (1) Study CVAL489B0107 (a Phase III, randomized, double-blind, parallel group, placebo-controlled study in chronic symptomatic HF patients), (2) Study CVAL489E0108 (a Phase III, randomized, double-blind, parallel group, active-controlled study in post-MI patients with symptomatic HF or asymptomatic left ventricular systolic dysfunction).

Efficacy of valsartan in the proposed indication of HF was considered well established. In most of the EU, valsartan is recommended for**:** Treatment of symptomatic heart failure when ACE inhibitors cannot be used, or as add-on therapy to ACE inhibitors when beta blockers cannot be used.

LCZ696

The main studies investigating the efficacy and safety of LCZ696 are outlined in table E1.

Table E1: Overview of efficacy safety trials

Study	Study objective	Number of patients	Treatment and duration	Efficacy endpoints
[Study CLCZ696B2314] PARADIGM-HF (Phase III **pivotal study**)	Efficacy and safety of LCZ696 compared to enalapril in patients with HF (NYHA class II – IV) and reduced ejection fraction (LVEF ≤ 40%)	Event-driven study with 8,442 patients randomized	LCZ696 200 mg bid vs Enalapril 10 mg bid Median 24 months (double-blind period)	Primary endpoint: Time to composite endpoint: • CV death • HF hospitalization Key secondary endpoints: • Time to all-cause mortality • Clinical summary score for HF symptoms and physical limitations assessed by KCCQ at 8 months • Time to new onset of atrial fibrillation • Time to composite renal endpoint

Study	Study objective	Number of patients	Treatment and duration	Efficacy endpoints
[Study CLCZ696B2214] PARAMOUNT (Phase II **proof-of-concept study in HFpEF**)	Efficacy, safety and tolerability of LCZ696 compared to valsartan in patients with HF (NYHA class II – IV) and preserved ejection fraction (LVEF ≥ 45%)	301 patients randomized	LCZ696 200 mg bid vs Valsartan 160 mg bid Median 252 days (double-blind treatment period)	Primary endpoint: Change from baseline in NT-proBNP at Week 12 Key secondary endpoints: • KCCQ • Clinical composite score based on NYHA functional classification, global patient assessment and major adverse CV events • Echocardiographic measures • Reduction in NT-proBNP at Week 36 • Changes in eGFR, serum creatinine and proteinuria measured by UACR
[Study CLCZ696B2228] TITRATION (Phase II **Dose titration in HFrEF**)	Safety and tolerability of initiating LCZ696 in HFrEF patients who were either ACEi/ARB naïve or who were taking various doses of ACEis or ARBs.	538 patients enrolled and took at least one dose of study medication, and among them, 498 were randomized.	two up-titration regimens the target dose of LCZ696 200 mg bid: condensed (titration over 3 weeks) vs conservative (titration over 6 weeks). 12 weeks including the run-in phase	The primary variables were AEs and laboratory assessment outcomes. Secondary variables were the proportion of patients : • who achieved and maintained the target dose • who tolerated a regimen of LCZ696 200 mg bid for at least 2 weeks leading to study completion, regardless of previous dose interruption or down-titration.

bid = twice daily; CV = cardiovascular; HF= heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association

2.4.1. Dose response studies

No phase II or dose finding studies were conducted for LCZ696 in HFrEF patients. The applicant argued that using surrogate and biomarker endpoints has thus far not been shown to be predictive of cardiovascular phase III outcomes trial results precluding the necessity to perform such studies. As mentioned before in the PD section, the applicant justified using the target dose of 200 mg bid LCZ696 for the pivotal study because it delivered an exposure of valsartan that was similar to the valsartan 160 mg dose which is the regimen recommended by international guidelines for the treatment of HF (McMurray et al 2012, Yancy et al 2013). In addition, LCZ696 200 mg/day was associated with ~84% of maximum cGMP increase (AUEC) in healthy subjects, indicating nearly maximal NEP inhibition via sacubitril [Study A2102]. A sustained, approximately 2-fold increase in 24-hour urinary cGMP excretion was observed in HF patients in response to LCZ696 200 mg bid treatment, consistent with a 24-hour pharmacodynamic effect of NEP inhibition in the target patient population. In the phase 2 dose-ranging hypertension study [Study A2201], incremental BP lowering resulting from NEP inhibition was similar on top of RAS blockade for both 200 mg and 400 mg once daily doses of LCZ696

against corresponding doses of valsartan 160 mg and 320 mg once daily, confirming the near-maximal BP effect from NEP inhibition with LCZ696 200 mg. The twice daily dosing was chosen as plasma cGMP levels were increased at 12 hours, but returned to baseline levels at 24 hours in healthy volunteers - indicating a need for bid dosing to achieve 24 hour neprilysin inhibition. Also it was chosen to mitigate the risk of post-dose hypotension.

2.4.2. Main study

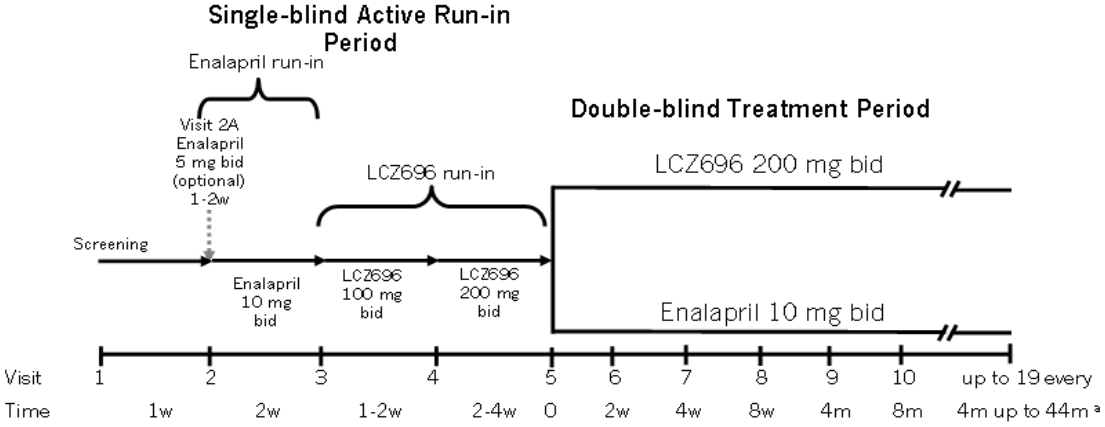
CLCZ696B2314 (PARADIGM-HF)

Study CLCZ696B2314 (PARADIGM-HF) is the phase III pivotal study to support the proposed indication. PARADIGM-HF was a randomized, double-blind, parallel group, active-controlled study to evaluate the superiority of LCZ696 200 mg bid as compared to enalapril 10 mg bid, on morbidity and mortality reduction in patients with HFrEF.

Methods

As illustrated in Figure E1, the study consisted of three periods: (1) screening period; (2) single-blind active run-in period ranging from 5 to 10 weeks during which patients received (2a) enalapril 10 mg bid, followed by (2b) LCZ696 100 mg bid up-titrated to the target dose of LCZ696 200 mg bid; and (3) double-blind period where patients who were able to tolerate the target doses of enalapril and LCZ696 for at least 2 weeks during the active run-in were randomized 1:1 to receive double-blind treatment with LCZ696 200 mg bid or enalapril 10 mg bid. Patients were followed up until the trial was completed.

Figure E1: Study CLCZ696B2314 Study design



The run-in period served to ensure that a minimal mean daily dose of enalapril 16.6 mg was achieved during the long term follow-up period. It also served to maximize the number of randomized patients able to tolerate the target dose of both LCZ696 and enalapril and minimize the number of early dropouts in the study after randomization. In the absence of prior phase 2 safety experience with LCZ696 in HFrEF, the run-in period was used to assess the safety and tolerability of the target doses of enalapril (10 mg bid) and LCZ696 (200 mg bid) prior to randomization.

The durations of the enalapril run-in and LCZ696 run-in were different: a shorter duration (2-4 weeks) for the enalapril run-in (median 15 days) and a longer duration (3-6 weeks) for the LCZ696 run-in (median 29 days).

Patients were to remain in the trial until either (1) the projected number of primary endpoints (CV death or HF hospitalization) was reached, or (2) the trial was terminated prematurely at the recommendation of the DMC when pre-specified early-stopping criteria for efficacy and/or safety criteria were met.

Study participants

Patient eligibility at screening included age ≥ 18 years, NYHA class II-IV symptoms and left ventricular ejection fraction (LVEF) ≤ 40%. The LVEF criterion was amended to ≤ 35% by a protocol amendment one year after trial start, to ensure the projected primary endpoint and CV death event rate was met. Eligible patients were also required to have an elevated plasma B-type natriuretic peptide (BNP) ≥ 150 pg/mol (or N-terminal of the prohormone B-type natriuretic peptide (NT-proBNP) ≥ 600 pg/mol). Patients who had been hospitalized ≤ 12 months prior to enrolment were required to have a BNP ≥ 100 pg/mol (or NT-proBNP ≥ 400 pg/mol). The inclusion of elevated BNP or NT-proBNP as a key entry criterion served as an enrichment factor enhancing the event rate. For at least 4 weeks before screening, patients had to have received a stable dose of an ACEi or ARB equivalent to enalapril 10 mg per day, a stable dose of a β-blocker unless intolerant and an MRA as indicated.

Patients were excluded from entering the study for symptomatic hypotension and/or systolic blood pressure (BP) <100 mmHg at screening (or <95 mmHg during run-in or at randomization), serum potassium > 5.2 mmol/L at screening (or >5.4 mmol/L during run-in or at randomization), or estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m2 (or a >35% decline in eGFR during run-in).) or elevated liver enzymes.

Treatments

Enalapril was chosen as the active comparator because treatment guidelines have established ACEis as the standard of care, first-line RAS-based pharmacotherapy for HFrEF patients, unless ACEi-intolerant. Enalapril has been well-studied in a number of large outcome HF studies such as CONSENSUS (The CONSENSUS Trial Group 1987), SOLVD-Treatment (The SOLVD Investigators 1991), SOLVD-Prevention (The SOLVD Investigators 1992), VHeFT II (Cohn et al 1991) and OVERTURE (Packer et al 2002). Enalapril 10 mg bid was selected as the target dose for the PARADIGM-HF study because this dose was previously shown to reduce the risk of death as well as the risk of HF hospitalization in HFrEF patients (The SOLVD Investigators 1991). The choice of active comparator and dose was agreed to by SA obtained from the EMA.

Objectives

The primary objective was to demonstrate that LCZ696 was superior to enalapril in delaying the time to first occurrence of the composite endpoint of CV death or HF hospitalization.

Outcomes/endpoints

The composite of time to first occurrence of either CV death or HF hospitalization was specified as the primary endpoint. There were four secondary endpoints:

1. Time to all-cause mortality
2. Symptoms and physical limitations as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ).
3. Protocol-defined composite renal endpoint: delay in time to first occurrence of any one of the following: a. A 50% decline in eGFR relative to baseline b. A >30 mL/min/1.73m2 decline in eGFR relative to baseline to a value below 60 mL/min/1.73m2. and c. Reaching end stage renal disease (ESRD).
4. Time to new onset atrial fibrillation.

Sample size

The trial was designed to show convincing evidence on cardiovascular mortality alone, which was the primary determinant of the planned sample size (approximately 8,000 patients) and for which a statistically compelling effect was required to stop the trial early for CV mortality benefit in addition to the composite primary endpoint. It was estimated that the annual event rate of the primary composite endpoint would be 14.5% and the annual event rate of CV death would be 7.0% in the enalapril group.

Calculation of the study sample size was based on CV death. It was estimated that approximately 7,980 patients would need to be randomized with 1,229 CV deaths to provide the study with 80% power to detect a significant relative risk reduction of 15% in CV death for the LCZ696 group compared to enalapril (using the log-rank test). On the basis of these calculations, it was then estimated that the primary composite endpoint would occur in 2,410 patients, which would provide 97% power to detect a significant risk reduction assuming a 15% relative reduction in the risk of this composite outcome. Therefore, this trial was designed to provide definitive evidence demonstrating that LCZ696 is superior to enalapril in reducing the risk of CV death and HF hospitalization in a broad HFrEF patient population.

Randomisation

After the active run-in period, all eligible patients were randomised using an interactive voice response system (IVRS) in a 1:1 ratio to either LCZ696 or enalapril. In addition to the IVRS, a web-based system was also available and had the same functionalities as the IVRS.

Statistical methods

The primary efficacy variable was analysed using the Cox proportional hazards model with treatment and region as fixed-effect factors. The estimated hazard ratio (HR) and the corresponding two-sided 95% confidence interval and one-sided p-values were provided. The full analysis set (FAS) was used for the primary analysis. Similarly, the above analysis was repeated for the per protocol (PP) population as a supportive analysis. The overall type I error was planned to be controlled at 2.5% (one-sided) with the adjustment for the interim efficacy analyses (IA). Since the study was stopped at the 3rd IA, the significance level allocated to this IA (one-sided α=0.001) was used for the formal significance test of the primary endpoint in the final analysis.

Pre-specified subgroup analyses were performed for the FAS. To explore the consistency of beneficial effects in subgroups, the estimated HR, two-sided 95% confidence interval and p-value were provided for each of the subgroups based on the Cox proportional hazards model in which treatment and region were included as fixed-effect factors. Interaction between the subgroup and treatment was evaluated and p-values were provided using the above model plus additional terms for subgroup and the interaction between subgroup and treatment. No adjustment for multiple comparisons was made for subgroup analyses.

Change from baseline in the clinical summary score of KCCQ was analysed based on a repeated measures analysis of covariance (ANCOVA) model in which treatment, region, visit (Month 4 and Month 8) and treatment-by-visit interaction were included as fixed-effect factors and baseline value as a covariate, with a common unstructured covariance matrix among visits for each treatment group.

The time-to-event secondary endpoints were analysed using the Cox proportional hazards model with treatment and region as fixed-effect factors. The estimated hazard ratio and the corresponding two-sided 95% confidence interval were provided for the FAS. The secondary hypotheses were formally tested and statistical inferences were made only if the primary hypothesis was rejected. The four secondary efficacy variables were tested for superiority of LCZ696 to enalapril for the FAS. A sequentially rejective multiple test procedure (MTP) was used

for the secondary efficacy comparisons in order to provide strong family-wise control of the α level, across the primary and all secondary endpoints, across all potential interim and final analyses.

The assessment of safety was based primarily on the frequency of AEs, SAEs and laboratory abnormalities that occurred in the run-in periods and double-blind period. Data from other tests (e.g., electrocardiogram (ECG) or vital signs) were listed, notable values were flagged and any other information collected was listed as appropriate. Safety analyses were performed based on the safety population (SAF).

It was planned to have three interim efficacy analyses at 1/3, 1/2 and 2/3 of information time. The Haybittle-Peto type of boundary was used for the IA to assess superiority, with the boundary spent approximately an alpha of 0.0001 (one-sided) at the first IA and 0.001 (one-sided and nominal) at the second and third interim analyses. For each IA, the analysis dataset comprised all patients who were randomized before the IA cut-off date. Interim analyses were performed by an independent statistician who was not involved in the trial conduct. The results were reviewed by the independent DMC. Investigators, Novartis employees and others who were involved in the conduct of the trial remained blinded to the treatment codes and IA results until all monitoring decisions had been made and the database had been locked for final analysis.

Alpha levels for the primary and secondary endpoints were planned to be adjusted in a manner to ensure strong control of the family-wise error rate across all primary and secondary endpoints and across all interim analyses and the final analysis. As per protocol, since the trial was stopped at the 3rd interim analysis, the 0.001 alpha level used for the primary endpoint boundary at that analysis was also to be used as the basis for testing the secondary endpoints using the sequentially rejective procedure described above .

It should be noted that this approach may be considered highly conservative for the secondary endpoints, since the generalized Bonferroni alpha splitting approach used for the primary endpoint assigned very small alpha to each interim, which was then allocated across secondary endpoints; and, also, correlations between endpoints were not taken into account. Therefore, considering that the secondary endpoint did not influence the decision of early stopping, did not determine the success of the study and were only planned to be tested once during the course of the study, in addition to applying the planned conservative method of strong control of the family-wise error rate (strict MTP), the results of the secondary endpoints may also be interpreted based on the commonly used approach to assign the remaining alpha for the final analysis of $0.025 - 0.0001 - 2 \times 0.001 = 0.0229$ to the set of secondary endpoints and applying the pre-specified sequentially rejective MTP to control for multiplicity across the four secondary endpoints (alternative MTP).

Results

Participant flow

As of the 31-Mar-2014 cut-off date, 10,513 patients entered the enalapril run-in period, 9,419 patients entered the LCZ696 run-in period and 8,442 patients were randomized. The trial was stopped early for compelling efficacy (for both CV death and the primary composite of CV death or HF hospitalization) by the DMC on 28-Mar-2014, according to pre-specified stopping rules.

Of the enalapril run-in set (all patients who received at least one dose of enalapril), 1,102 failed the run-in. Of the 9,419 patients in the LCZ696 run-in set (all patients who received at least one dose of LCZ696; this also included 8 patients who were exposed to LCZ696 without first being exposed to enalapril), 982 failed the run-in [table E2]. Thus, a similar percentage of patients failed the enalapril run-in (10.48%) and the LCZ696 run-in (10.43%).

Table E2: Patient disposition and vital status by treatment group (Screened set)

Disposition and vital status at study end	LCZ696 n (%)	Enalapril n (%)	Total n (%)
Screen set (1)			18071 (100)
Screen failure (2)			7534 (41.69)
Run-in set (2)			10521 (100)
Enalapril run-in (3)			10513 (99.92)
Failed in enalapril run-in			1102 (10.47)
Dead			55 (0.52)
LCZ696 run-in			9419 (89.53)
Failed in LCZ696 run-in			982 (9.33)
Dead			63 (0.60)
Run-in failure			2084 (19.81)
Randomized			6 (0.06)
Run-in complete			8437 (80.19)
Not randomized			1 (0.01)
Randomized set	4209 (100)	4233 (100)	8442 (100)
Mis-randomized (4)	4 (0.10)	2 (0.05)	6 (0.07)
GCP violations	18 (0.43)	19 (0.45)	37 (0.44)
Discontinued from double-blind period	8 (0.19)	10 (0.24)	18 (0.21)
Dead	2 (0.05)	2 (0.05)	4 (0.05)
Lost to follow-up	5 (0.12)	7 (0.17)	12 (0.14)
Patient's request	1 (0.02)	1 (0.02)	2 (0.02)
Full analysis set	4187 (99.48)	4212 (99.50)	8399 (99.49)
Discontinued from double-blind period	741 (17.61)	862 (20.36)	1603 (18.99)
Dead (5)	724 (17.20)	844 (19.94)	1568 (18.57)
Lost to follow-up	2 (0.05)	5 (0.12)	7 (0.08)
Patient's request	15 (0.36)	13 (0.31)	28 (0.33)
Safety set	4203 (99.86)	4229 (99.91)	8432 (99.88)
Per-protocol set	4166 (98.98)	4187 (98.91)	8353 (98.95)

Source: Table 14.1-1.1
(1) All screened patients are included. Re-screened patients with different patient IDs are counted as different screened patients.
(2) Three screen-failure patients died and there are 16 patients excluded from the Run-in set who had run-in visit but never took run-in study medication and 2 of them died.
(3) There were 8 run-in patients who didn't take enalapril but took LCZ696 during run-in period.
(4) Misrandomized means unintentionally performed IVRS randomization calls but never received study medication.
(5) Three patients who died after the completion of the study are not included in this category of "Dead".

Conduct of the study

Approximately 12% of randomized patients had at least one protocol deviation. Most deviations occurred in a small and similar percentage of patients in each treatment group. There were more patients in the enalapril group (1.37%) than in the LCZ696 group (0.86%) who used an open-label ACEI or ARB concomitantly with study medication at some point in the study.

Baseline data

The LCZ696 and enalapril groups were well-balanced with respect to baseline patient characteristics (Table E3). The mean age of randomized patients was 63.80 years. Approximately half of the patients were ≥ 65 years

(49.08%), 18.59% were ≥ 75 years and 78.12% were male. The majority of patients were in HF NYHA class II (70.33%) or class III (24.11%) at randomization and the mean LVEF was 29.48%. At the screening visit, the mean (median) NT-proBNP and BNP levels were elevated at 2,888 (1,610) pg/mL and 419 (253) pg/mL, respectively. Mean SBP was 121.38 mmHg and mean eGFR was 67.66 mL/min/1.73 m2, with over one-third of patients having had an eGFR < 60 mL/min/1.73m2.

Table E3: Baseline patient demographic and disease characteristics for double-blind period by treatment group (Randomized set)

Variable / Statistic / category	LCZ696 N=4209	Enalapril N=4233	Total N=8442
Age (years)			
N	4209	4233	8442
Mean	63.78	63.82	63.80
Median	64.00	64.00	64.00
Age category - n (%)			
< 65 years	2122 (50.42%)	2177 (51.43%)	4299 (50.92%)
>= 65 years	2087 (49.58%)	2056 (48.57%)	4143 (49.08%)
< 75 years	3423 (81.33%)	3450 (81.50%)	6873 (81.41%)
>= 75 years	786 (18.67%)	783 (18.50%)	1569 (18.59%)
Gender - n (%)			
Male	3321 (78.90%)	3274 (77.34%)	6595 (78.12%)
Female	888 (21.10%)	959 (22.66%)	1847 (21.88%)
Region(1)			
North America	310 (7.37%)	292 (6.90%)	602 (7.13%)
Latin America	726 (17.25%)	732 (17.29%)	1458 (17.27%)
Western Europe	1029 (24.45%)	1028 (24.29%)	2057 (24.37%)
Central Europe	1398 (33.21%)	1439 (33.99%)	2837 (33.61%)
Asia/Pacific and other	746 (17.72%)	742 (17.53%)	1488 (17.63%)
Baseline LVEF (%)			
N	4209	4232	8441
Mean	29.55	29.41	29.48
Median	30.00	30.00	30.00
Baseline LVEF group- n (%)			
<= 35%	3736 (88.76%)	3742 (88.40%)	7478 (88.58%)
> 35%	473 (11.24%)	490 (11.58%)	963 (11.41%)
NYHA class at randomization- n (%)			
Class I	183 (4.35%)	213 (5.03%)	396 (4.69%)
Class II	3007 (71.44%)	2930 (69.22%)	5937 (70.33%)
Class III	979 (23.26%)	1056 (24.95%)	2035 (24.11%)
Class IV	33 (0.78%)	27 (0.64%)	60 (0.71%)
Baseline eGFR (mL/min/1.73 m^2)			
n	4209	4233	8442
Mean	67.60	67.73	67.66
Median	66.00	66.00	66.00

Variable / Statistic / category	LCZ696 N=4209	Enalapril N=4233	Total N=8442
Baseline eGFR group - n (%)			
< 60 (mL/min/1.73 m^2)	1552 (36.87%)	1530 (36.14%)	3082 (36.51%)
>= 60 (mL/min/1.73 m^2)	2657 (63.13%)	2703 (63.86%)	5360 (63.49%)
Baseline NT-proBNP (pg/mL)			
n	4204	4224	8428
Mean	2891	2886	2888
Median	1629	1593	1610
Treated with ACEi (2) - n (%)			
No	930 (22.10%)	952 (22.49%)	1882 (22.29%)
Yes	3279 (77.90%)	3281 (77.51%)	6560 (77.71%)
Treated with ARB (2) - n (%)			
No	3271 (77.71%)	3264 (77.11%)	6535 (77.41%)
Yes	938 (22.29%)	969 (22.89%)	1907 (22.59%)
Treated with beta-blocker (2) - n (%)			
No	234 (5.56%)	249 (5.88%)	483 (5.72%)
Yes	3975 (94.44%)	3984 (94.12%)	7959 (94.28%)
Treated with an aldosterone antagonist (2) -n(%)			
No	1805 (42.88%)	1706 (40.30%)	3511 (41.59%)
Yes	2404 (57.12%)	2527 (59.70%)	4931 (58.41%)
Prior HF hospitalization (2) – n (%)			
No	1589 (37.75%)	1554 (36.71%)	3143 (37.23%)
Yes	2620 (62.25%)	2679 (63.29%)	5299 (62.77%)

(1) Region: North America: USA, Canada; Latin America (including Central America): Argentina, Brazil, Chile, Colombia, Dominican Republic, Ecuador, Guatemala, Mexico, Panama, Peru, Venezuela. Western Europe: Belgium, Denmark, Finland, France, Germany, Iceland, Italy, Netherlands, Portugal, Spain, Sweden, Israel, South Africa, UK. Central Europe: Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Rep. of Slovakia, Romania, Russia, Turkey. Asia/Pacific and other: China, Hong Kong, India, Rep of Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand. (2) All assessments were performed at Visit 1.
Source: [Study CLCZ696B2314 Table 14.1-3.1]

Ischemic cardiac disease was the primary cause for HF in the majority of patients (59.91%). Recruited patients had a high incidence of CV and metabolic comorbidities, including prior HF hospitalization (62.77%), hypertension (70.72%), chronic kidney disease (36.51%), diabetes mellitus (34.67%) and atrial fibrillation (36.46%). Use of an implantable cardioverter defibrillator (ICD) of any type was reported in 14.83% of the LCZ696 patients and in 14.69% of the enalapril patients. Use of a cardiac resynchronization therapy (CRT) device (CRT-D or CRT-P) was reported in 6.94% and 6.68% of the LCZ696 group and enalapril group, respectively. Common concomitant HF medications included: ACEi (77.71%), ARB (22.59%), beta-blocker (94.28%) and MRA (58.41%). The majority of patients were also taking diuretics (82.58%). In addition, the use of beta-blockers, MRAs and diuretics after randomization remained consistently high throughout the follow-up period.

The median duration of follow-up was 27 months. Among patients who were taking study medication at the final visit, the mean daily dose was 374.8 mg/day in the LCZ696 group and 18.9 mg/day in the enalapril group. A

higher percentage of patients were on the target dose of LCZ696 treatment (69.6%) compared to the number of patients on enalapril treatment (67.5%) at the end of the study.

Numbers analysed

In the run-in period, the median duration of exposure to LCZ696 was 29 days, while the median duration of exposure to enalapril was 15 days. Overall, the vast majority of targeted HFrEF patients were able to complete the active run-in phase and were randomized. The reasons for treatment discontinuation during the run-in period were similar between enalapril and LCZ696, with 5.62% and 5.85% of patients having discontinued due to AEs (including those patients who met the protocol-specified discontinuation safety criteria) while taking enalapril and LCZ696, respectively.

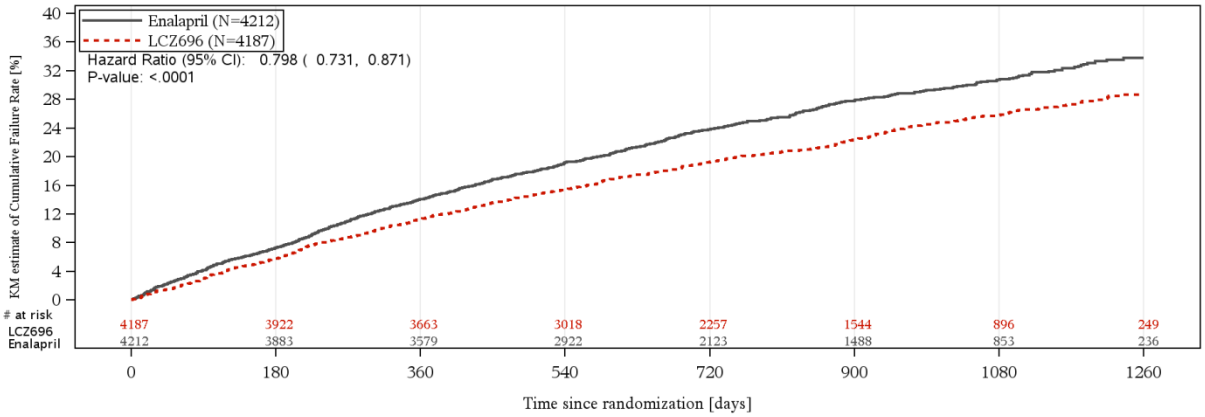
A total of 43 randomized patients (0.5%) were excluded from all efficacy analyses (6 patients were randomized erroneously and never received study medication and 37 patients were excluded due to serious GCP violations). Thus, the full efficacy analysis set (FAS) consisted of 8,399 patients. At the end of the study, vital status was not known in only 20 patients in the FAS, including 7 patients lost to follow up (2 patients in the LCZ696 group and 5 patients in the enalapril group) and 13 per patients' request (9 patients in the LCZ696 group and 4 patients in the enalapril group).

Outcomes and estimation

Compared with enalapril, LCZ696 reduced the risk of the composite of CV death or first HF hospitalization by 20% (HR 0.80, 1-sided p=0.00000021); reduced the risk of CV death by 20% (HR 0.80, 1-sided p=0.00003998); and reduced the risk of first HF hospitalization by 21% (HR 0.79, 1-sided p=0.00003897) in the full analysis set (FAS). The absolute risk reductions were 4.7% for the composite of the CV death or HF hospitalization 3.1% for CV death alone and 2.8% for first HF hospitalization alone. Therefore, over the duration of the trial (median duration 27 months), the number of patients needed to treat (NNT) to prevent one primary event (CV death or HF hospitalization) was 21, to prevent one CV death was 32 and to prevent one HF hospitalization was 36.

The benefit of LCZ696 treatment was seen early and was sustained for the entire study duration for the primary endpoint (Figure E2). Results were further confirmed in per protocol analysis.

Figure E2: Kaplan-Meier plot of cumulative rate of first adjudicated-confirmed event of CV death or initial HF hospitalization for the double-blind period (PARADIGM-HF, FAS)



Source: [SCE-Figure 3-1]

Although LCZ696 produced a greater BP lowering effect compared to enalapril (see Safety) a post-hoc Cox regression analysis using post-baseline SBP as the time-dependent covariate showed that the benefit of LCZ696 over enalapril was maintained, ie, the HR remained 0.78 (95% CI, 0.71 to 0.85) for the primary composite endpoint. Thus, the CV death and HF hospitalization benefit observed with LCZ696 treatment relative to enalapril was independent of its effect on BP.

With regards to the causes of CV death, the most common mode of CV death in randomized patients was sudden death (44.82% of CV deaths), followed by pump failure (26.48% of CV deaths), consistent with disease progression in HFrEF patients. Lower event rates occurred for both in the LCZ696 group compared to the enalapril group (sudden death: LCZ696 5.97% vs enalapril 7.38%, HR 0.80, 95% CI 0.68 to 0.94, p = 0.0082; pump failure-related death: LCZ696 3.51% vs enalapril 4.37%, HR 0.79, 95% CI 0.64 to 0.98, p = 0.0338).

There were also numerically more first resuscitated sudden deaths in the enalapril group (28 patients, 0.66%) than in the LCZ696 group (16 patients, 0.38%) (p = 0.0681). When a post-hoc analysis was conducted analyzing the time to the first composite event of sudden death or resuscitated sudden death, LCZ696 treatment was associated with a significantly lower risk, with a HR of 0.78 (95% CI, 0.67 to 0.92; p = 0.0025) vs enalapril.

Secondary Endpoints

Delaying time to all-cause mortality

A total of 711 patients (16.98%) in the LCZ696 group and 835 patients (19.82%) in the enalapril group died due to any cause. Time to all-cause mortality was significantly delayed with LCZ696 relative to enalapril (HR 0.84; 95% CI, 0.76 to 0.93; one-sided p = 0.0005). The reduction in all-cause mortality is mainly driven by the risk reduction of CV death.

Improvement of HF symptoms and physical limitations as assessed by KCCQ

Patients in the LCZ696 group showed less reduction compared to enalapril from baseline to Month 8 in the clinical summary score for HF symptoms and physical limitations. The between-group mean difference for the clinical summary score was 1.64, with a 95% CI of 0.63 to 2.65 (one-sided p = 0.0007). This reduction in the decline of the clinical summary scores for LCZ696 vs enalapril did not meet the threshold for significance using the strict MTP at an alpha = 0.001 as pre-specified in the statistical analysis plan (ie, required $p \leq 0.0002$), but it met the threshold for significance using the alternative MTP (requiring one-sided $p \leq 0.00458$).

At 8 months, NYHA functional class (supportive analysis) was improved for more patients in the LCZ696 group than in the enalapril group and NYHA functional class worsened for fewer patients in the LCZ696 group than in the enalapril group (p=0.0002).

Delaying time to new onset Atrial Fibrillation

There was no difference in delaying the time to new onset atrial fibrillation between the LCZ696 and enalapril treatment groups (HR 0.97; 95% CI, 0.72 to 1.31; one-sided p = 0.4183).

Delaying time to renal composite endpoint

The difference between LCZ696 and enalapril in delaying the time to this renal composite endpoint (HR 0.86; 95% CI, 0.65 to 1.13; one-sided p = 0.1424) was not significant.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table: Summary of efficacy for PARADIGM-HF

Title:	A 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 (HF) and reduced ejection fraction		
Study identifier	CLCZ696B2314		
Design	This was a study to evaluate the superiority of LCZ696 200 mg bid as compared to enalapril 10 mg bid, on morbidity and mortality reduction in patients with chronic heart failure (CHF) (New York Heart Association [NYHA] class II-IV) and reduced ejection fraction defined by a left ventricular ejection fraction (LVEF) ≤ 40% (changed to ≤ 35% by protocol amendment 1). The trial consisted of two main periods: (1) a single-blind run-in period that lasted between 5 to 10 weeks and (2) a double-blind randomized treatment period (median 27 months).		
	Duration	Main phase:	median 27 months of follow-up
		Run-in phase:	5-10 weeks
		Extension phase:	not applicable
Hypothesis	Superiority (LCZ696 is superior to enalapril in mortality and morbidity reduction)		
Treatments	LCZ696	LCZ696 200 mg bid, median 27 months of follow-up, N=4209	
	enalapril	enalapril 10 mg bid, median 27 months of follow-up, N=4233	
Endpoints	Primary endpoint	Time to CV death or HF hospitalization	Time from randomization to first occurrence of (adjudicated) CV death or hospitalization for HF *
	Component of primary endpoint	Time to CV death	Time from randomization to first occurrence of (adjudicated) CV death *
	Component of primary endpoint	Time to HF hospitalization	Time from randomization to first occurrence of (adjudicated) hospitalization for HF *
	Secondary endpoint	Time to all-cause mortality	Time from randomization to all-cause death (adjudicated) *
	Secondary endpoint	KCCQ	Change from baseline (randomization) at month 8 of the clinical summary score of the Kansas City Cardiomyopathy Questionnaire
	Secondary endpoint	Delay of renal dysfunction	Time from randomization to first occurrence of any one of the following (adjudicated) *: 1. A 50% decline in estimated glomerular filtration rate (eGFR) relative to baseline 2. >30 mL/min/1.73m^2 decline in eGFR relative to baseline to a value below 60 mL/min/1.73m^2 3. Reaching end stage renal disease.
	Secondary endpoint	New onset atrial fibrillation	Time from randomization to occurrence of new onset atrial fibrillation (adjudicated) *
Database lock	18-Jul-2014		

* shown as Exposure-adjusted incidence rate per 100 patient years.

Primary Analysis

Population	Full analysis set		
Time points	The study was stopped at the 3rd interim analysis (due to compelling efficacy). The significance level allocated to this interim analysis was one-sided α=0.001.		
Descriptive statistics	Treatment group	**LCZ696**	**Enalapril**
	Number of subjects	4187	4212
	CV death or 1st HF hosp. (Per 100 PY)	10.48	13.15
	95%-CI	9.81, 11.18	12.39, 13.95
	• CV death (Per 100 PY)	5.99	7.50
	95%-CI	5.51,6.51	6.96,,8.08
	• 1st HF hospitalization (Per 100 PY)	6.16	7.75
	95%-CI	5.65,6.70	7.17, 8.36
	All-cause mortality (Per 100 PY)	7.639	9.042
	95%-CI	7.088, 8.221	8.439, 9.677
	Number of subjects	3833	3873
	KCCQ – clinical summary score at month 8 (LSM of CFB)	-2.99	N-4.63
	SE	0.364	0.364
	Delay of renal dysfunction (Per 100 PY)	1.022	1.184
	95%-CI	0.826,1.251	0.971,1.430
	Number of subjects	2670	2638
	New onset atrial fibrillation (Per 100 PY)	1.446	1.472
	95%-CI	1.153,1.790	0.7151, 1.3119

Effect estimate per comparison		Comparison groups	**LCZ696 vs. enalapril**
	CV death or 1st HF hospitalization	Hazard ratio	0.80
		95%-CI	0.73, 0.87
		P-value	0.00000021 (one-sided)
		Absolute risk reduction (%)	4.69
	• CV death	Hazard ratio	0.80
		95%-CI	0.71, 0.89
		P-value	0.00003998 (one-sided)
		Absolute risk reduction (%)	3.13
	• 1st HF hospitalization	Hazard ratio	0.79
		95%-CI	0.71, 0.89
		P-value	0.00003897 (one-sided)
		Absolute risk reduction (%)	2.80
	All-cause mortality	Hazard ratio	0.8445
		95%-CI	0.7642, 0.9334
		P-value	0.0005 (one-sided)
		Absolute risk reduction (%)	2.84
	KCCQ – Clinical Summary Score at	LSM of difference	1.64
		95%-CI	0.63, 2.65

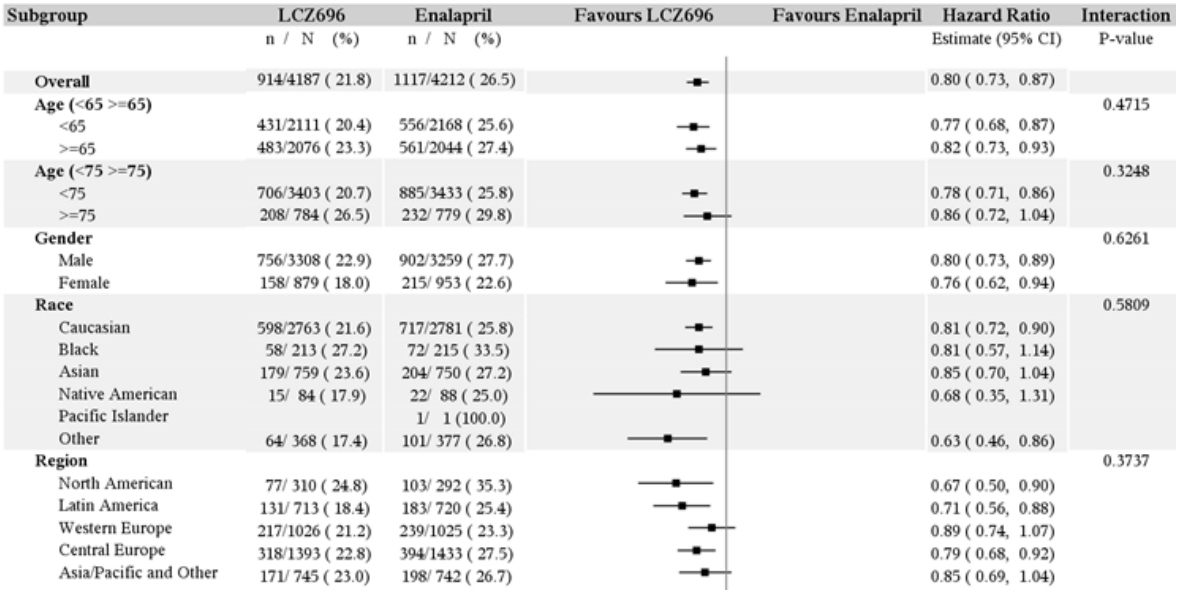
	month 8	P-value	0.0007 (one-sided)

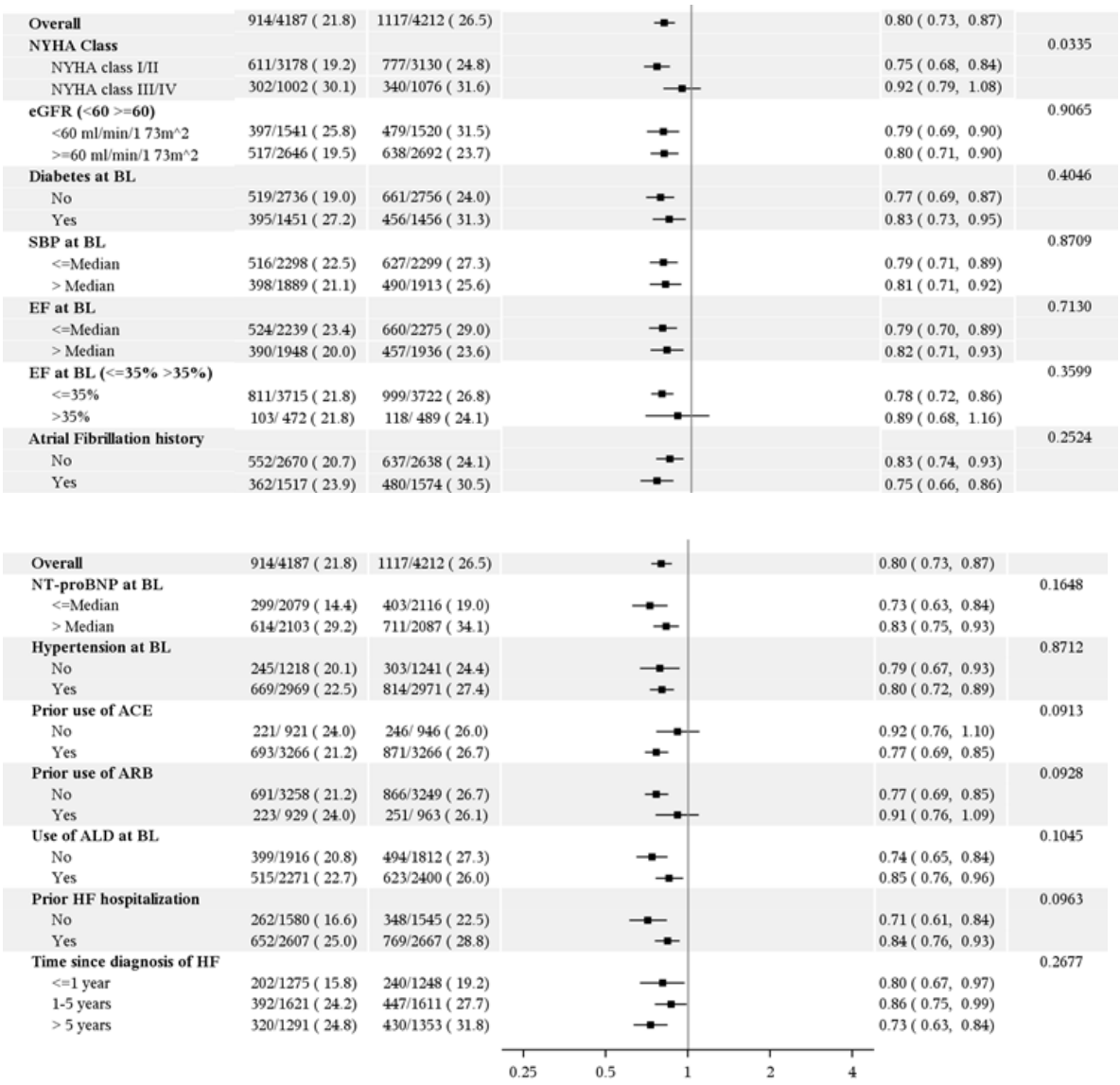
Effect estimate per comparison (continued)		Comparison groups	**LCZ696 vs. enalapril**
	Delay of renal dysfunction	Hazard ratio	0.8600
		95%-CI	0.6522, 1.1338
		P-value	0.1424 (one-sided)
	New onset atrial fibrillation	Hazard ratio	0.9686
		95%-CI	1.173,1.825
		P-value	0.4183 (one-sided)

Clinical studies in special populations

LCZ696 consistently reduced CV death or HF hospitalization across the subgroups of age, gender, race, region, baseline ejection fraction, baseline relevant concomitant medical conditions, prior use of relevant concomitant medications, prior HF hospitalization and time from HF diagnosis (figure E3).

Figure E3: Study CLCZ696B2314 Forest plot for first confirmed primary endpoint (CV death or HF hospitalization) – subgroup analysis (Full analysis set)





ALD = aldosterone antagonist
(a) Hazard ratio and its confidence interval are calculated using a Cox regression model with treatment and region as fixed factors within each subgroup.
(b) The interaction p-value is calculated using the previous Cox's model with the additional terms of subgroup and subgroup treatment interaction
Source: [Study CLCZ696B2314 Figure 14.2-1.3.1]

Main efficacy results of patients with different degrees of renal function are presented in table E5. Main efficacy results of patients with different degrees of hepatic impairment are presented in table E6.

Table E5: Between-treatment comparison of CEC-confirmed first primary endpoint (CV death or HF hospitalization) by renal function subgroups at baseline (CLCZ696B2314, double-blind period, FAS)

Renal function subgroup	LCZ696 200mg bid n/N (%)	Enalapril 10mg bid n/N (%)	LCZ696 vs. enalapril			
			LCZ696 n/T (EAIR)[1] (95% CI)	Enalapril n/T (EAIR)[1] (95% CI)	Hazard ratio (95% CI)	p-value
Normal renal function	90/525 (17.14)	116/541 (21.44)	90/10.99 (8.192) (6.587,10.069)	116/10.62 (10.927) (9.029,13.105)	0.755 (0.573,0.994)	
Mild renal impairment	427/2121 (20.13)	522/2151 (24.27)	427/44.81 (9.529) (8.647,10.478)	522/44.45 (11.744) (10.758,12.796)	0.809 (0.712,0.919)	
Moderate renal impairment Stage IIIa	258/1076 (23.98)	318/1054 (30.17)	258/22.29 (11.575) (10.206,13.077)	318/20.91 (15.211) (13.585,16.978)	0.773 (0.656,0.911)	
Moderate renal impairment Stage IIIb	136/453 (30.02)	154/453 (34.00)	136/8.90 (15.273) (12.814,18.067)	154/8.71 (17.672) (14.991,20.694)	0.853 (0.677,1.075)	
Severe renal impairment	3/12 (25.00)	7/13 (53.85)	3/0.23 (13.11) (2.704,38.314)	7/0.24 (28.909) (11.623,59.564)	0.575 (0.133,2.478)	0.8102[2]

CEC = Clinical Endpoint Adjudication Committee; CI = confidence interval; FAS = Full analysis set
1EAIR = exposure-adjusted incidence rate per 100 patient years = n/T: T(100 patient years): total up-to-event/censoring duration-time summarized over patients in the respective treatment group.
2Interaction-by-subgroup p-value
Source: [D120 Appendix 1 Table Q9.2.1]

Table E6: Between-treatment comparison of first primary endpoint (CV death or HF hospitalization) by hepatic function subgroups (CLCZ696B2314, double-blind period, FAS)

Hepatic function subgroup	LCZ696 200mg bid n/N (%)	Enalapril 10mg bid n/N (%)	LCZ696 vs. enalapril			
			LCZ696 n/T (EAIR)[1] (95% CI)	Enalapril n/T (EAIR)[1] (95% CI)	Hazard ratio[2] (95% CI)	p-value[3]
Child-Pugh Class A	903/4167 (21.67)	1106/4195 (26.36)	903/86.95 (10.385) (9.718,11.085)	1106/84.77 (13.047) (12.289,13.839)	0.797 (0.730,0.870)	0.83602
Child-Pugh Class B	11/19 (57.89)	11/17 (64.71)	11/0.23 (48.559) (24.240,86.885)	11/0.16 (70.314) (35.101,125.81)	0.895 (0.383,2.093)	

CI = confidence interval; FAS = Full analysis set
1EAIR = n/T: T(100 patient years): total up-to-event/censoring duration-time summed over patients in the respective treatment group.
2Hazard ratio and its confidence interval are calculated using a Cox model with treatment and region as fixed factors within each subgroup.
3The interaction p-value (2- sided) is calculated using the previous Cox's model with the addition terms of subgroup and subgroup by treatment interaction.
Source: [D120 Appendix 1 Table Q9.3.1]

Supportive studies

Study CLCZ696B2228 (TITRATION; Phase II Dose titration in HFrEF)

The primary objective of this 12-week study was to characterize the safety and tolerability of initiating and up-titrating LCZ696 in HFrEF patients based on reported adverse events (AEs) and laboratory assessments including hypotension, renal dysfunction and hyperkalemia, using a 3-week vs 6 week up-titration regimen to achieve the target dose of 200 mg bid. A starting dose of LCZ696 50 mg bid was selected for this study because the recommended starting dose of valsartan for HF patients is 40 mg bid, which is equivalent to the delivered valsartan exposure in LCZ696 50 mg bid.

Method

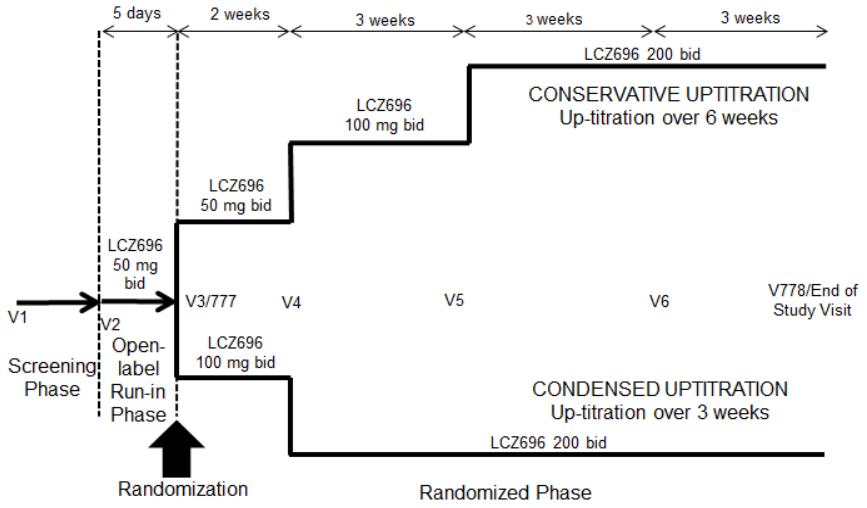
This was a multicenter, randomized, double-blind, parallel group, phase II study conducted in clinically stable HFrEF outpatients or hospitalized patients. The study population was comparable to that of the pivotal study PARADIGM-HF. Patients were stratified based on the level of RAS inhibition (low vs high). Patients in the low RAS inhibition stratum were either ACEi/ARB-naïve or on a low dose of ACEi/ARB (enalapril ≤ 10 mg/day or valsartan ≤ 160 mg/day or equivalent doses of other ACEis/ARBs).

The study consisted of three phases: (1) screening phase, including a 36-hour ACEi washout period; (2) open-label LCZ696 run-in phase where patients received LCZ696 50 mg bid for one week; and (3) randomized phase lasting approximately 11 weeks (figure E4). Patients were randomized to one of the following two treatment arms in a 1:1 ratio in a double-blind manner:

• Conservative up-titration: LCZ696 was up-titrated from 50 mg bid to 200 mg bid over 6 weeks (including the run-in phase)

• Condensed up-titration: LCZ696 was up-titrated from 50 mg bid to 200 mg bid over 3 weeks (including the run-in phase) (figure E4).

Figure E4 : Study CLCZ696B2228 Study design



Results

A total of 538 HFrEF patients entered run-in and took at least one dose of study medication and 498 patients were randomized, including 33 (6.6%) RAS-naïve patients and 56 (11.2%) hospitalized patients. The majority of patients in this study achieved and maintained the target dose of LCZ696 200 mg bid over the 12-week study duration (ie, run-in and randomized periods) without any dose adjustment or interruption, regardless of baseline RAS exposure (including ACEi/ARB naïve patients) (70.3% overall and 76.2% if discontinuations due to non-AE reasons are excluded).

During the 11-week randomized period, 84.9% of low RAS stratum patients were able to achieve and maintain the LCZ696 200 mg bid dose when up-titrated over 6 weeks (conservative regimen), as compared to 73.6% of low RAS stratum patients up-titrated over 3 weeks (condensed regimen). This difference was mainly due to fewer occurrences of hypotension, hyperkalaemia and renal dysfunction in patients who underwent the 6-week up-titration regimen. Similar proportions of patients in the high RAS stratum were able to achieve and maintain

the LCZ696 200 mg bid dose regardless of the up-titration regimen (82.6% for condensed and 83.8% for conservative).

During the 11-week randomized period, the rate of protocol-defined tolerability (tolerating LCZ696 200 mg bid for at least 2 weeks leading to study completion, regardless of previous dose interruption or down-titration) in the overall population was comparable between the two up-titration regimen groups (83.0% for condensed vs 87.3% for conservative). Tolerability in the low RAS stratum patients was slightly higher when patients were up-titrated over 6 weeks (86.6%) vs 3 weeks (80.2%). High rates of tolerability were observed in the high RAS stratum patients following either the condensed (86.2%) or conservative (88.0%) up-titration regimen.

Study CLCZ696B2214 (PARAMOUNT; Phase II proof-of-concept study in HFpEF)

This study aimed to demonstrate the efficacy of LCZ696 in HFpEF (≥ 45%) patients by testing the hypothesis that the reduction from baseline in NT-proBNP with LCZ696 200 mg bid is greater than that with valsartan 160 mg bid after 12 weeks of treatment.

Design

This was a multicenter, randomized, double-blind, parallel group, active-controlled phase II proof-of-concept study of LCZ696 in HFpEF patients. The study population consisted of male or female outpatients ≥ 40 years of age with stable chronic HF, NYHA class II-IV, LVEF ≥ 45% and baseline NT-proBNP > 400 pg/mL. In addition, patients were required to be on diuretic therapy before entering the study. The study consisted of two periods: 1) a 1-2 week single-blind, placebo run-in period during which patients continued their HF background therapies until 24 hours before randomization when ACEis or ARBs were stopped; and 2) a 12-week, core double-blind period during which patients were randomized 1:1 to LCZ696 200 mg bid or valsartan 160 mg bid followed by a 24-week double-blind extension period.

The primary efficacy endpoint of this study, change from baseline in NT-proBNP, was assessed after 12-weeks of treatment. Persistence of the treatment effect on NT-proBNP was further evaluated at 36 weeks.

Results

There were a total of 301 HFpEF patients in the randomized set for analysis: 149 in the LCZ696 treatment group and 152 in the valsartan treatment group. Baseline characteristics were comparable between the two groups. The majority of patients were elderly (mean age 71.0 years), female and in NYHA class II (79.4%). Mean LVEF was 58.1%, with 79.1% of patients having a LVEF ≥ 50%. The baseline NT-proBNP was elevated, with a mean of 1,228.21 pg/mL. Blood pressure was well-controlled, with a mean sitting BP of 135.03/77.25 mmHg.

The study demonstrated a significantly greater reduction in NT-proBNP from baseline to Week 12 for LCZ696 compared to valsartan, with a relative difference of 23% (ratio LCZ696/valsartan = 0.77; 95% CI, 0.64 to 0.92; p = 0.0050) between the two treatment groups. The effect of LCZ696 on NT proBNP was evident as early as 4 weeks after LCZ696 treatment initiation and persisted at Week 36, with a relative difference of 15% (ratio LCZ696/valsartan = 0.85; 95% confidence interval (CI), 0.65 to 1.09) between the two treatment groups, but this difference was no longer statistically significant (p = 0.2023). There were improvements noted in some echocardiographic parameters e.g left atrial dimension (LAD), left atrial volume (LAV) and left atrial volume index (LAVI) in the LCZ696 group compared with the valsartan group.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

From the clinical development program of LCZ696, the applicant submitted data pertaining to the fixed dose combination (FDC) LCZ696, as well as for the mono-component valsartan. A combination of an ARB/ACEi and NEPi was already investigated previously in another development program with omapatrilat (ACEi and NEPi), which showed promising results but also emerging safety issues (angioedema) which halted further development. Those experiences supported the rationale of such an FDC from an efficacy perspective, while leading to the substitution of the ACEi with an ARB to minimise the risk of angioedema. Sacubitril was also considered to be a more selective NEPi than omapatrilat.

Efficacy of sacubitril (alone) in the proposed indication was not investigated. No data were available to clarify the relative contribution of the sacubitril component in relation to a well titrated valsartan treatment. It would have been preferred to establish its efficacy in this setting however this omission was accepted by the CHMP. Data pertaining to valsartan mono-component were not discussed further in this report as efficacy of valsartan in the proposed indication of HF is well established. In most of the EU countries, valsartan is recommended for treatment of symptomatic heart failure when ACE inhibitors cannot be used, or as add-on therapy to ACE inhibitors when beta blockers cannot be used.

Dose selection

There were no dedicated dose-finding studies submitted within the current application. LCZ696 contains valsartan which is already approved for HF in a comparable dose (i.e. different content but comparable exposure). For the other component (sacubitril) the dose was chosen following the results of available PD studies that indicated the dose that achieved near maximum NEP inhibition. In parallel, there was the then ongoing PARAMOUNT study which studied LCZ696 in HFpEF patients, using the same dose. The study was concluded before PARADIGM -HF and gave also some support to the dose used in the HFrEF program. In general, the dose was considered to be justified.

Design of main clinical study (PARADIGM-HF)

According to the applicant the **active run-in period** allowed careful assessment of the tolerability of patients to the target doses of enalapril and LCZ696 prior to randomization. This approach was acceptable in order to improve tolerability and was also feasible to ensure on treatment compliance and thus avoid major dropout rates in the study. However, using enalapril in the first run-in period precluded direct interpretation of the tolerability of LCZ696. The wash-out period of 36 hours between the last ACEi dose and LCZ696 implemented in the study (to minimise risk of angioedema) is now also recommended in section 4.2 of the SmPC. The inclusion and exclusion criteria generally reflect the target population with HFrEF.

The **choice of enalapril** as the active comparator was endorsed, as it represented one of the most commonly used ACEI in the management of HF. It was noted that the investigated dose of enalapril of 10 mg bid was lower than the recommended one in the ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 (European Heart Journal [2012] 33, 1787–1847; doi:10.1093/eurheartj/ehs104) or the EU SmPC of enalapril 20 mg bid (SE/H/0406/004). However, CHMP acknowledged that this high dose of enalapril might have not been tolerated by many patients in the study. Registry data indicated that almost half of patients could not tolerate the maximal doses of ACE inhibitors prescribed (EURObservational Research Programme Maggioni et al., European Journal of Heart Failure [2010]; 12, 1076–1084). In addition, a mean enalapril dose of 16.6 mg showed a survival benefit in the SOLVD trial. There was also further evidence that the 20 mg/day enalapril was associated with robust clinical benefits (NETWORK study Clinical outcome with enalapril in symptomatic chronic

heart failure; a dose comparison. Eur Heart J. 19 1998:481-489). The chosen dose of enalapril had previously been also agreed in a scientific advice procedure by the CHMP. Still, considering that LCZ696 contains the highest approved dose of valsartan for the treatment of HF, it cannot be excluded that the choice of the enalapril dose may have favoured LCZ696 arm. Although it would have been preferable to enable investigators to uptitrate the enalapril dose as tolerated. However, additional post-hoc analyses demonstrated that the clinical benefits of LCZ696 over enalapril were consistent among the HFrEF patients regardless of their daily enalapril equivalent doses received prior to study entry.

The chosen primary endpoints reflect the main objective of treatment in HFrEF patients. However, the **definition of HF hospitalisation (HFH)** was further discussed. Since patients with HF may be often hospitalised for non-cardiac causes or for reasons unrelated to worsening of HF, objective evidence of cardiovascular de-compensation as cause of hospitalisation was considered as relevant. The threshold for hospitalization is known to be highly variable across and within regions of the world and this may affect the interpretability and applicability of study results. The applicant presented the criteria used for adjudication of HFH. These included an overnight stay in a hospital in patients with at least one symptom, 2 signs of HF in addition to the need of specific IV therapy or intensification of oral therapy. This definition was in line with accepted standardised definition (*Hicks et al., 2014*) and was accepted by the CHMP. The adjudication process was also considered acceptable. There were some differences in the frequency of the presenting signs and symptoms of HF across regions which could be expected.

The first secondary endpoint of **all-cause mortality** was considered relevant to support an overall benefit. The other endpoints helped to elucidate additional benefits of LCZ 696 which are relevant to patients with HF e.g. renal function or onset of AF. The letter endpoint was elevated to a secondary endpoint in 2013 in protocol amendment 3 after observation of reverse left atrial remodelling with LCZ696 in the phase 2 study (PARAMOUNT).

Statistical methods

The analysed populations, the primary and key secondary endpoints analysed and subgroup analyses were acceptable. The applicant had clearly described the changes done after the database lock (DBL) and unblinding of the study. The date for database lock and unblinding of the treatment codes was 18-Jul-2014. The changes to the plan included both additional analyses and changes to the statistical methods. The changes made after DBL were not considered to change the interpretation and the conclusions drawn. Additional clarifications about the process related to the interim analyses and the final analysis were given. The process for the final analysis was acceptable. In addition, the applicant was requested to clarify if there were any deaths, CV deaths or HF hospitalizations in the time period between the cut-off at 31 March 2014 and the last patient last visit on 19 May 2014. The primary and secondary analyses were performed using all available endpoint data prior and up to 31 Mar 2014, hence the request for the additional information. The additional events were evenly distributed in the 2 treatment groups and should not change the conclusion of the primary analysis. The censoring rules were adequate for the study design.

The analyses were adjusted to ensure strong control of the family-wise type I error rate, both across the primary and key secondary endpoints and across the interim analyses. The planned adjustment used the Haybittle-Peto type of boundary to assess the efficacy at the interim analyses and a sequentially rejective multiple test procedure across the primary and secondary endpoints. This planned procedure was acceptable.

Since the study was stopped at the 3rd interim analysis, the significance level allocated to this interim analysis (one-sided α=0.001) had to be used for the formal significance test of the primary subsequent secondary analyses. It was agreed with the applicant that this approach is highly conservative. However, the alternative

approach of the applicant, allocating the remaining (unused) alpha to the secondary endpoints did not ensure strong control of the type I error rate, especially with correlated endpoints. Further, the alternative approach appeared to be data driven. A less conservative approach than the one in the initial protocol could have been possible, if it would have been in the trial protocol from the start, with a clear justification and, if possible, proof of the type I error control. Therefore only the conservative approach was considered appropriate.

Results

There was a high rate of **screening failures** due to the low NT-pro BNP levels (n=4661; 61.87%). The applicant clarified that recruitment based on a high NT-proBNP levels was used as an enrichment factor and not to establish the diagnosis of HF in these patients. Presented data showed that even patients who failed screening because of low NT-proBNP, had on average levels of NT-proBNP (median 238 pg/ml) which were above those qualifying for a CHF diagnosis and had already an established diagnosis of HF. The median run-in period for LCZ696 was double that of enalapril, indicating that patients need a longer time to tolerate the full dose of LCZ696. During both run-in periods, a comparable **drop-out rate** (LCZ696: 5.85% vs enalapril 5.62%) was observed due to tolerability issues (renal dysfunction, hypotension, hyperkalaemia). It is not known what the dropout rate in the LCZ696 arm would have been if it would have been the first run-in. However, it can be concluded that not all patients who can tolerate enalapril can also tolerate LCZ696 and that it takes longer to build up the LCZ696 dose safely. Tolerability for LCZ696 was further discussed, particularly in patients naïve to ACEi/ARB who were not investigated in the pivotal study and are represented to a limited extent in study CLCZ696B2228.

Generally, the patients recruited were representative of a **population with HFrEF** regarding demographics, comorbidities and co-medications allowing extrapolation of the current results to this population. The majority of the patients had NYHA class II (70%) or class III (24%), but most also had a previous history of HF hospitalisation (around 63%), reflecting a veteran HF population. There was very limited representation of patients with NYHA class IV (less than 1%). The median NT-ProBNP was around 1600 pg/ml, which was comparable to that of 1387 pg/mL measured in a HF Registry (*EURObservational Research Programme Maggioni et al., European Journal of Heart Failure [2010]; 12, 1076–1084*). There was an adequate representation of patients from the EU. Also, the prescribed co-medications at baseline reflected an adequate standard of care. However, there was little representation of patients with cardiac devices compared to current standard of care e.g. 23.6 % with ICD and 12.7 % with CRT according to an EU heart failure registry (*Maggioni et al., 2013; Eu. J HF (2013) 15, 1173–1184*). However, these figures were comparable to those observed in the previously conducted clinical studies SHIFT and EMPHASIS. Further analysis of data showed that the prevalence of cardiac device use differed per region. The favourable results were applicable to both patients with and without implantable cardiac devices, which was reassuring. The average daily dose of enalapril achieved in PARADIGM HF (18.9 mg) was higher than that achieved in the SOLVD trial (16.6 mg) and comparable to that achieved in the CONSENSUS trial (18.4 mg). Both trials demonstrated a mortality benefit for enalapril over placebo in HFrEF patients, supporting the validity of the currently achieved dose. Overall, treatment compliance was very similar for both LCZ696 and enalapril during the run-in, as well as during the double-blind treatment period (over 80% compliance at each visit).

Primary endpoints

Results showed significant and clinically relevant improvements in the endpoints of **CV mortality** and **hospitalisation for HF**, respectively, as well as the composite endpoint of both, in patients administered LCZ696 compared to enalapril. The results were obtained against the established standard of care and particularly on a robust endpoint of CV death. The study was specifically powered to show **superiority with regards to CV death** and it was prematurely stopped when this endpoint was achieved. LCZ696 reduced the

risk of CV deaths due to sudden cardiac death and pump failure compared to enalapril. LCZ696 also reduced the risk of first hospitalisation for HF which was also a relevant endpoint, as such hospitalisations are known to denote a major deterioration of this disease. The current results are similar in its effect size to those achieved by enalapril when compared to placebo (SOLVD study, 1991), with a **4.8% absolute risk reduction in CV death over 41 months**, which translates into an NNT of 32 patients over 27 months assuming hazards are constant over time. It was difficult to attribute these benefits to one of the separate components of LCZ696. Although there were no randomised clinical trials directly comparing valsartan against enalapril, there was robust evidence establishing the benefits of ACEi in HF and evidence that the use of ARBs in HFrEF is reserved only for patients who cannot tolerate ACEi. The VAL-HeFT study investigated the use of valsartan against placebo on top of standard HF therapy which included ACEi. No difference in overall mortality was shown between the treatment groups. Only in a subgroup of patients not receiving ACEi (n=366), all-cause mortality was significantly reduced with valsartan compared to placebo by 33% (95% CI: – 6% to 58%;17.3% valsartan vs. 27.1% placebo). No data were available to independently establish the efficacy of sacubitril, which was noted by the CHMP as a weakness of this development program.

Secondary endpoints

In line with the benefit with regard to CV death, LCZ696 also significantly improved **all-cause mor**tality compared to enalapril which was further reassuring, also regarding the overall safety profile of LCZ696.

The favourable results of LCZ696 on the **patient-reported symptoms** as assessed by the clinical summary score of KCCQ supported the efficacy of LCZ696 from the patient's perspective. The use of PRO-questionnaires depends on the availability of validated translations of the instrument and the literacy of the trial subject. The applicant explained that most of the full analysis set (FAS) was included in the KCCQ subset. The main exclusion due to lack of validated translations was for 316 patients from 6 countries. For the rest of the responders of the KCCQ the population was largely comparable to the FAS. Five point's difference in the KCCQ score had been considered to be a clinically relevant difference. The arguments for establishing five points difference in KCCQ clinical summary score as clinically relevant were supported. The clinical relevance of the observed positive impact of LCZ696 on KCCQ CSS was supported by the responder analyses demonstrating significantly fewer LCZ696 patients with at least a 5 point or 10-point deterioration compared to enalapril and such benefit was evident throughout the study duration. However, the differences in responders were small: around 3.4% after correction for mortality. The results were consistent with the changes in NYHA functional class from the prescribers 'perspective, although the differences in NYHA classification were small.

There were no significant differences in the endpoint of time to **new onset AF** (NOAF). The number of confirmed new onset AF was low in both groups (84/2670 in LCZ696-treated patients vs. 84/2638 in enalapril-treated patients), which was a somewhat surprising finding in the context of the beneficial effects on HF observed for mortality and hospitalisation. Infrequent (ECG) monitoring during the long term follow up (annually) as well as this low rate of AF might have contributed to why no benefit with regard to reducing the risk of NOAF could be demonstrated with LCZ696. The low incidence of AF might have been also partly due to sampling issues. A tendency for lower absolute rates of AF in the LCZ 696 arm was observed during the first years but a small difference already at baseline must be taken into account.

No benefits were shown on the renal composite endpoint, only (numerical) trends were shown with regard to renal function in the LCZ696 treatment arm.

Efficacy of LCZ696 was further confirmed in the major **subgroups** investigated. Of note, a significant subgroup by treatment interaction (p=0.0335) for the primary composite endpoint was observed for the baseline NYHA class I/II vs. III/IV subgroups, with the HR for LCZ696 vs. enalapril numerically higher in NYHA class III/IV

patients (HR 0.92) compared to class I/II patients (HR 0.75). Further data showed that the reduction in CVS death among the NYHA III/IV classes was consistent with the overall study results whereas the hospitalization rates were higher than in the enalapril group (HR 1.08). However, a number of additional analyses taking other disease severity markers into account (LVEF baseline terciles, NT-proBNP, KCCQ) supported the conclusion that a similar benefit could be expected in these severely affected patients as observed in the overall HFrEF population. There were consistent risk reductions observed for other subgroups of varying severity including EF (across terciles), NT-proBNP (across terciles) and prior HF hospitalizations (yes/no) which diminished the importance of this finding.

Patients with NYHA class IV

The applicant argued that the limited recruitment of patients of NYHA IV in PARADIGM-HF (n=60) was in line with previously completed HF trials (e.g. HEAAL N=38, CHARM-added N=76, SHIFT N=111) (*McMurray et al 2014*). In addition, the applicant indicated that patients with NYHA class III could be attributed to NYHA IV: 1195 patients (537 in the LCZ696 group and 658 in the enalapril group) were hospitalized for worsening HF. These patients might have been considered NYHA class IV and subsequently fewer LCZ696-treated patients experienced multiple hospitalizations for HF (N=170) compared to enalapril treated patients (N=240), which gave additional evidence that continued LCZ696 treatment provided benefit in patients with NYHA class IV. This argument was considered valid for patients who were NYHA III at baseline and who deteriorated to NYHA IV, but was not considered to apply to NYHA IV patients at baseline by CHMP. NYHA IV is considered a specific population at a higher risk of SAE, related to renal function and serum potassium. Specifically in this population, changes in salt and water balance can exaggerate or attenuate the cardiovascular and renal effects of RAAS inhibitors. Overall, CHMP was reassured that the general efficacy results of the study pointed to the same trends as the rest of the NYHA groups.

Measurement of LV ejection fraction (LVEF)

The main terminology used to describe HF was based on measurement of LV ejection fraction (LVEF). Submitted data showed that efficacy was maintained for patients with LVEF ≤ 35% and >35%. In addition, a post hoc assessment based on baseline LVEF tercile values showed comparable risk reduction of LCZ696 against enalapril across the subgroups of EF (HRs of 0.79 to 0.81 across the terciles) including patients in the upper tercile (EF ≥ 33%). These results supported the efficacy of LCZ696 around a range of EF below 40% and this was reflected in the SmPC.

Special populations

There was adequate representation of patients with mild and moderate **renal impairment** in PARADIGM-HF (n= 4291 and n=3051 respectively). There was very little representation of patients with severe renal impairment eGFR < 30 mL/min/1.73 m2 as this was an exclusion criteria; in the double-blind period, experience pertained to n=12 patients on LCZ696 and n=13 on enalapril. The applicant further divided patients with moderate renal impairment into 2 subgroups, with the idea that the benefit-risk of patients with lower eGFR (30-45 mL/min/1.73 m2) could fill the gap in the knowledge of the severe renal impairment subgroup. This approach was supported but the fact remained that there was very limited clinical experience in patients with severe renal impairment. However, efficacy data of the different subgroups was generally in line with the main study results.

Hepatic function status was not assessed as part of the study protocol of PARADIGM-HF. However, as patients with severe hepatic impairment (Child Pugh C classification), biliary cirrhosis and cholestasis were excluded from the study, the use in these patients should be contraindicated and this is reflected in the SmPC. This is also in line with the product information of valsartan. The applicant performed a post-hoc analysis using

Child-Pugh classification based on available data. However these analyses had a number of limitations including the fact that not all data were available and the very limited number of patients with more advanced stages of hepatic impairment. These data show that essentially most of the patients had no hepatic impairment. Overall, efficacy data based on the Child-Pugh classification were consistent with efficacy results of the study i.e, superior efficacy with LCZ696 compared with enalapril, but as expected with wide confidence intervals in patients with Child-Pugh B due to the limited representation did not allow firm conclusions. The SmPC was adapted with no dose adjustments required when administering LCZ696 to patients with mild hepatic impairment (Child Pugh A classification). As there is limited clinical experience in patients with moderate hepatic impairment (Child Pugh B classification) or with AST/ALT values more than twice the upper limit of the normal range, LCZ696 should be used with caution in these patients and the recommended starting dose is 24 mg/26 mg twice daily.

Supportive studies

Study CLCZ696B2228

Study CLCZ696B2228 was conducted following the main pivotal study to address tolerability. Titration started from 50 mg LCZ696 (instead of 100 mg used in the pivotal study), followed by a 3 or 6 weeks titration period to the target of 200 mg LCZ696. Tolerability appeared to be better (less hypotension, hyperkalemia and renal dysfunction) in treatment naïve or patients initially on low doses of ACEis/ARBs whereas this low starting dose did not impact results in patients initially on high doses of ACEis/ARBs. Regarding the titration period, a 6 weeks titration was associated with better tolerability in patients already on low RAS (or naïve) compared to 3 weeks, but results did not differ in the high RAS stratum. The study therefore supported the recommendation in section 4.2 of the SmPC to start with 50 mg LCZ696 in the former group of patients.

Study CLCZ696B2214

Study CLCZ696B2214 was conducted before the PARADIGM-HF study and could be considered a proof of concept study for LCZ696 in HFpEF. Results showed that LCZ696 treatment (200 mg bid) resulted in significant reduction in NT-proBNP at week 12 compared to valsartan (160 mg bid) though this reduction was not significant later. The results were generally supportive of those of PARADIGM, but were not related to the same indication and so cannot be reflected in section 5.1 of the SmPC. An important conclusion from this study, which also was supported by the pivotal study results, was that the NT-proBNP decrease appeared to be largely independent of the blood pressure reduction.

2.4.4. Conclusions on the clinical efficacy

Efficacy of LCZ696 200 mg bid was shown to be superior to enalapril 10 mg bid in terms of cardiovascular mortality and heart failure hospitalisation in a well-designed and executed study, PARADIM-HF. LCZ696 treated patients had a significantly lower rate of the primary endpoint of the composite of CV death or first HF hospitalization (21.83%) compared to enalapril treated patients (26.52%). The absolute risk reductions were 4.7% for the composite of the CV death or HF hospitalization, 3.1% for CV death alone and 2.8% for first HF hospitalization alone. The benefit of LCZ696 treatment was seen early and was sustained for the entire study duration for the primary endpoint. The first secondary endpoint of all-cause mortality was relevant to support an overall benefit. The other endpoints helped to elucidate additional benefits of LCZ 696 which are also relevant to patients with heart failure. Efficacy of LCZ696 was further confirmed to be applicable also to the major subgroups investigated.

The patients included in the pivotal trial were selected by the requirement of prior ACEi/ARB treatment and then further selected by the two titrations periods preceding randomization. During the procedure the CHMP discussed whether it is appropriate to administer LCZ696 to ACEi/ARB naïve patients. However, taking into account the demonstrated benefit and the support of the sensitivity analyses performed, the external validity of the study was considered adequate. Regarding efficacy, it seems likely that benefits seen are not expected to be different in these groups. Also analysis by time of HF diagnosis in recruited patients confirmed that newly diagnosed patients (less than 3 months) have comparable efficacy to more "veteran" patients. Therefore the CHMP concluded that a similar benefit to the one observed in ACEi/ARB naïve patients can be expected in patients not previously treated with ACEi/ARB. Tolerability of LCZ696 should be mitigated by slow titration of this medicinal product as reflected in the SmPC and are further discussed in the safety sections of this report.

In conclusion, the efficacy results supported the use of LCZ696 in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

2.5. Clinical safety

Patient exposure

Overall, a total of 14937 patients and healthy volunteers have been exposed to LCZ696. Of these, there were 10155 patients with heart failure, 3874 patients with hypertension, 870 were healthy volunteers, 22 subjects were with renal impairment and 16 subjects were with hepatic impairment. These numbers include all active run-in periods with LCZ696 as well.

A number of 3606 patients was exposed to LCZ696 for at least one year. At least 71% used the actually planned dose of 200 mg at each visit.

The safety evaluation in the current application was primarily based on the pivotal study (PARADIGM-HF) and supplemented by phase 2 studies in HFrEF (TITRATION) and HFpEF (PARAMOUNT) (table S1).

Table S1: Number (%) of patients exposed to treatment in the double-blind treatment period, by duration, study and treatment group in the HF program (Safety set)

	PARADIGM-HF				PARAMOUNT				TITRATION	
	LCZ 200 mg bid N=4203		ENA 10 mg bid N=4229		LCZ 200 mg bid N=149		VAL 160 mg bid N=152		LCZ 200 mg bid N=497	
Exposure	n (%)	Person years	n (%)	Person years	n (%)	Person years	n (%)	Person years	n (%)	Person years
≥ 1 day	4203 (100.0)	8635.76	4229 (100.0)	8426.65	149 (100.0)	89.28	152 (100.0)	89.72	497 (100.0)	108.88
≥ 1 month (30 days)	4132 (98.3)	8632.81	4140 (97.9)	8422.71	142 (95.3)	88.96	142 (93.4)	89.37	482 (97.0)	108.03
≥ 3 months (90 days)	4019 (95.6)	8614.84	4003 (94.7)	8401.39	127 (85.2)	86.38	129 (84.9)	87.08	15 (3.0)	3.82
≥ 6 months (180 days)	3886 (92.5)	8566.28	3845 (90.9)	8343.53	120 (80.5)	83.79	122 (80.3)	84.86	0 (0.0)	0
≥ 9 months (270 days)	3743 (89.1)	8478.24	3671 (86.8)	8234.04	10 (6.7)	7.71	5 (3.3)	3.75	0 (0.0)	0
≥ 1 year	3606 (85.8)	8357.26	3512 (83.0)	8095.34	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
≥ 2 year	2153 (51.2)	6071.79	2044 (48.3)	5800.67	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

Source: [SCS-Appendix 1-Table 14.3-1.2]
Person Years are calculated as total number of years of exposure summed up from all patients who are on treatment at each defined time point.

Treatment exposure is defined as the time between the first and last treatment dose, including the first day on study drug.

The applicant selected the following safety topics of special interest:

- hypotension,
- renal impairment,
- hyperkalemia,
- angioedema,
- embryo-fetal and infantile toxicity,
- hypersensitivity reaction,
- hepatotoxicity,
- change in bone growth and/or bone mineral density,
- cognitive impairment,
- stimulation of lipolysis,
- gastric lesions,
- QT prolongation and
- cancer promotion.

Adverse events

As discussed under efficacy, around 10% of enrolled patients discontinued study treatment during the run-in period, primarily due to adverse events or protocol-defined discontinuation criteria. The reasons for discontinuation are shown in Table S2.

Table S2 Primary reason for treatment discontinuation during run-in period (Enrolled set)

	Enalapril run-in N=10513 n (%)	LCZ696 run-in N=9419 n (%)
Adverse Event(s)	591 (5.62)	551 (5.85)
Cough	49 (0.47)	15 (0.16)
Hyperkalaemia	174 (1.66)	125 (1.33)
Hypotension	146 (1.39)	164 (1.74)
Renal dysfunction	181 (1.72)	174 (1.85)
Other	102 (0.97)	132 (1.40)
Abnormal laboratory value(s)	55 (0.52)	50 (0.53)
Abnormal test procedure result(s)	11 (0.10)	9 (0.10)
Unsatisfactory therapeutic effect	4 (0.04)	10 (0.11)
Patients condition no longer requires study drug	1 (0.01)	2 (0.02)
Patient withdrew consent	171 (1.63)	100 (1.06)
Lost to follow-up	39 (0.37)	26 (0.28)
Administrative problems	20 (0.19)	29 (0.31)
Death	49 (0.47)	47 (0.50)
Protocol deviation	79 (0.75)	92 (0.98)
Other	81 (0.77)	65 (0.69)
Missing treatment discontinuation information	1 (0.01)	1 (0.01)

Source: PARADIGM-HF Table 14.1-1.3.a

The applicant has presented the number (%) of patients with most common adverse events (occurring ≥ 2% in any treatment group) in the double-blind treatment period (Table S3). Hypotension, hyperkalaemia and renal impairment were the most commonly reported AEs. These were also defined as topics of special interest and are further discussed below.

Table S3 Number (%) of patients with most common adverse events in double-blind treatment period, by preferred term, study and treatment group in HF program (PARADIGM-HF Safety set)

Preferred term (PT)	LCZ 200 mg bid N=4203 n (%)	ENA 10 mg id N=4229 n (%)
Any adverse event	3419(81.35)	3503(82.83)
Hypotension	740 (17.61)	506 (11.97)
Cardiac failure	730 (17.37)	832 (19.67)
Hyperkalaemia	488 (11.61)	592 (14.00)
Renal impairment	426 (10.14)	487 (11.52)
Cough	369 (8.78)	533 (12.60)
Dizziness	266 (6.33)	206 (4.87)
Atrial fibrillation	251 (5.97)	236 (5.58)
Pneumonia	227 (5.40)	237 (5.60)
Oedema peripheral	215 (5.12)	213 (5.04)
Dyspnoea	213 (5.07)	306 (7.24)
Nasopharyngitis	204 (4.85)	175 (4.14)
Upper respiratory tract infection	203 (4.83)	201 (4.75)
Urinary tract infection	199 (4.73)	195 (4.61)
Diarrhoea	194 (4.62)	189 (4.47)
Bronchitis	183 (4.35)	224 (5.30)
Angina pectoris	172 (4.09)	170 (4.02)
Anaemia	168 (4.00)	201 (4.75)
Back pain	164 (3.90)	138 (3.26)
Influenza	159 (3.78)	132 (3.12)
Hypokalaemia	139 (3.31)	107 (2.53)
Cardiac failure chronic	135 (3.21)	155 (3.67)
Cardiac failure congestive	133 (3.16)	167 (3.95)
Arthralgia	126 (3.00)	119 (2.81)
Hypertension	126 (3.00)	193 (4.56)
Fatigue	125 (2.97)	129 (3.05)
Diabetes mellitus	123 (2.93)	134 (3.17)
Gout	121 (2.88)	120 (2.84)
Renal failure	112 (2.66)	144 (3.41)
Hyperuricaemia	108 (2.57)	151 (3.57)
Ventricular tachycardia	108 (2.57)	137 (3.24)
Non-cardiac chest pain	106 (2.52)	122 (2.88)
Headache	103 (2.45)	106 (2.51)
Renal failure acute	95 (2.26)	93 (2.20)
Syncope	94 (2.24)	114 (2.70)
Chronic obstructive pulmonary disease	93 (2.21)	106 (2.51)
Insomnia	92 (2.19)	92 (2.18)
Pain in extremity	92 (2.19)	100 (2.36)
Asthenia	88 (2.09)	78 (1.84)
Nausea	88 (2.09)	100 (2.36)
Cardiac death	86 (2.05)	114 (2.70)

Preferred term (PT)	LCZ 200 mg bid N=4203 n (%)	ENA 10 mg id N=4229 n (%)
Constipation	86 (2.05)	124 (2.93)
Pyrexia	78 (1.86)	85 (2.01)
Cardiac failure acute	72 (1.71)	100 (2.36)
Vomiting	71 (1.69)	85 (2.01)

Most common AEs are the AEs reported ≥ 2% in any group for each PT.
A subject with multiple AEs in the double-blind treatment period is counted only once in "any AE" row.
A subject with multiple occurrences of an AE (PT) term is counted only once in the same AE category.
PTs are sorted by descending frequency in the LCZ696 200 mg bid group in PARADIGM-HF.
Source: [SCS-Appendix 1-Table 14.3.1-1.3], SCS Table 2-3.

Of the safety topics of special interest, in PARADIGM-HF only hypotension and confirmed angioedema occurred more frequently in LCZ696 than with enalapril (Table S4).

Table S4 Event rates for safety topics of special interest in double-blind treatment period for PARADIGM-HF (Safety set)

Topic	LCZ696 200 mg bid N=4203 n (%)	Enalapril 10 mg bid N=4229 n (%)
Hypotension	1027 (24.4)	786 (18.6)
Renal impairment	682 (16.2)	746 (17.6)
Hyperkalemia	500 (11.9)	605 (14.3)
Angioedema (SMQ AE)	300 (7.1)	312 (7.4)
Angioedema (confirmed)	19 (0.5)	10 (0.2)
Hepatotoxicity	138 (3.3)	184 (4.4)
Cognitive impairment (Dementia broad SMQ)	86 (2.0)	83 (2.0)
Cognitive impairment (Dementia narrow SMQ)	12 (0.3)	15 (0.4)
Hypersensitivity reaction	329 (7.8)	369 (8.7)
Change in bone growth/bone mineral density	83 (2.0)	80 (1.9)
Stimulation of lipolysis	515 (12.3)	524 (12.4)
Gastric lesions	427 (10.2)	435 (10.3)
Cancer promotion	130 (3.1)	150 (3.5)

Source: [SCS-Table 2-11]

LCZ696 caused more events of **hypotension** and dizziness than enalapril and more discontinuations in the double blind phase.

Hypotension events were more frequently reported in the following subgroups of patients in PARADIGM-HF:

- Patients ≥ 65 years old
- Patients with renal disease at screening
- Patients with systolic BP at baseline of <median
- Patients not using MRAs at baseline
- Patients using phosphodiesterase-5 inhibitors (however, the number of patients was low).

Overall, lower incidences of **renal impairment-related AEs**, SAEs and AEs leading to study drug discontinuation were reported in PARADIGM-HF for LCZ696-treated patients compared to enalapril-treated

patients despite a greater BP lowering effect associated with LCZ696 therapy. Categorical changes in eGFR and serum creatinine were consistent with the AE data, with lower rates in the LCZ696 group vs. the enalapril group. A lower incidence of renal impairment-related AEs was also observed for LCZ696-treated patients with moderate and severe renal impairment compared to enalapril-treated patients with moderate and severe renal impairment.

The results of PARADIGM-HF showed a lower incidence of **hyperkalaemia** for patients treated with LCZ696 than for patients treated with enalapril as well as less frequent hyperkalaemia-related SAEs and AEs leading to discontinuation compared with enalapril. This may be explained by the natriuretic and diuretic effect of LCZ696 through NEPi.

Angioedema. During the enalapril run-in period there were 15 patients (0.14%) with AAC-confirmed angioedema events and during the LCZ696 run-in, 10 patients (0.11%) had AAC-confirmed angioedema events. During the LCZ696 run-in period, 1 and 3 cases of confirmed angioedema occurred within 1 and 7 days, respectively. All but one cases of confirmed angioedema during the run-in period were non-serious, except for one serious case during the enalapril run-in period, which did not involve airway compromise or death. During the double blind period, most of the AAC-confirmed angioedema events were non-serious. Serious, severity grade III or IIIa (i.e. the event involved hospitalization, but with no airway compromise) events were reported in 3 patients in the LCZ696 group compared to 1 patient in the enalapril treatment group. All of these serious events were confounded by alternative etiologies for the development of the event of angioedema and none of them involved airway compromise or required airway support.

In PARADIGM-HF, the incidence of **hepatotoxicity related AEs** was lower for LCZ696 compared with enalapril (3.3% vs. 4.4%, RR 0.7, 95% CI 0.6-0.9). Despite small imbalances in the incidence of mild hepatic transaminase elevations compared with enalapril, LCZ696 was not associated with a higher rate of combined elevations in hepatic transaminases and serum bilirubin [SCS Table 2-18]. There was no signal of hepatotoxicity from PARADIGM-HF or other data in the dossier.

No increased incidence of **cognition- or dementia-related AEs** has been reported in the HF or HTN clinical program with LCZ696.

In PARADIGM-HF, the incidence of **hypersensitivity-related AEs**, other than angioedema, was slightly lower for LCZ696 compared to enalapril (7.8% vs. 8.7%, RR 0.9, 95% CI 0.8-1.0). Also, the LCZ696 and enalapril groups had low and comparable rates of hypersensitivity SAEs (1.64% vs. 1.82%) and AEs that led to discontinuation (0.38% vs. 0.28%).

There was no signal regarding growing **bones** or changes in Bone Mineral Density.

In PARADIGM-HF, the incidence of AEs related to **cancer promotion** (which included PTs for malignancies) was low in PARADIGM-HF. If an effect of cancer promotion would exist, it could easily take many years to manifest itself as cancer. Therefore, AEs in PARADIGM-HF are not considered sensitive to this evaluate risk.

Results from PARADIGM-HF showed no undesirable **metabolic effects** of LCZ696 in patients with HF. The incidence of AEs related to stimulation of lipolysis was comparable between treatment groups: LCZ696 12.3% vs. enalapril 12.4%. There was no imbalance in events related to hyperglycemia or new onset of diabetes and no imbalance in changes from baseline of plasma glucose, HbA1c, or triglycerides between the LCZ696 and enalapril groups.

There is no signal of **QT prolongation** based on the thorough QTc study and PARADIGM-HF.

The Applicant selected ADR candidates for **inclusion in section 4.8 of the SmPC** applying clinical judgment, an understanding of LCZ696 preclinical information, safety information from the literature where applicable, class effect information and the LCZ696 mechanism of action, to determine the potential causality of reported events.

Sources were

- known class effects for drugs acting on the RAAS,
- events potentially associated with neprilysin inhibition,
- events plausibly associated with the mechanism of action of LCZ696,
- AEs in PARADIGM-HF that occurred statistically significantly more frequently for LCZ696 compared to enalapril and
- AEs in PARAMOUNT that occurred statistically significantly more frequently for LCZ696 compared to valsartan

The analysis of trials found no additional AEs.

Serious adverse events / deaths / other significant events

All-cause **mortality** was lower for LCZ696 compared to enalapril. This result was driven by CV mortality and is covered in the efficacy section. Non-Cardiovascular death occurred slightly more frequently with LCZ696 compared to enalapril.

For each PT, incidences of **SAEs** were comparable between treatment groups or were lower in the LCZ696 group compared to the enalapril group, including hypotension (1.4% for the LCZ696 group and 1.6% for the enalapril group).

Laboratory findings

In PARADIGM-HF, the proportion of patients with hypokalaemia (K <3.5 mmol/L) was higher in the LCZ696 group compared to the enalapril group (7.46% vs. 5.71%) which may be explained by the effect of diuresis and natriuresis associated with LCZ696 therapy via sacubitril. SAEs and study drug discontinuations due to hypokalaemia in LCZ696 were comparable to enalapril. Hyperkalaemia is discussed above.

In the double blind period PARADIGM-HF, the effect of LCZ696 compared to enalapril on **renal function** was slightly favourable. The occurrence of **liver enzyme increases** is similar to enalapril and valsartan. No serious cases were found.

The effect of LCZ696 on BP is described with the AE ‘hypotension’. Analysis of other **vital** signs and ECGs revealed no new safety issues.

The ratio of urine albumin to creatinine ratio to baseline values in the LCZ696 group was approximately 28% higher in the LCZ696 group compared to the enalapril group at 4 weeks and 8 months post-randomization (both p=0.0001).

Safety in special populations

In PARADIGM-HF, most patients had mild (4291/8432, 50.9%) or moderate (3051/8432, 36.2%) **renal impairment**. Obviously, the adverse event profile in these groups mimics the overall AE profile, although AEs are more frequent as renal function deteriorates. Subjects with severe renal failure were excluded from the trial; still data were available for 25 such patients. In these patients, the AE profile seemed comparable to enalapril. However, the AE profile was much more severe than in mild or moderate renal impairment.

The profile of selected AEs of special interest (hypotension, renal impairment, and hyperkalemia) in patients with moderate and severe renal impairment was shown in table S5. Patients with moderate or severe renal impairment at baseline experienced a higher frequency of hypotension, renal impairment and hyperkalemia-related AEs than the overall population, but the incidence was generally higher in enalapril-treated patients than in LCZ696-treated patients except hypotension. Hypotension-related AEs leading to discontinuation examined using the NMQ grouping were not more frequent for patients with stage IIIb (0.88% in the LCZ696 group; 1.10% in the enalapril group) than for patients with stage IIIa (0.83% in the LCZ696 group; 0.47% in the enalapril group) renal impairment.

Table S5: Selected AEs of interest for patients with moderate and severe renal impairment at baseline (CLCZ696B2314, double-blind period, Safety set)

	Moderate renal impairment							
	All patients with moderate renal impairment		Stage IIIa renal impairment		Stage IIIb renal impairment		Severe renal impairment	
Safety topic	LCZ696 n/m (%)	Enalapril n/m (%)	LCZ696 n/m (%)	Enalapril n/m (%)	LCZ696 n/m (%)	Enalapril n/m (%)	LCZ696 n/m (%)	Enalapril n/m (%)
Hypotension (NMQ)	454/1535 (29.6)	338/1516 (22.3)	297/1080 (27.5)	228/1062 (21.5)	157/455 (34.5)	110/454 (24.2)	4/12 (33.3)	4/13 (30.8)
Renal impairment (SMQ)	372/1535 (24.2)	438/1516 (28.9)	223/1080 (20.6)	244/1062 (23.0)	149/455 (32.7)	194/454 (42.7)	4/12 (33.3)	8/13 (61.5)
Serum creatinine increase by >50%	66/544 (12.1)	64/530 (12.1)	65/537 (12.1)	63/520 (12.1)	1/7 (14.3)	1/10 (10.0)	0/12 (0)	0/13 (0)
Hyperkalemia[1]	243/1535 (15.8)	300/1516 (19.8)	154/1080 (14.3)	180/1062 (16.9)	89/455 (19.6)	120/454 (26.4)	3/12 (25.0)	4/13 (30.8)
Serum potassium ≥5.5 mmol/L	389/1484 (26.2)	398/1446 (27.5)	263/1044 (25.2)	261/1012 (25.8)	126/ 440 (28.6)	137/ 434 (31.6)	4/9 (44.4)	4/11 (36.4)

SMQ = Standardised MedDRA Query
eGFR <30 mL/min/1.73m^2 = severe; ≥30 <60 mL/min/1.73m^2 = moderate; ≥45 <60 mL/min/1.73m^2 = stage IIIa, ≥30 <45 mL/min/1.73m^2 = stage IIIb
% = 100*n/m, where n is the number of patients with an event of interest in each subgroup meeting specified category and m is the number of patients at risk for specified category
[1] MedDRA 17.0 preferred terms Hyperkalaemia, Hyperkaliuria, Pseudohyperkalaemia, Blood potassium, Blood potassium abnormal, Blood potassium increased
Source: [D120 Appendix 1-Table Q38.8.1, Table Q38.8.2, Table Q38.9.1, Table Q38.9.2, Table Q38.9.3]

The proposed fixed quantitative composition that results in relatively higher exposure to sacubitril compared to valsartan in renal impairment was not of clinical importance regarding safety, because the effect of sacubitril was saturated at therapeutic dose levels.

Post hoc analyses of adverse events were performed for the approximated **hepatic subgroups** described above. For a closer examination of safety, the group of patients with mild hepatic impairment was also further examined by the score from the Child-Pugh approximation:

- Class A total score 5 points (n=8162)
- Class A total score 6 points (n=233)

In general, in patients with an estimated hepatic impairment Child Pugh score of 6 points (LCZ696 86.36%, enalapril 85.37%) or who were Child Pugh class B (LCZ696 89.47%, enalapril 94.12%), relatively more adverse events were reported as compared to patients with a Child Pugh score of 5 points (LCZ696 81.17%, enalapril 82.71%) (Table S6). Regardless of LCZ696 or enalapril treatment, a higher incidence of hyperkalemia-related events, and renal impairment-related events was observed in the limited number of patients with higher degrees of hepatic impairment. In all groups, events of hypotension were reported more frequently in the LCZ696 treatment group compared to the enalapril group, which was consistent with the safety profile observed

in the general studied population. Similarly, other relevant safety events, including hyperkalemia, renal impairment, and cough were reported less frequently in the LCZ696 treatment group compared to the enalapril group, which was also consistent with the observations in the general studied population.

Table S6: AEs occurring in at least 10% of patients in either treatment group with approximated Child-Pugh mild and moderate hepatic impairment (CLCZ696B2314, double-blind period, Safety set)

Child-Pugh class	class A (mild)						Class B (moderate)	
Child Pough points	5 or 6		5		6		7	
Preferred term	LCZ696 N=4183 n (%)	Enalapril N=4212 n (%)	LCZ696 N=4073 n (%)	Enalapril N=4089 n (%)	LCZ696 N=110 n (%)	Enalapril N=123 n (%)	LCZ696 N=19 n (%)	Enalapril N=17 n (%)
Total	3401 (81.31)	3487 (82.79)	3306 (81.17)	3382 (82.71)	95 (86.36)	105 (85.37)	17 (89.47)	16 (94.12)
Hypotension	737 (17.62)	505 (11.99)	718 (17.63)	491 (12.01)	19 (17.27)	14 (11.38)	3 (15.79)	1 (5.88)
Cardiac failure	722 (17.26)	824 (19.56)	694 (17.04)	789 (19.30)	28 (25.45)	35 (28.46)	8 (42.11)	8 (47.06)
Hyperkalaemia	485 (11.59)	589 (13.98)	473 (11.61)	574 (14.04)	12 (10.91)	15 (12.20)	2 (10.53)	3 (17.65)
Renal impairment	425 (10.16)	486 (11.54)	413 (10.14)	472 (11.54)	12 (10.91)	14 (11.38)	1 (5.26)	1 (5.88)
Cough	365 (8.73)	531 (12.61)	355 (8.72)	513 (12.55)	10 (9.09)	18 (14.63)	4 (21.05)	2 (11.76)
Pneumonia	227 (5.43)	235 (5.58)	220 (5.40)	221 (5.40)	7 (6.36)	14 (11.38)	0	2 (11.76)
Dyspnoea	211 (5.04)	306 (7.26)	208 (5.11)	297 (7.26)	3 (2.73)	9 (7.32)	2 (10.53)	0
Diarrhoea	192 (4.59)	189 (4.49)	184 (4.52)	182 (4.45)	8 (7.27)	7 (5.69)	2 (10.53)	0
Influenza	157 (3.75)	131 (3.11)	155 (3.81)	127 (3.11)	2 (1.82)	4 (3.25)	2 (10.53)	1 (5.88)
Hypokalaemia	138 (3.30)	105 (2.49)	136 (3.34)	95 (2.32)	2 (1.82)	10 (8.13)	1 (5.26)	2 (11.76)
Headache	102 (2.44)	104 (2.47)	101 (2.48)	103 (2.52)	1 (0.91)	1 (0.81)	1 (5.26)	2 (11.76)
Cardiac death	86 (2.06)	112 (2.66)	81 (1.99)	107 (2.62)	5 (4.55)	5 (4.07)	0	2 (11.76)
Pleural effusion	39 (0.93)	50 (1.19)	36 (0.88)	47 (1.15)	3 (2.73)	3 (2.44)	2 (10.53)	0
Cardio-respiratory arrest	24 (0.57)	25 (0.59)	22 (0.54)	24 (0.59)	2 (1.82)	1 (0.81)	1 (5.26)	2 (11.76)
Toothache	20 (0.48)	17 (0.40)	20 (0.49)	16 (0.39)	0 (0.00)	1 (0.81)	2 (10.53)	0
Ascites	13 (0.31)	22 (0.52)	12 (0.29)	20 (0.49)	1 (0.91)	2 (1.63)	2 (10.53)	0
Hepatic function abnormal	7 (0.17)	14 (0.33)	7 (0.17)	12 (0.29)	0 (0.00)	2 (1.63)	2 (10.53)	0

Source: [D120 Appendix 1 Table Q10.1.1, Table Q10.1.1a, Table Q10.1.1b, Table Q10.1.2]

The profile of serious adverse events (SAEs) during the double-blind period of study CLCZ696B2314 was similar for patients with mild and moderate approximated degrees of hepatic impairment (Table S7). The most common SAEs were related to heart failure.

Table S7 : SAEs by hepatic function subgroups occurring in at least 2 patients in either treatment group with approximated Child-Pugh moderate hepatic impairment (CLCZ696B2314, double-blind period, Safety set)

Child-Pugh class	class A (mild)						Class B (moderate)	
Child Pough points	5 or 6		5		6		7	
Preferred term	LCZ696 N=4183 n (%)	Enalapril N=4212 n (%)	LCZ696 N=4073 n (%)	Enalapril N=4089 n (%)	LCZ696 N=110 n (%)	Enalapril N=123 n (%)	LCZ696 N=19 n (%)	Enalapril N=17 n (%)
Total	1924 (46.00)	2130 (50.57)	1847 (45.35)	2048 (50.09)	77 (70.00)	82 (66.67)	12 (63.16)	12 (70.59)
Cardiac failure	580 (13.87)	642 (15.24)	556 (13.65)	610 (14.92)	24 (21.82)	32 (26.02)	8 (42.11)	7 (41.18)
Pneumonia	155 (3.71)	179 (4.25)	150 (3.68)	167 (4.08)	5 (4.55)	12 (9.76)	0	2 (11.76)
Cardiac death	85 (2.03)	112 (2.66)	80 (1.96)	107 (2.62)	5 (4.55)	5 (4.07)	0	2 (11.76)
Cardio-respiratory arrest	24 (0.57)	25 (0.59)	22 (0.54)	24 (0.59)	2 (1.82)	1 (0.81)	1 (5.26)	2 (11.76)

Source: [D120 Appendix 1 Table Q10.2.1, Table Q10.2.1a, Table Q10.2.1b, Table Q10.2.2]

Few patients in the approximated Child-Pugh class A with 6 points or Child-Pugh class B had AEs leading to treatment discontinuation during the double-blind period. The most common reasons were related to heart failure.

Race has no relevant effect on the safety profile of LCZ696, except the increased risk of angioedema and hypersensitivity in Black subjects: A higher incidence of angioedema in the pivotal study was observed in Black patients on LCZ696 compared to non-Black patients. It seems that the overall hypersensitivity reactions were more common in Black patients (11.3%) compared to Caucasians (7.2%) treated with LCZ696 in the pivotal study. This was adequately reflected in the SmPC.

Gender had no relevant effect on the safety profile of LCZ696.

Although increasing **age** was associated with more AEs, in comparison to enalapril the safety profile was consistently favourable. As for all ages, hypotension events occurred for all age groups more frequently with LCZ696 than with enalapril (table S8 and S9). There were no data related to LCZ696 in **paediatric** patients. LCZ696 is not indicated in paediatric population.

Table S8 Adverse events by age groups for the double-blind period for PARADIGM-HF (Safety set)

	Any age		Age <65 years		Age 65-74 years		Age 75-84 years		Age 85+ years	
MedDRA terms	LCZ696 n (%) N=4203	Enalapril n (%) N=4229	LCZ696 n (%) N=2120	Enalapril n (%) N=2174	LCZ696 n (%) N=1297	Enalapril n (%) N=1272	LCZ696 n (%) N=718	Enalapril n (%) N=729	LCZ696 n (%) N=68	Enalapril n (%) N=54
Patients with any AE	3419 (81.35)	3503 (82.83)	1659 (78.25)	1760 (80.96)	1081 (83.35)	1063 (83.57)	621 (86.49)	627 (86.01)	58 (85.29)	53 (98.15)
Patients with AEs of max severity mild	874 (20.79)	823 (19.46)	482 (22.74)	464 (21.34)	257 (19.81)	232 (18.24)	127 (17.69)	121 (16.60)	8 (11.76)	6 (11.11)
Patients with AEs of max severity moderate	1158 (27.55)	1130 (26.72)	540 (25.47)	555 (25.53)	380 (29.30)	351 (27.59)	223 (31.06)	205 (28.12)	15 (22.06)	19 (35.19)
Patients with AEs of max severity severe	1387 (33.00)	1550 (36.65)	637 (30.05)	741 (34.08)	444 (34.23)	480 (37.74)	271 (37.74)	301 (41.29)	35 (51.47)	28 (51.85)
Patients with any SAE	1937 (46.09)	2142 (50.65)	864 (40.75)	1036 (47.65)	629 (48.50)	649 (51.02)	403 (56.13)	417 (57.20)	41 (60.29)	40 (74.07)
Patients with AEs leading to dose adjustment	1162 (27.65)	1135 (26.84)	489 (23.07)	502 (23.09)	404 (31.15)	369 (29.01)	248 (34.54)	247 (33.88)	21 (30.88)	17 (31.48)
Patients with AEs leading to discontinuation	450 (10.71)	516 (12.20)	206 (9.72)	239 (10.99)	129 (9.95)	155 (12.19)	103 (14.35)	116 (15.91)	12 (17.65)	6 (11.11)
Patients with drug-related AEs	910 (21.65)	976 (23.08)	409 (19.29)	458 (21.07)	301 (23.21)	318 (25.00)	184 (25.63)	189 (25.93)	16 (23.53)	11 (20.37)

Source CO Table 7-2

Table S9 Adverse events by age groups for the double-blind period for PARADIGM-HF (Safety set) – Safety topics of special interest as defined in [PARADIGM-HF-Appendix 16.1.9]

	Any age		Age <65 years		Age 65-74 years		Age 75-84 years		Age 85+ years	
MedDRA terms	LCZ696 n (%) N=4203	Enalapril n (%) N=4229	LCZ696 n (%) N=2120	Enalapril n (%) N=2174	LCZ696 n (%) N=1297	Enalapril n (%) N=1272	LCZ696 n (%) N=718	Enalapril n (%) N=729	LCZ696 n (%) N=68	Enalapril n (%) N=54
Hypotension	1027 (24.43)	786 (18.59)	453 (21.37)	350 (16.10)	341 (26.29)	244 (19.18)	213 (29.67)	179 (24.55)	20 (29.41)	13 (24.07)
Renal impairment	682 (16.23)	746 (17.64)	272 (12.83)	301 (13.85)	235 (18.12)	270 (21.23)	159 (22.14)	161 (22.09)	16 (23.53)	14 (25.93)
Hyperkalemia	500 (11.90)	605 (14.31)	216 (10.19)	262 (12.05)	175 (13.49)	199 (15.64)	99 (13.79)	135 (18.52)	10 (14.71)	9 (16.67)
Angioedema	300 (7.14)	312 (7.38)	133 (6.27)	152 (6.99)	95 (7.32)	98 (7.70)	67 (9.33)	58 (7.96)	5 (7.35)	4 (7.41)
Developmental toxicity	11 (0.26)	19 (0.45)	6 (0.28)	7 (0.32)	3 (0.23)	8 (0.63)	2 (0.28)	4 (0.55)	0 (0.00)	0 (0.00)
Hypersensitivity reactions incl. pruritus	329 (7.83)	369 (8.73)	148 (6.98)	173 (7.96)	117 (9.02)	113 (8.88)	61 (8.50)	74 (10.15)	3 (4.41)	9 (16.67)
Hepatotoxicity	138 (3.28)	184 (4.35)	75 (3.54)	98 (4.51)	33 (2.54)	58 (4.56)	27 (3.76)	27 (3.70)	3 (4.41)	1 (1.85)
Change in bone growth/bone mineral density	83 (1.97)	80 (1.89)	31 (1.46)	22 (1.01)	27 (2.08)	32 (2.52)	21 (2.92)	23 (3.16)	4 (5.88)	3 (5.56)
Cognitive impairment –(Dementia broad SMQ)	86 (2.05)	83 (1.96)	32 (1.51)	22 (1.01)	24 (1.85)	28 (2.20)	26 (3.62)	30 (4.12)	4 (5.88)	3 (5.56)
Cognitive impairment – (Dementia narrow SMQ)	12 (0.29)	15 (0.35)	1 (0.05)	0 (0.00)	3 (0.23)	2 (0.16)	8 (1.11)	12 (1.65)	0 (0.00)	1 (1.85)
Stimulation of lipolysis	515 (12.25)	524 (12.39)	279 (13.16)	267 (12.28)	150 (11.57)	162 (12.74)	82 (11.42)	86 (11.80)	4 (5.88)	9 (16.67)
Gastric lesions	427 (10.16)	435 (10.29)	165 (7.78)	189 (8.69)	156 (12.03)	145 (11.40)	93 (12.95)	90 (12.35)	13 (19.12)	11 (20.37)
QT prolongation	959 (22.82)	1022 (24.17)	430 (20.28)	498 (22.91)	320 (24.67)	303 (23.82)	192 (26.74)	197 (27.02)	17 (25.00)	24 (44.44)
Cancer promotion	130 (3.09)	150 (3.55)	36 (1.70)	47 (2.16)	52 (4.01)	68 (5.35)	40 (5.57)	32 (4.39)	2 (2.94)	3 (5.56)

Source CO Table 7-2

The adverse event (AE) profile for **ACEI/ARB naïve patients** compared to the overall population was summarized across HF studies in Table S10. Although the analysis was limited due to small numbers of ACEI/ARB-naïve patients, the safety/tolerability was comparable for the LCZ696-treated ACEI/ARB-naïve patients vs the overall population. In addition, a lower incidence of AEs was reported in the LCZ696 group compared to the enalapril or valsartan groups among the ACEI/ARB-naïve patients.

Table S10: Adverse event profile in ACEI / ARB-naïve patients (CLCZ696B2314, CLCZ696B2214, CLCZ696B2228, Safety set)

	B2314				B2214				B2228	
	ACEI/ARB-naïve patients		All patients		ACEI/ARB-naïve patients		All patients		ACEI/ARB-naïve patients	All patients
	LCZ696 N=11 n (%)	ENA N=10 n (%)	LCZ696 N=4203 n (%)	ENA N=4229 n (%)	LCZ696 N=10 n (%)	VAL N=11 n (%)	LCZ696 N=149 n (%)	VAL N=152 n (%)	LCZ696 N=33 n (%)	LCZ696 N=497 n (%)
SAEs	4 (36.4)	4 (40.0)	1937 (46.1)	2142 (50.7)	1 (10.0)	3 (27.3)	22 (14.8)	30 (19.7)	3 (9.1)	37 (7.4)
AEs leading to discontinuation	1 (9.1)	2 (20.0)	450 (10.7)	516 (12.2)	1 (10.0)	2 (18.2)	15 (10.1)	17 (11.2)	5 (15.2)	34 (6.8)
Selected AEs of special interest										
Hypotension	1 (9.1)	1 (10.0)	1027 (24.4)	786 (18.6)	3 (30.0)	7 (63.6)	30 (20.1)	28 (18.4)	7 (21.2)	64 (12.9)
Hyperkalemia	0	2 (20.0)	500 (11.9)	605 (14.3)	0	2 (18.2)	12 (8.1)	9 (5.9)	3 (9.1)	31 (6.2)
Renal impairment	0	1 (10.0)	682 (16.2)	746 (17.6)	1 (10.0)	5 (45.5)	5 (3.4)	8 (5.3)	6 (18.2)	39 (7.8)
Angioedema (adjudicated)	0	0	19 (0.5)	10 (0.2)	0	0	1 (0.7)	0	0	2 (0.4)

ENA = enalapril; SAE = serious adverse event; VAL = valsartan
Source: [D120 Appendix 1- Table Q40.2, Table Q40.3, Table Q40.4], [SCS Appendix 1-Table 14.3.1-2.1, Table 14.3.1-2.2, Table 14.3.1-5.1]

Safety related to drug-drug interactions and other interactions

The information about interactions was primarily based on theoretical arguments and clinical pharmacology studies and class effects for RAAS agents.

Co-administration of LCZ696 increased the Cmax of **atorvastatin** and its metabolites by up to 2-fold. There was no significant increase in potential statin-related AEs in the 2369 patients that received both LCZ696 200 mg bid and a statin in PARADIGM-HF according to the applicant. Problems would likely occur primarily in subjects on the highest statin doses. The applicant has clarified that, due to the relatively small half-life of sacubitril, the interaction between LCZ696 and statins may impact AUC less than Cmax. This will be further investigated in a healthy volunteer interaction study, the results of which are expected in Q4 2015. The Applicant's main arguments to support the lack of a clinically relevant interaction between statins and LCZ696, despite the clear PK interaction, were based on comparison of AEs with statin/enalapril in PARADIGM-HF. Statistical considerations suggested that a relative risk of 1.25 to 1.54 would have been detected in this trial. The analysis was based on the assumption that no interaction exists between statins and enalapril, which may not be true (Tian L, 2011, Effect of organic anion-transporting polypeptide 1B1 (OATP1B1) polymorphism on the single- and multiple-dose pharmacokinetics of enalapril in healthy Chinese adult men.). The data showed that subjects who used trial medication in combination with low-dose statin experienced only little more AEs than subjects not using statins; however, in both groups the number of AEs increased for high-dose statin use, more for LCZ696 than for enalapril and especially for the highest recommended dose. Obviously, this increase may be more attributable to the statins than to interactions, although the different patterns for LCZ696 and enalapril suggested a role of the co-medications.

Table % AEs and SAEs in PARADIGM-HF, by statin dose

Statin dose	No statin	Low dose	High dose	Highest dose
AEs				
LCZ	79.12	79.69	88.79	91.49
ENA	80.82	83.82	86.88	90.63
SAEs				
LCZ	44.17	44.47	52.77	57.98
ENA	48.26	49.44	56.64	61.46

The AEs were mostly not coded as 'myalgia' (which would be the usual description in the context of statins) but rather musculoskeletal pain, arthralgia, back pain and pain in extremity. The number of SAEs was too low to detect patterns in specific PTs; the narratives provided for rhabdomyolysis and pancreatitis did not raise new concerns.

When examining the AEs at the highest dose of each statin, it became clear that tolerability at the highest dose for the various statins was not the same, which was less evident combination with enalapril.

Table % AEs in PARADIGM-HF, by statin at highest dose

Statin dose	No statin	Atorvastatin	pravastatin	simvastatin	rosuvastatin
AEs					
LCZ	79.12	84.72	97.44	100.00	88.89
ENA	80.82	89.61	97.37	90.91	92.86

It was agreed with the Applicant, that pending the results of the PK interaction trial, the recommendation in the SmPC of 'caution' was adequate to address this interaction. The results of the PK interaction study were agreed to be provided when available (Q4 2015).

Co-administration of the OAT3 substrate **furosemide** 40 mg (single dose) and LCZ696 200 mg bid (steady state) compared with furosemide 40 mg (single dose) alone resulted in a decreased furosemide exposure, the Cmax and AUC were decreased by 50% and 28%, respectively. Sodium excretion and urinary volume during the first hours were also markedly decreased. The applicant analysed furosemide doses before and after the double blind period to further address the issue. In this analysis, dose was more increased in the enalapril (21.7 mg) group compared to the LCZ696 group (11.4 mg). The issue was adequately reflected in the SmPC.

Discontinuation due to adverse events

During the double-blind period, discontinuations due to AEs were comparable in both groups (table S11). During each run-in period, around 10% of participants discontinued, both because of AEs and because of protocol specified discontinuation criteria (most importantly: hypotension, hyperkalaemia, renal impairment) (table S2 above).

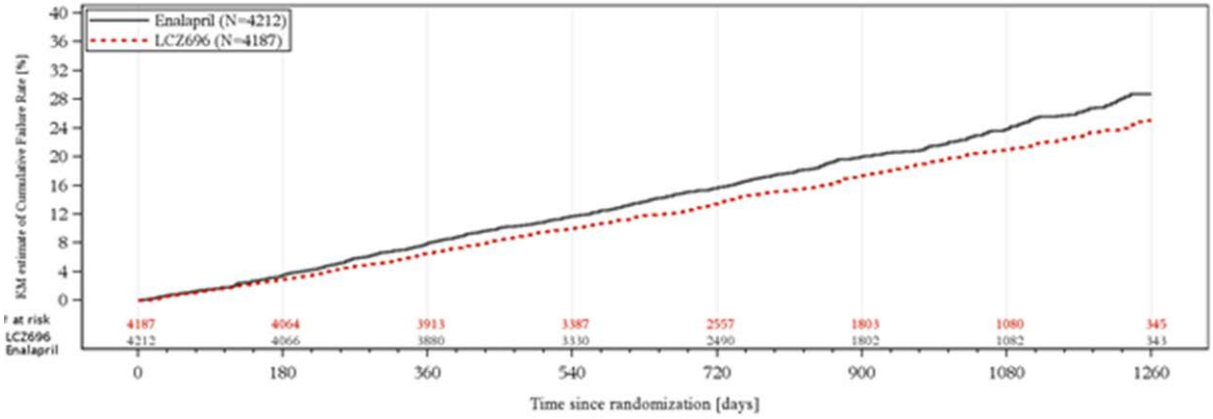
Table S11: Reasons for study drug dose reduction during double-blind period by treatment group for PARADIGM-HF (Safety set)

	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)
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: [SCS-Table 2-8]

Most of the patient discontinuations were due to death. The curves for the two treatment arms separated early and continue to separate for the entire duration of the trial as the deaths occured at a differential rate between the two arms. The LCZ696 arm remains below the enalapril arm for the entire duration of the trial (figure S1).

Figure S1: Kaplan-Meier plot for discontinuation from Study CLCZ696B2314 (death is treated as event) by treatment group (Full Analysis Set)



2.5.1. Discussion on clinical safety

The **safety profile of sacubitril** was not separately investigated in the target population, as discussed in the *Discussion on clinical efficacy section*. The safety profile of valsartan was considered well-known. The safety evaluation was primarily based on the pivotal study (PARADIGM-HF) and supplemented by phase II studies in HFrEF (TITRATION) and HFpEF (PARAMOUNT). The data from these phase II studies were not further discussed in the current AR, considering the limited databases of these studies, different follow-up durations and different indications (in case of PARAMOUNT study).

The selected **topics of special interest** were supported as signals were identified in the preclinical studies, or were associated with RAAS inhibitors or the target population (patients with HF). Topics of special interest

covered the safety aspects that have emerged from the class experience with RAAS-acting agents, the experience gained with omapatrilat and preclinical evaluations. The approach to safety assessment was considered adequate. The documented safety exposure exceeded the requirements of *ICH-E1 Guideline* and was considered sufficient for adequate assessment of the safety profile of LCZ696.

Estimation of the **true incidence of AE** in PARADIGM-HF was hampered by the run-in period and the sequence of enalapril run-in, followed by LCZ696. Patients who discontinued during the run-in period were not included in the safety assessment during the double-blind period. Patients who discontinued during enalapril run-in may be frail patients who would also have dropped out if LCZ696 had been the first run-in. Thus, patients not tolerating LCZ696 were actually the sum of discontinuations in the LCZ696-run-in, in the LCZ696-arm during double blind period, in addition to some of the patients who had previously discontinued enalapril during the first run-in period. There was a further basic selection bias in PARADIGM-HF that only patients on stable treatment with ACEi or ARB were recruited. All these factors likely lead to an under-estimation of the number of AEs in clinical practice. In their response provided during the procedure, the applicant showed that although this underestimation may occur, the frequency categories in the SmPC did not change. The number of **ACEI / ARB-naïve patients** in the LCZ696 studies in HF was low. The experience in hypertension with naïve patients did not suggest a different safety pattern.

As valsartan is one of the components of the fixed dose combination LCZ696, all **events listed for valsartan** were expected to be ADRs of LCZ696. This was achieved after inclusion of hypersensitivity, pruritus, and rash as agreed following the response provided by the applicant during the procedure.

Furthermore, AEs were assessed as compared with **AEs occurring with enalapril**, another medicinal product acting on the RAAS system that likely has a similar AE profile to LCZ696. Therefore, an AE occurring less frequently than with enalapril was considered to be an ADR of LCZ696. The applicant discussed the ADRs listed of enalapril and added anemia, gastritis and hypoglycemia to the originally proposed list of ADRs. Thrombocytopenia and neutropenia were included as potential risks in safety specification of the agreed RMP. AEs affecting white cells were more frequent with LCZ696 than with enalapril. Thrombocytopenia occurred comparably to enalapril but was an ADR in the label of valsartan.

In their approach to the safety analysis, the applicant mentioned that the extent of exposure would allow detection of **rare AEs**. No rare ADRs were found that were not already known from enalapril or valsartan. The **most frequent** AEs with LCZ696 were hypotension (17.6% v enalapril 14.1%), hyperkalaemia (11.6% v enalapril 14.0%), renal impairment (10.1% v enalapril 11.5%), cough (8.8% v enalapril 12.6%) and dizziness (6.3% v enalapril 4.9%).

Of the safety topics of **special interest**, in PARADIGM-HF only hypotension and angioedema occurred more frequently than with enalapril, which was reassuring. Based on PARAMOUNT study also hyperkalaemia, hepatotoxicity, stimulation of lipolysis and gastric lesions could be more frequent than with valsartan alone.

LCZ696 caused more events of **hypotension** and dizziness than enalapril and more discontinuations in the double blind phase. Initiation and up-titration of LCZ696 was associated with decreasing blood pressure values; the effect was stronger than with enalapril. The difference persisted throughout the trial. Blood pressure values decreased during run-in by around 7 mmHg. Thereafter, mean increase from baseline to study end was 0.4 mmHg in the LCZ696 group and 2.9 mmHg in the enalapril group. However, serious events related to hypotension occurred more with enalapril, suggesting that down-titration and discontinuation, as prescribed by the protocol, were adequate to manage these events. Special patients subgroups (patients $\geq$ 65 years old, patients with renal disease and patients with low systolic BP <112 mmHg) were vulnerable to this hypotensive effect. Management of this risk required careful clinical monitoring. For the clinician, this was expected to be

similar to other RAS-acting medicinal products like ACEis or ARBs. Appropriate warning was included in the SmPC.

Both HF and treatment of HF with agents acting on the RAS may be associated with **hyperkalaemia** and **renal impairment.** Therefore, it may be impossible to correctly assign causality of these AEs based on a trial comparing LCZ696 to enalapril in HF. It was reassuring that such AEs were occurring less frequently with LCZ696 than with comparators. Still the risks should be taken into account when using LCZ696, especially in patients with risk factors. Risk factors for renal impairment are advanced age, pre-existing renal impairment and diabetes mellitus. It may be unexpected for prescribers, that the RAS-acting agent LCZ696 could cause **hypokalaemia** besides hyperkalaemia therefore this was reflected in the paragraph regarding potassium in section 4.4 of the SmPC.

Angioedema events were carefully documented in PARADIGM-HF and centrally adjudicated. The risk of angioedema was slightly higher during double blind treatment with LCZ696 (0.45%) compared to enalapril (0.24%), which was of concern especially that most patients were experienced users of ACEi, so patients prone to angioedema were not actually included. In the proposed SmPC, a contra-indication was included for subjects having experienced angioedema during ACEi/ARB use. Three serious adverse events were described were angioedema occurred and other intercurrent therapy was involved. Angioedema will be further monitored post-authorisation as per agreed RMP. In line with the SmPC of enalapril, a contra-indication for use in hereditary or idiopathic angioedema was added to the SmPC. Due to the design of the PARADIGM-HF study, it was not possible to conclude on the incidence of angioedema in ACE/ARB naïve patients in this study. Higher incidence of angioedema was also observed in this study in Black patients treated with LCZ696 (2.35%) compared to non-Black patients (0.35%) and this is reflected in the SmPC.

A theoretical risk associated with neprilysin inhibition is related to the accumulation of the neprilysin substrate **amyloid**-β (Aβ) in the brain. The problem was confirmed in a non-clinical study in young cynomolgus monkeys, where administration of LCZ696 increased total cerebrospinal fluid levels of Aβ1-42, 1-40 and 1-38. In healthy volunteers there were no changes in cerebrospinal fluid concentrations of Aβ1-40 and 1-42, but Aβ1-38 was increased. The clinical relevance of this finding was considered uncertain. Literature regarding this amyloid isoform was sparse. No disease was characterized until now by an isolated increase of Aβ1-38. No increased incidence of cognition- or dementia-related AEs had been reported in the HF or HTN clinical programs with LCZ696. However, it was unlikely to detect an effect if it existed in these programs, because development of dementia may take longer than the observation period in the trials so far. Also, subjects with mild dementia were not expected to participate. It was agreed to continue evaluation the potential for cognitive impairment in HF patients and this was reflected in the agreed RMP. Cognitive Function Assessments (CFA) would be implemented in the ongoing Phase III study, PARAGON-HF (CLCZ696D2301) which is a multicenter, randomized, double-blind, parallel group, active controlled study to evaluate the efficacy and safety of LCZ696 compared to valsartan, on morbidity and mortality in heart failure patients (NYHA Class II-IV) with preserved ejection fraction.

Preclinical signals included effects on **growing bones** and **Bone Mineral Density (BMD)**. Only small numbers of subjects with growing bones were expected in the PARADIGM-HF trial. Therefore, AEs assessment in PARADIGM-HF was not considered sensitive to evaluate this risk. Measurements of BMD were unfortunately not very accurate and biologically relevant changes occurre only after several years. Even if an unexpectedly low BMD result was obtained in a patient, it would only unlikely be reported as an AE because large variability in the results was expected. Therefore, AEs in PARADIGM-HF were also not considered sensitive to evaluate this risk.

ARBs have been reported to improve **insulin sensitivity** but inhibition of NEP by LCZ696 increases systemic ANP levels, potentially resulting in stimulation of lipolysis. As a result, the increase in free fatty acid content and

the muscle's cellular and hepatocellular uptake of free fatty acid may decrease insulin sensitivity. In PD study LCZ696B2207 in obese hypertensive patients, insulin sensitivity increased from baseline with LCZ696, which was not observed for amlodipine. Results from PARADIGM-HF did not suggest undesirable metabolic effects of LCZ696 in patients with HF. The incidence of AEs related to stimulation of lipolysis was comparable between treatment groups: LCZ696 12.3% vs. enalapril 12.4%. There was no imbalance in events related to hyperglycemia or new onset of diabetes and no imbalance in changes from baseline of plasma glucose, HbA1c, or triglycerides between the LCZ696 and enalapril. Therefore, LCZ696 was not considered to have any undesired metabolic effects in HF patients. The net effect on insulin sensitivity seemed to be a small improvement.

Preclinical data indicated that LCZ696 was teratogenic and associated with increased **embryo-fetal toxicity**. There have been reports of injury to the developing foetus, when pregnant women have taken valsartan, especially in the second and third trimester. It was agreed to restrict the contraindication in pregnancy to the second and third trimester. The pregnancy contraindication was based on adverse effects of valsartan, which when dosed as a single agent is contraindicated during the second and third trimester only.

It was not known whether LCZ696 was excreted in human milk; however, the components of LCZ696, sacubitril and valsartan were excreted in the milk of lactating rats. Because of the potential risk for adverse drug reactions in breastfed newborns/infants, LCZ696 is not recommended during **breastfeeding**.

All-cause **mortality** was lower for LCZ696 compared to enalapril. This result was driven by CVS mortality and was covered in the efficacy section. Non-cardiovascular death occurred slightly more frequently with LCZ696 compared to enalapril. The difference was small and was considered to be related to 'competing risks'. Similarly, the analysis of SAEs has not identified new safety issues.

In PARADIGM-HF, most patients had mild (4291/8432, 50.9%) or moderate (3051/8432, 36.2%) **renal impairment**. The adverse event profile in these groups mimicked the overall AE profile, although AEs were more frequent as renal function deteriorated. Despite subjects with **severe renal failure** were excluded from the trial, data for 25 such patients were still available. In these patients, the AE profile was comparable to enalapril. However, the AE profile was much more severe than in mild or moderate renal impairment which precluded straightforward extrapolation of the results of the trial to these patients. The limited representation of patients with severe renal impairment was reflected in the SmPC, with an adequate warning. The main risk in mild and moderate renal impairment was in line to that observed in the main cohort, i.e. hypotension. However, the starting dose in the run-in period deserved some discussion. Further data showed that in patients with moderate renal impairment and for AEs leading to treatment discontinuation and serious AEs, AEs events were almost halved by halving the initial dose. It cannot be excluded that initiating such vulnerable patients with the lowest dose (50 mg) would further improve the tolerability, knowing that ultimately most of these patients were able to tolerate the recommended dose supporting the current maintenance dose. This was advised in section 4.2 of the SmPC.

Based on free concentrations, the increase in sacubitril AUC in patients with **mild to moderate renal impairment** was 2-fold compared with subjects with normal renal function but there was no change for valsartan. The applicant was asked to discuss if the proposed fixed quantitative composition that resulted in relatively higher exposure to sacubitril compared to valsartan in patients with renal impairment is of clinical importance regarding safety. The applicant explained that the fixed quantitative composition has no unacceptable safety issue in renal/hepatic impairment. This was explained by saturation of the effect of sacubitril and agreed with the CHMP.

Subjects with normal renal function (1065/8432, 12.6%) were much less frequent than subjects with mild real impairment. The efficacy and safety data related to this subgroup were reviewed and showed results comparable to or slightly better than the overall population.

Regarding patients with **hepatic impairment**, adverse events were more frequent with higher Child-Pugh scores (5 points: 81.17%; 6 points: 86.36%; 7 points: 89.47%). A comparable increase occurred with enalapril users. The results were in line with the main safety results. Results of serious AEs and AEs leading to treatment discontinuation did not point to any AE specific to this subgroup, with the caveat that the number if patients with moderate hepatic impairment was very limited. This was of importance considering the PK data showing the increased exposures of both sacubitril and valsartan in such patients e.g., the exposures of sacubitril increased by 3.4 fold, LBQ657 increased by 1.9 fold, and valsartan increased by 2.1 fold compared to matching healthy subjects. Also exposures in these patients of free concentrations of LBQ657 increased by 3.08 fold, and valsartan increased by 2.20 fold, compared to matching healthy subjects. A warning was included regarding patients with moderate hepatic impairment in the SmPC of LCZ696.

Pharmacokinetic of LCZ696 in patients with **increased AST/ALT**, whether or not caused by congestion or non-alcoholic fatty liver (NAFLD), was unknown. The applicant clarified that patients with liver congestion due to HF or steatosis/ NAFLD were not excluded from enrolment as these are conditions relevant to the study population. In total, there were 760 patients with these conditions: n= 361 randomised to LCZ696 and n= 407 randomised to enalapril. It was not clear how many of these patients completely recovered from these conditions by the start of the trial. Based on (almost) normal AST and ALT values (as required for inclusion) it was unlikely that they had active disease. This was a limitation of the external validity of the study and it was agreed to reflect this in the SmPC. This recommendation was not only based on possible hepatic conditions of patients but also on the notion that (some of) these patients may have HF characterised by massive oedema, e.g. right heart failure, and may represent a special subgroup of the target population which was not investigated. In the end a recommendation was included in the SmPC that there is limited clinical experience of administering LCZ696 in patients with moderate hepatic impairment (Child-Pugh B classification) or AST/ALT values above 2 times the upper limit of the normal range. LCZ 696 should be used with caution in these patients and the recommended starting dose is 24 mg/26 mg twice daily.

The information about **interactions** was primarily based on theoretical arguments and clinical pharmacology studies. In the SmPC, information was included about class effect for RAAS agents. In clinical pharmacology studies, no clinically relevant PD drug-drug interaction was observed for LCZ696 with digoxin, warfarin, hydrochlorothiazide, amlodipine, omeprazole, carvedilol, or a combination of levonorgestrel/ethinyl estradiol. On theoretical grounds, no interaction was expected with atenolol, indomethacin, glyburide, or cimetidine. LCZ696 does not induce or inhibit CYP450 enzymes.

Co-administration of LCZ696 increased the Cmax of **atorvastatin** and its metabolites by up to 2-fold. There was no significant increase in potential statin-related AEs in the patients that received both LCZ696 and a statin in PARADIGM-HF. Based on further analysis of the data in the applicant's responses, higher doses of statins were associated with more AEs, both in the LCZ696 and enalapril groups, although the patterns were different depending on the specific statin. The applicant agreed to provide the results of an interaction study between simvastatin and LCZ696 to further clarify the issues as reflected in the agreed RMP. Pending the results of this study, a recommendation of caution was considered adequate.

LCZ696 decreased Cmax and AUC of oral **furosemide**. To address this, the applicant analysed furosemide doses before and after the double blind period. In this analysis, dose was more increased in the enalapril (21.7 mg) group compared to the LCZ696 group (11.4 mg). However, this analysis was not sufficient to exclude a clinically relevant interaction. It cannot be excluded that LCZ696 caused an overall improvement that resulted

in decreased diuretic use. More importantly, dose adaptations during run-in were not captured in the analysis. Based on the PK/PD result, the interaction was described as a potentially relevant PK/PD interaction in section 4.5 of the SmPC.

A total of 54 HF patients treated with Entresto were **ACEI / ARB-naïve** (no treatment during the last 4 months) across the three HF studies. Consequently, the experience was very limited. On the other hand, a similar profile of adverse events was observed in the ACEI/ARB-naïve patients treated with LCZ 696 in the hypertension studies (n=1012) compared to overall essential hypertension population. It was agreed to highlight that the experience is limited in this patient group and to recommend a lower starting dose in these patients together with a longer titration period as reflected in the SmPC.

From the safety database all the adverse reactions reported in clinical trials have been included in the SmPC.

2.5.2. Conclusions on the clinical safety

The documented safety exposure exceeded the requirements of ICH-E1 Guideline and was considered sufficient for adequate assessment of the safety profile of LCZ696. Overall, a total of 14937 patients and healthy volunteers have been exposed to LCZ696, including 10,155 patients with heart failure. Exposure for more than one year was documented in 3,606 patients. The most commonly reported adverse reactions during treatment with LCZ696 were hypotension, hyperkalaemia and renal impairment. Reported AEs were generally in line with that reported for other medicinal products acting on the RAAS. Safety issues in specific subgroups and interactions were adequately reflected in the SmPC. Several identified and possible risks need to be further evaluated post-authorisation as per agreed RMP. These include: angioedema, hypotension, hyperkalemia, renal impairment, hepatotoxicity, effects on cognitive function and drug-drug interaction with statins.

2.6. Risk Management Plan

The PRAC considered that the risk management plan version 1.2 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

As requested by the PRAC, the applicant implemented the changes in the RMP version 1.3.

The CHMP endorsed the Risk Management Plan version 1.3 with the following content:

Safety concerns

Summary of safety concerns

Important identified risks	Hypotension
	Renal impairment
	Hyperkalemia
	Angioedema
	Embryo-foetal toxicity/lethality
Important potential risks	Neonatal/infantile toxicity through exposure from breast milk
	Hepatotoxicity
	Cognitive impairment
	Statin DDI
	Thrombocytopenia
	Neutropenia

Important identified risks	Hypotension
	Renal impairment
	Hyperkalemia
	Angioedema
	Embryo-foetal toxicity/lethality
Missing information	Paediatric patients
	Patients with severe renal impairment
	Long term data on LCZ696 use in HF patients
	Use in ACEI/ARB naïve HF patients

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final Reports** (planned or actual)
PASS 1: Non-interventional post-authorization European database safety study (Category 3)	To further characterize specific safety outcomes (angioedema, hypotension, hyperkalemia, renal impairment, hepatotoxicity) in HF patients newly starting treatment with LCZ696 (regardless of prior use of ACEIs or ARBs)	Angioedema Use in ACEi/ARB naïve patients Hypotension Hyperkalemia Renal impairment Hepatotoxicity	Planned	Yearly progress reports (1st report planned to be submitted Q4 2017, or with PBRER in 2018). Final report submission within 12 months after end of data collection (i.e., after reaching the necessary number of cases) – latest in Q2 2020
PASS 2: Multicenter, randomized, double-blind, active-controlled study (CLCZ696B2320) (Category 3)	To evaluate the effects of LCZ696 compared to valsartan on cognitive function as assessed by comprehensive neurocognitive battery and brain amyloid plaque deposition as assessed by PET imaging in patients with chronic heart failure with preserved ejection fraction	Cognitive impairment	Planned	Planned March 2022 (Final report submission)
PASS 3: Non-interventional post-authorization European database safety study (Category 3)	To assess the risk of statin-related events associated with concomitant exposure to LCZ696 and statins compared to statin exposure alone in HF patients	Statin DDI	Planned	- planned Q2 2020 (Final report submission)

Cognitive function assessment in study CLCZ696D2301 (PARAGON HF study) (Category 3)	To evaluate cognitive function in patients with chronic heart failure with preserved ejection	Cognitive impairment	Started	Planned March 2020 (final report)
Observational US database study (Category 3)	To assess the risk of serious angioedema in association with sacubitril/valsartan (Entresto) use in Black heart failure patients in the United States	Angioedema in US Blacks	Planned	Planned Q3 2019 (final report)

Risk minimisation measures

Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**
Important identified risks		
Hypotension	To communicate the risk of hypotension and to reduce the risk of clinically significant hypotension. **Section 4.2 (Posology and method of administration)** **Section 4.4 (Special warnings and precautions for use)** **Section 4.8 (Undesirable effects)** **Section 4.5 (Interaction with other medicinal products and other forms of interaction)** **Section 4.9 (Overdose)**	None
Renal impairment	To communicate the risk of renal impairment and to reduce the risk of clinically significant renal impairment. **Section 4.2 (Posology and method of administration)** **Section 4.4 (Special warnings and precautions for use)** **Section 4.8 (Undesirable effects)** **Section 4.5 (Interaction with other medicinal products and other forms of interaction)** **Section 5.2 (Pharmacokinetic properties)**	None
Hyperkalemia	To communicate the risk of hyperkalemia and to reduce the risk of clinically significant hyperkalemia. **Section 4.2 (Posology and method of administration)** **Section 4.4 (Special warnings and precautions for use)** **Section 4.8 (Undesirable effects)** **Section 4.5 (Interaction with other medicinal products and other forms of interaction)**	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Angioedema	To communicate the risk of angioedema and to reduce the risk of clinically significant angioedema. **Section 4.2 (Posology and method of administration)** **Section 4.3 (Contraindications)** **Section 4.4 (Special warnings and precautions for use)** **Section 4.8 (Undesirable effects)** **Section 4.5 (Interaction with other medicinal products and other forms of interaction)**	None
Embryo-foetal toxicity/lethality	To communicate the risk of teratogenicity, embryo-feto toxicity and embryo-fetal lethality, protect unborn children from exposure to LCZ696. **Section 4.3 (Contraindications)** **Section 4.6 (Fertility, pregnancy and lactation)**	None
Important potential risks		
Neonatal/infantile toxicity through exposure from breast milk	To communicate the potential risk of ADRs in breastfed newborns/infants. **Section 4.6 (Fertility, pregnancy and lactation)**	None
Hepatotoxicity	To communicate the risk of hepatotoxicity from LCZ696 use, especially in patients with hepatic impairment. **Section 4.2 (Posology and method of administration)** **Section 4.3 (Contraindications)** **Section 5.2 (Pharmacokinetic properties)**	None
Cognitive impairment	To convey the relevant findings from clinical and preclinical studies. **Section 5.1 (Pharmacodynamic properties)** **Section 5.3 (Preclinical safety data)**	None
Statin DDI	To warn about the risks associated with concomitant use of LCZ696 and statins. **Section 4.5 (Interaction with other medicinal products and other forms of interaction)**	None
Thrombocytopenia	Currently available data do not support the need for risk minimization for this risk in HF patients.	None
Neutropenia	Currently available data do not support the need for risk minimization for this risk in HF patients.	None
Missing information		
Paediatric patients	To inform that the safety and efficacy of LCZ696 in paediatric patients is not known. Risk is communicated through **sections 4.2** and **5.2** of the SmPC.	None
Patients with severe renal impairment	To recommend caution including starting with a lower dose of LCZ696 and periodic monitoring when treating patients with severe renal impairment impairment (eGFR < 30 mL/min/1.73 m^2). **Section 4.2 (Posology and method of administration)** **Section 4.4 (Special warnings and precautions for use)**	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	Section 5.2 (Pharmacokinetic properties)	
Long term data on LCZ696 use in HF patients	Currently available data do not support the need for risk minimization for long-term use in HF patients.	None
Use in ACEi/ARB naïve patients	To recommend caution by using a lower starting dose of LCZ696 when treating ACEI/ARB naive HF patients due to limited experience in clinical trials.	None
	Section 4.2 (Posology and method of administration)	

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Entresto (SACUBITRIL / VALSARTAN) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

To support the proposed indication the applicant conducted a single phase III study, the PARADIGM-HF trial, that was a randomized, double-blind, parallel group, active-controlled study to evaluate the superiority of

LCZ696 200 mg bid compared to enalapril 10 mg bid, on morbidity and mortality reduction in patients with heart failure and reduced ejection fraction (HFrEF).

The trial was stopped early for compelling efficacy (for both CV death and the primary composite endpoint of CV death or HF hospitalization). LCZ696 treated patients had a significantly lower rate of the **primary endpoint (PEP) of the composite of CV death or first HF hospitalization** (914/4187; 21.83%) compared to enalapril treated patients (1117/4212; 26.52%). The absolute risk reductions were 4.7% for the composite endpoint of CV death or HF hospitalization, 3.1% for CV death alone and 2.8% for first HF hospitalization alone. LCZ696 reduced the risk for patients to reach the composite PEP by 20% (HR 0.80, 95% CI: 0.73-0.87; 1-sided p<0.001); reduced the risk of CV death by 20% (HR 0.80; 95% CI: 0.71-0.89: 1-sided p<0.001); and reduced the risk of first HF hospitalization by 21% (HR 0.79; 95% CI:0.71-0.89 1-sided p<0.001) in the full analysis set (FAS) compared to enalapril. The benefit of LCZ696 treatment was seen early and was sustained for the entire study duration for the primary endpoint. Results were further confirmed in the per protocol analysis.

LCZ696 **consistently** reduced CV death or HF hospitalization **across the investigated subgroups** by age, gender, race, region, baseline ejection fraction, relevant medical conditions at baseline, prior use of relevant concomitant medications, prior HFH and time from HF diagnosis. There was limited representation of patients with implantable cardiac devices in PARADIHM-HF. However, this was shown to be comparable to what has been observed in recent registration studies (SHIFT, EMPHASIS). The prevalence of implantable cardiac device (ICD) use differed per region but was comparable to that observed in other studies/observational data. The favourable results were applicable to both patients with and without ICDs.

Regarding **secondary endpoints**, fewer patients died from any cause in the LCZ696 group (a total of 711 patients; 16.98%) than in the enalapril group (835 patients; 19.82%; absolute difference: 2.84%; HR 0.84; 95% CI, 0.76 to 0.93; one-sided p<0.001). The reduction in all-cause mortality was mainly driven by the risk reduction of CV death.

Uncertainty in the knowledge about the beneficial effects.

No phase II or **dose finding studies** were conducted for LCZ696 in HFrEF patients. Dose selection was based on previous experience with valsartan and PD data from sacubitril. There were also **no separate clinical trial data for sacubitril,** as mono-component of the FDC. Such data would have helped better elucidate the mechanism of action and estimate its additive effect on top of valsartan.

There was a **high rate of screening failures due to low NT-proBNP level** (n=4661; 61.87%). It was clarified that this high NT-proBNP level was meant as an enrichment factor in the study and was not meant to establish the diagnosis of HF in these patients. Patients who failed screening because of NT-proBNP, had levels of NT-proBNP (median 238 pg/ml) above those qualifying for HF diagnosis and had already an established diagnosis of HF.

All patients were required to be on stable doses of ACEI/ARBs prior to randomisation that raised the issue of **extrapolation of the results to ACEI / ARBs-naïve patients**. PARADIGM-HF had two run-in periods, first for enalapril during which 1102 (10.47%) patients dropped out, followed by an LCZ696 run-in period during which a further 982 (9.33%) patients dropped out. Therefore the **tolerability of LCZ696** might be reduced in patients not preselected in that way.

Patients in the LCZ696 group showed **less worsening** in the clinical summary score for HF symptoms and physical limitations (KCCQ assessment) compared to enalapril from baseline to Month 8. A responder analysis showed that clinical deterioration by 5 points was prevented in 30.85% of LCZ696 patients versus 35.27% of enalapril patients (treatment effect 4.42%).

There was no difference in delaying the time to new onset atrial fibrillation between the LCZ696 and enalapril treatment groups (HR 0.97; 95% CI, 0.72 to 1.31; one-sided p = 0.4183), suggesting that LCZ696 treatment **did not prevent new onset atrial fibrillation**. Likewise, there was also no significant difference between LCZ696 and enalapril in the **composite endpoint measuring renal function** (HR 0.86; 95% CI, 0.65 to 1.13; one-sided p = 0.1424). Also, the available data on renal biomarkers investigated as exploratory parameters showed conflicting results.

Representation of patients with **NYHA class IV** was very limited (n=60; 0.71%). The results in NYHA class III/IV patients were less compelling compared to less symptomatic patients. Further analysis showed that CV death among patients with NYHA class III/IV was consistent with the overall study results while the hospitalisation rate was actually higher than in the enalapril group (HR 1.08). However, taking other disease severity markers into account (LVEF baseline tertiles, NT-proBNP, KCCQ) the conclusion was reached that a similar benefit can be expected in NYHA IV patients as observed in the overall HF-rEF population.

Efficacy data for patients with **different degrees of hepatic impairment were not submitted** as hepatic function status was not assessed as part of the study protocol. A post-hoc analysis using Child-Pugh classification based on available data suggested that in the small number of patients with moderate hepatic impairment efficacy of LCZ696 compared with enalapril was similar as in the overall population.

Risks

Unfavourable effects

The documented **safety exposure** exceeded the requirements of ICH-E1 Guideline and was considered sufficient for adequate assessment of the safety profile of LCZ696. The description of the safety profile of LCZ696 was primarily based on the pivotal trial PARADIGM-HF. Overall, a total of 14937 patients and healthy volunteers have been exposed to LCZ696, including 10,155 patients with HF. Exposure for more than one year was documented in 3,606 patients.

The safety profile of agents acting on the renin-angiotensin-aldosterone system (RAAS) like ARBs in general and valsartan specifically, was considered well-established. Hypotension (17.6%), hyperkalaemia (11.6%) and renal impairment (10.1%) were the most commonly reported AEs in the double blind period. Only hypotension occurred more frequently than with enalapril (12.0%; hyperkalaemia: 14.0%; renal impairment: 11.5%). These conditions were also the reason for the majority of discontinuations.

Confirmed events of **angioedema** during the double-blind period were reported more frequently with LCZ696 (0.5%) compared to enalapril (0.2%). Occurrence of angioedema was centrally adjudicated. Most cases of angioedema did not require treatment or were treated with antihistamines. In the LCZ696 group, 6 cases were treated with catecholamines or corticosteroids and 3 patients were hospitalised (enalapril: 4 and 1 cases, respectively). Airway compromise was not observed. A higher incidence of angioedema was observed in Black patients treated with LCZ696 (2.4%) and enalapril (0.5%).

All-cause **mortality** was lower for LCZ696 compared to enalapril, in line with the efficacy data. Non-cardiovascular death occurred slightly more frequently with LCZ696 (120/4209, 2.9%) compared to enalapril (110/4233, 2.6%).

For each preferred term (PT), incidences of **serious adverse events** (SAEs) were comparable between the treatment groups or were lower in the LCZ696 group compared to the enalapril group, including for hypotension (1.4% for the LCZ696 group and 1.6% for the enalapril group), hyperkalaemia (0.4 vs. 1.0%) and renal impairment/acute renal failure (3.9 vs. 4.5%).

There were no signals of **hepatotoxicity** or **QTc** prolongation. Changes in metabolic status were comparable, the net effect of LCZ696 on insulin sensitivity was a small improvement and thus not unfavourable.

More safety issues occured in patients with advancing age; however also in these patients, the safety profile was favourable compared to enalapril. Race and gender had no influence on the safety profile of LCZ696.

Uncertainty in the knowledge about the unfavourable effects

The safety profile of sacubitril as a single component has not been explored and remains largely unknown.

There is limited safety data in ACEI/ARB-naïve patients. A total of 54 patients treated with LCZ696 were ACEI/ARB-naïve (no treatment during the preceding 4 months) across the three HF studies. On the other hand, a similar profile of adverse events was observed between ACEI/ARB-naïve patients treated with LCZ696 and controls in a hypertension study program with LCZ696.

A theoretical risk associated with NEPi relates to the accumulation of the neprilysin substrate **amyloid-β** (Aβ) in the brain. This concern was confirmed in a non-clinical study in young cynomolgus monkeys, where administration of LCZ696 increased total cerebrospinal fluid levels of Aβ1-42, 1-40 and 1-38. In a study in human healthy volunteers, no changes in cerebrospinal fluid concentrations of Aβ1-40 and 1-42, were found, but Aβ1-38 was increased. The clinical relevance of these findings remain uncertain. There is no disease correlate known at present which would be characterizedby an isolated increase of Aβ1-38. No increased incidence of cognition- or dementia-related AEs has been reported in the HF or HTN clinical programs with LCZ696. It was agreed that the cognitive function following the administration of LCZ 696 will be further evaluated post-authorisation and this was included in the pharmacovigilance plan of the agreed RMP.

There was very little representation of patients with **severe renal impairment** (eGFR < 30 mL/min/1.73 m2) as this was an exclusion criterion in the PARADIGM-HF trial. In the double-blind period, experience pertains to n=12 patients on LCZ696 and n=13 on enalapril and this limitation is now reflected in the SmPC. However, in these patients, the AE profile seemed comparable to enalapril.

There are no safety data for patients with **severe hepatic impairment**, biliary cirrhosis or cholestasis as those were excluded from the study. These conditions are contraindicated in the SmPC. AEs were more frequent with higher Child-Pugh scores (5 points: 81.17%; 6 points: 86.36%; 7 points: 89.47%). The results were in line with the main safety results, with hypotension more frequent with LCZ696, with the caveat that the number of patients with moderate hepatic impairment was very limited, precluding robust conclusions about safety in this subgroup. No data were presented about subjects with AST or ALT values exceeding 2×ULN, this may include subjects with liver congestion due to HF.

Based on PK/PD data, interactions with **statins** (increased exposure to atorvastatin) and furosemide (reduced exposure) may be clinically relevant and this is reflected in the SmPC. Data from PARADIGM-HF were inconclusive about this. Therefore the applicant committed to provide the results of an interaction study with statins as reflected in the agreed RMP.

Promotion of cancer, effects on **growing bones** and **Bone Mineral Density (BMD)** were identified as safety topics of special interest for LCZ696 based on pre-clinical findings, however there were no signals related to these issues in the pivotal trial.

Benefit-risk balance

Importance of favourable and unfavourable effects

The current application was based on the results of a **single pivotal study** PARADIGM-HF which was a well conducted study, fulfilling the EMA requirements for a submission of a marketing authorisation application with a single pivotal study as per *EMA Guideline Points to consider on applications with 1 Meta-analyses, 2 Single pivotal trial (CPMP/EWP/2330/99)*.

Following routine **GCP inspections** in 2 of the investigators sites where the pivotal study was conducted, several critical and major findings were observed. Further analysis showed that the findings did not affect the measurements of the primary endpoint. This was confirmed by several sensitivity analyses. The applicant demonstrated that the measurement of AEs was sufficiently accurate to support benefit-risk assessment. The applicant had sufficient oversight to protect the patients' rights and safety.

The endpoints investigated were considered to represent robust outcomes and relevant to HFrEF patients. The **active comparator was enalapril**, which is the standard of care in HFrEF. The investigated dose of enalapril of 10 mg bid was considered to be one of the lower doses recommended according to the product information of enalapril and the *ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (2012)*. Still, there was sufficient evidence from clinical trials and observational data to support that this dose represents a valid comparator although it would have been more in line with clinical practice to allow investigators to titrate the patient to a higher tolerated enalapril dose, especially as valsartan contained in LCZ696 was used in its highest approved dose in HF.

The results showed a significant and clinically relevant improvement in both components of the composite endpoint of **CV mortality and hospitalisation for HF** in patients administered LCZ696 compared to enalapril. The study was prematurely stopped due to superiority with regard to CV mortality. LCZ696 reduced both the risk of sudden death and pump failure compared to enalapril. In addition, LCZ696 reduced the risk of first hospitalisation for HF which is also a relevant endpoint, as hospitalisations represent a major deterioration in this disease. Analyses showed that the benefit withLCZ696 benefit seems likely to be independent of its greater BP lowering effect. There was also a significant improvement in **total mortality** compared to enalapril. The slightly higher non-cardiovascular mortality may be explained by 'competing risks' and therefore did not raise a concern. The benefits with LCZ696 observed in PARADIGM-HF were larger than the benefits of ARB blockade with valsartan observed in other studies so far and seems likely to be due to neprilysin inhibition (by sacubitril) however no conclusive data on this is available.

The **Quality of Life** (QOL) results were considered to be of very limited relevance due to a number of issues such as imputation of data and how the questionnaire was used.

The **safety profile** did not show unexpected findings and was largely in line with what can be expected based on the pharmacodynamics profile of LCZ696. Hypotension, hyperkalaemia and renal impairment were the most commonly reported AEs in the double blind period. Only hypotension occurred more frequently than with enalapril. These conditions also caused most discontinuations.

The **sequential design of the run-in** followed by randomisation precluded accurate estimation of the true drop-out rate of patients administered LCZ696, which necessitated further analysis of the data. Data show that the baseline demographics and medical conditions of patients who dropped out during the run-in period (due to intolerance to enalapril or LCZ696) were generally comparable to those who tolerated both medicinal products and proceeded to randomisation. Still there were some parameters, which suggest that patients who failed the run-in were belonging to a sicker population, in particular having a higher NYHA classification (more patients being NYHA class III than II), higher NT-proBNP and lower blood pressure. How and if these factors have

influenced tolerability was not clear as the differences were small. Submitted data do not point to an efficacy issue related to the sicker population as improved efficacy with LCZ696 compared to enalapril was maintained in patients with different NYHA classification (II/III), NT-proBNP cut-offs or blood pressure cut-offs.

Additional analyses were provided in an attempt to quantify the underestimation of AEs resulting form the design of the run-in phase during the double-blind period of the study. These were considered adequate to investigate the influence of the run-in periods on the safety and efficacy results. The additional analyses on safety showed that the pattern of AEs and the difference between treatment groups remained approximately the same when the run-in period is taken into account. However, the inverse probability weighting (IPW) assumes that run-in failures could be appropriately represented by randomized patients with similar characteristics, which was considered unlikely. Also, the adjustment did not appear to take into account whether a patient discontinued in the enalapril or the LCZ696 run-in period. Complimentary **sensitivity analyses** were presented, in order to increase the understanding of the potential impact the 2084 patients who discontinued their treatment during the run-in periods would have had on an Intention to Treat analysis of efficacy outcomes. In the most conservative scenario (with the assumptions that in subjects who discontinued 25% more events occurred and they all behaved like being on enalapril), the estimate of the primary endpoint diluted to 15% relative risk reduction instead of 20% as in the original analysis. Using another approach (matching discontinuing subjects to completers), the estimates of the relative risk reduction for the primary endpoint and CV death were both 16%.

Management of patients with **hypotension, hyperkalaemia and renal impairment** requires careful clinical monitoring. This is expected to be comparable to the management of patients on other products acting on RAAS like ACEis or ARBs and is adequately reflected in the SmPC.

The clinical relevance of the **increase in Aβ 1-38 in the brain** remains uncertain. Dementia-related AEs in the trial were not more frequent with LCZ696. However, it is unlikely that capturing of AEs would be able to detect an effect if it exists, because development of dementia may take longer than the observation period in the trial and subjects with mild dementia are not expected to participate, precluding observations of accelerated development of dementia. It was agreed that the cognitive function following the administration of LCZ696 will be further evaluated post-authorisation and this is included in the pharmacovigilance plan of the agreed RMP.

Finally, importantly in the context of earlier findings with a combination of an ACE-inhibitor and a NEP-inhibitor (omapatrilat), occurrence of **angioedema** was low (0.5%) although still somewhat higher compared to the enalapril group (0.2%) and a few patients needed to be hospitalised. In the trial, no airway compromise occurred and potential angioedema was believed to be manageable in the clinical practice. The CHMP agreed that patients with known history of angioedema related to previous ACE inhibitor or ARB therapy or with hereditary or idiopathic angioedema should be contraindicated. Furthermore, a warning was included in the SmPC related to a risk of possible angioedema.

Benefit-risk balance

The benefits of LCZ696 in terms of significant reductions of mortality and morbidity compared to enalapril were accompanied by limited and manageable risks resulting in the conclusion of a positive benefit risk balance in the treatment of adult patients with symptomatic chronic heart failure and reduced ejection fraction.

Divergent position to the majority recommendation is appended to this report.

Discussion on the benefit-risk balance

The goals of treatment in patients with established HF are to relieve symptoms and signs (e.g. dyspnoea and oedema), prevent hospital admission and to improve survival. LCZ696 has shown a **clinically relevant efficacy** on these parameters when compared to the current standard of care which are ACEi. The safety profile was also considered manageable. However, certain issues needed to be addressed during the procedure in order to further improve the B/R profile of LCZ696.

A main issue was the **selection of the patients** and the external validity of the pivotal study. The study design may have contributed to masking tolerability issues with LCZ696 in daily practice. It was of concern that the possibilities to estimate the benefit-risk balance in a true ITT perspective were limited, which was considered a major disadvantage of this design. Only HF patients on stable doses of ACEi/ARBs were recruited in PARADIGM-HF. It was discussed whether it is appropriate to administer LCZ696 to ACEi/ARB naïve patients. Regarding efficacy, it could be assumed that benefits seen re not expected to be different in these groups. Also analysis by time of HF diagnosis in recruited patients confirmed that newly diagnosed patients (less than 3 months) have comparable efficacy to veteran patients. Therefore the CHMP concluded that a similar benefit can be expected in patients not previously treated with ACEi/ARB. Tolerability may still be an issue, with hypotension and renal impairment being the most relevant risks in such patients, even after starting with the lowest dose and slowly up-titrating as implemented in the TITRATION study. The proposal of the applicant to implement such posology in the SmPC together with a warning regarding the limited data was therefore agreed, considering also the dose-dependency of the pharmacodynamics, but nevertheless this did not alleviate all concerns. However, these risks were considered acceptable in light of the expected benefits compared to the standard of care, i.e. significantly improved survival and reduced hospitalisations. For the same reason, limiting the use of LCZ696 only to patients who failed ACEI or ARB treatment (second line therapy) was considered not justified. Initiating patients first on ACEI/ARB and then switching them to LCZ696 was not considered to ensure tolerability as there seemed still a significant tolerability issue with RAAS inhibitors in general with 12.06 % already dropping out during the enalapril double-blind period due to AEs, even when these patients were already treated with ACEI or ARB prior to the study.

Patients with symptomatic hypotension or SBP <100 mmHg or eGFR < 30 mL/min/1.73m2 or serum potassium > 5.4 mmol/L were also excluded from the study. There are adequate warnings implemented in the SmPC explaining the limited data in these patients, and an adapted posology is recommended (in case of low blood pressure and severe renal impairment).

There were **2 sequential run-in periods** with 10% of the patients dropping out in each phase, half of which due to tolerability issues. Patients in the LCZ696 arm were shown to take a longer time to build up their dose compared to enalapril. Thus, patients not tolerating LCZ696 were the sum of discontinuations in the LCZ696-run-in, in the LCZ696-arm during double blind period, in addition to some of the patients who had previously discontinued enalapril during the first run-in period. This design precluded a proper estimation of the B/R based on a true ITT analysis. Sensitivity analyses have been provided to address this issue and show that the impact on the result estimates was only limited. The applicant's proposal to summarize discontinuations and the most commonly reported AEs observed during the run-in period in the SmPC and to inform the prescribers that AE rates observed during the study may be lower than expected in clinical practice were endorsed by CHMP.

Thus, the patients included in the pivotal trial were selected by the requirement **of prior ACEi/ARB treatment** and then further selected by the two titrations periods preceding randomization. However, taking into account the demonstrated benefit and the support of the sensitivity analyses performed, the external validity of the study was considered adequate. A sufficient number of ACEi/ARB naïve patients are planned to be included in

the post-authorisation studies to confirm the estimations of the B/R balance in such patients in daily practice. This is reflected in the agreed version of the RMP.

The CHMP concluded that even though the patients included in the pivotal study were previously treated with ACE inhibitors or ARBs, the data provided by the applicant supported that a similar benefit can be expected in patients not previously treated with those products, and hence a first line indication was granted.

The presented data from **patients defined as NYHA class IV** at randomisation showed that efficacy and safety were comparable to those of different NYHA classes in comparison to the enalapril arm. Analyses using other parameters to indicate severity of the disease (LVEF, NT-ProBNP and MAGGIC score) showed similar results. Data also indicated that the patient's functional class was changing between NYHA III and IV during the study. Data from patients diagnosed as NYHA IV at different time points was presented and also supported a comparable profile to that of enalapril. Also due to the oscillation of patients between NYHA III to NYHA IV in clinical practice, it was agreed that exclusion of the latter group may be not appropriate. As such the data do not point to any particular efficacy/safety issue in patients with NYHA class IV treated with LCZ696, but the database was not very robust and the higher incidence of hypotension in NYHA IV group was observed. NYHA IV patients are a heterogeneous group of patients and not all of these patients are likely to be treated with LCZ696. Consequentially, the indication refers to "symptomatic chronic heart failure", with a warning in section 4.4 of the SmPC that there was limited representation of patients with NYHA IV, and also a description of the NYHA class representation in PARADIGM-HF in section 5.1 of the SmPC. Cut off values of the ejection fraction were an important part of the inclusion/exclusion of the patients in the pivotal trial and EF is of diagnostic and prognostic value in HF. The use of EF cut offs outside of studies has limitations and is not included in the indication but detailed in section 5.1 as an inclusion criterion of the PARADIGM-HF.

Regarding the B/R in mild and moderate **renal impairment**, this was considered comparable to that shown in the general population, i.e. the main risk compared to enalapril being hypotension. However, it was observed that in patients with moderate renal impairment and for AEs leading to treatment discontinuation and serious AEs, AEs events were almost halved when halving the initial dose. Therefore the lowest titration dose is recommended in the SmPC. There was very limited representation of patients with severe renal impairment which is reflected in the product information, with the recommendation for caution and to start these patients on the lowest dose.

Patients with **moderate hepatic impairment** (Child-Pugh B classification) or AST/ALT values above 2 times the upper limit of the normal range were represented to a very small extent. PK data showed increased exposures of both sacubitril and valsartan in such patients, warranting cautious use in these patients and starting with the lowest titration dose, as advised in the SmPC.

Occurrence of **angioedema** was carefully evaluated in PARADIGM-HF, based on the concerns raised by previous knowledge e.g. with omapatrilat. Indeed more events were observed with angioedema on LCZ696 compared to enalapril. However, incidence and/or severity may be higher in the general population and this will be further evaluated post-authorisation as reflected in the RMP.

A potential risk associated with NEPi relates to the accumulation of the neprilysin substrate **amyloid-β (Aβ)** in the brain. The clinical relevance of this finding remains uncertain. Complete understanding of the risk probably requires many years of targeted observation. The cognitive function following the administration of LCZ 696 will be further evaluated post-authorisation and this is included in the pharmacovigilance plan of the agreed RMP.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority that the risk-benefit balance of Entresto indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Divergent position to the majority recommendation is appended to this report.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that active substance LCZ696 is qualified as a new active substance.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0106/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

APPENDIX 1

DIVERGENT POSITION DATED 24 SEPTEMBER 2015

The undersigned member of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Entresto, indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

A positive benefit/risk ratio of Entresto in the general patient population with symptomatic patients with heart failure and reduced ejection fraction is not considered sufficiently demonstrated

The study population of the single pivotal trial is not fully representative of the overall population of patients with heart failure.

-The PARADIGM study included chronic symptomatic heart failure patients, mostly in NYHA class II, with a LVEF <35% who had been treated for at least 4 week before screening with stable dose of an ACE inhibitor or an ARB equivalent to enalapril 10 mg/day, a stable dose of a beta-blocker unless intolerant and an MRA as indicated and had evidence of plasma BNP ≥ 150 pg/mL (or NT-proBNP ≥ 600 pg/mL).

-The two sequential run-in periods of the pivotal study could have selected the population and hence magnified the benefit of Entresto and significantly attenuated the risk of adverse events such as angioedema.

-Moreover, the run-in periods led to the exclusion of a relevant number of patients who were not eligible due to ACEi tolerability issues. The sensitivity analyses requested by the CHMP and performed by the Applicant to evaluate the impact of the run-in periods on efficacy results showed effect dilution, had intrinsic methodological limitations, and did not take into account whether the discontinuation was due to enalapril or Entresto. Hence, the concerns on the potential selection introduced by the run-in periods remain.

Because of the potential effect of the vasopeptidase component of Entresto on the bradikinin axis there are serious concerns that ACEi-naïve patients treated with Entresto could be exposed to an increased risk of angioedema. Indeed, the trial design selected patients with an extremely low risk of angioedema by excluding all those patients with potential increased upper respiratory tract reactivity after ACEi challenge.

Moreover, Entresto cannot be considered as first-line therapy because the benefit on the reduction of mortality observed with the treatment with beta-blockers (CIBIS II, COPERNICUS, MERIT-HF studies) and MRA antagonists (RALES and EPHESUS studies) is greater (RRR approximately 34% for beta-blockers in each trial and 30% for MRAs in the RALES trial) compared with the benefit observed with Entresto; indeed the latter is similar to that observed with ivabradine, as for the EMA approved indication.

The above mentioned concerns support the restriction of Entresto indication to the second line therapy of patients with symptomatic chronic heart failure, in a patient population which reflects the one enrolled in the pivotal trial for which a clear benefit-risk ratio has been demonstrated.

Overall, for these reasons, I consider that the benefit/risk ratio is negative for Entresto in the claimed indication:

Entresto is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction (see section 5.1).

London, 24 September 2015

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Prof. Daniela Melchiorri (ITALY)