CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207620Orig1s000

MEDICAL REVIEW(S)

DNP Clinical Consult Memo

NDA	**207620**
Sponsor:	**Novartis**
Drug:	**LCZ696 (Entresto)**
Proposed Indication:	**Heart Failure (NYHA class II-IV)**
Material Submitted:	**NDA submission**
Consult Request Date:	**6/29/15**
Date Review Completed:	**6/30/15**
Clinical Reviewer:	**Teresa Buracchio, M.D.**
Nonclinical Reviewer:	**David B. Hawver, Ph.D.**
Clinical Team Lead:	**Nick Kozauer, M.D.**
Nonclinical Supervisor:	**Lois M. Freed, Ph.D.**
Division Director:	**Billy Dunn, M.D.**

DCRP has requested a consult from DNP to provide assistance in evaluating the theoretical potential for LCZ696 (Entresto) to increase the risk of developing Alzheimer's disease (AD). This memo will briefly summarize the relevant data discussed in the DCRP New Drug Application (NDA) reviews and will focus primarily on responding to the consult questions provided to DNP.

Background: Heart failure (HF) is a major cause of morbidity and mortality in the United States. It is estimated that over half of HF patients die within 5 years of diagnosis.[1] Novartis has studied LCZ696 for the treatment of heart failure (NYHA class II–IV) (b) (4) (b) (4) . LCZ696 is a dual angiotensin receptor neprilysin inhibitor (ARNi) that dissociates into valsartan, an angiotensin receptor (AT1) blocker (ARB), and the pro-drug sacubitril (AHU377) following oral administration. Sacubitril is rapidly hydrolyzed in vivo to the active neprilysin inhibitor LBQ657.

Neprilysin is an enzyme that degrades natriuretic peptides and vasoactive peptides. Neprilysin is also one of the major enzymes that breaks down the amyloid beta (Aβ) peptide, a pathological marker of Alzheimer's disease, in the central nervous system. While showing benefit in the treatment of heart failure, it is theorized that inhibition of neprilysin could potentially increase levels of Aβ in the brain and CSF and increase the risk of developing AD.

The following documents were reviewed for this consult: Clinical Pharmacology review by Luning Zhuang and Sreedharan Sabarinath; Clinical review by Kimberly Smith and Tzu-Yun McDowell; a synopsis of Study (b) (4) (focusing on cognitive outcomes (b) (4)) submitted by the Sponsor.

Study A2126, Phase 1 study Aβ in CSF: As stated in the Clinical Pharmacology review by Drs. Zhuang and Sabarinath, this was a placebo-controlled study in healthy subjects that examined the PK and PD effects of 400mg LCZ696 once daily for 14 days. At Day 14, there was about 50% increase in plasma Aβ 1-40 ($AUEC_{0-36h}$) with LCZ696 relative to placebo but there was no difference from placebo in the CSF. However, Aβ 1-38

[1] Go et al. *Circulation*. 2013;127:e6–e245

$AUEC_{0\text{-}36h}$ increased from baseline with LCZ696 by about 42% relative to placebo in the CSF. There was no significant difference with LCZ696 for amyloid-β 1-42 in CSF. It was estimated that blood brain barrier (BBB) penetrance for LZC696 was approximately 0.3%.

PARADIGM-HF, Phase 3 study pivotal study: This was a multicenter, randomized, double-blind, double-dummy, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril in patients with HF (NYHA class II-IV) and reduced ejection fraction (LVEF≤35%). The study was stopped early after a median of 27 months of follow-up after the third interim analysis showed benefit on the primary endpoint, a composite of cardiovascular death or first heart failure hospitalization. From the clinical reviews by Dr. McDowell and Smith, the study enrolled 8442 patients age 18 years and older. The mean age of the study subjects was 64 years with a range of 18-96 years, 4229 patients in the enalapril arm and 4203 patients in the LCZ696. Approximately 50% of the patients were age ≥65 years with 20% of all patients ≥75 years of age. Patients were evenly distributed between the two treatment arms with regard to age. Dementia and cognitive function were not prospectively assessed in the study or identified as adverse events of special interest. Dementia-related events were captured through standard adverse event (AE) collection. Dementia-related events using the broad Standard MEDDRA Query (SMQ) were seen equally in only 2% of patients in each treatment arm (Table 77 in the Clinical Review). This analysis used a broad search strategy which included preferred terms (PTs) such as "feeling abnormal" or "initial insomnia" that do not necessarily indicate dementia or cognitive impairment. For the narrow dementia SMQ which focuses on dementia diagnostic PTs, there were a total of 15/4229 (0.004%) dementia adverse events in the enalapril arm and 12/4203 (0.003%) in the LCZ696 arm. Of note, there were only 2 reports of Dementia Alzheimer's Type in each treatment arm.

Planned studies to assess cognition and amyloid

The Sponsor plans to further investigate the effects of LCZ696 on cognitive testing and amyloid by including (b) (4) . Preliminary discussions have occurred between the Sponsor and DCRP with respect to the design and goals of this trial.

The Sponsor is planning to conduct a (b) (4) study, (b) (4) , that will assess the impact of LCZ696 on cognitive testing (b) (4) as measured by positron emission tomography (PET) imaging. (b) (4) .

While neprilysin inhibitors such as sacubitril can potentially increase Aβ levels in the CNS, the impact of increasing Aβ in the CNS and subsequent risks of AD are unknown. Although animal models of neprilysin deficiency have shown increased Aβ brain accumulation, to date, neprolysin deficiency has not been identified as a significant causative factor in the pathophysiology of AD in humans and there have not been

consistent findings in the association between single nucleotide polymorphisms in neprolysin genes and risk of AD.[2,3,4] There are alternate clearance pathways and enzymes that participate in the breakdown of Aβ and it is possible that these alternate pathways may be able to compensate for any loss in neprilysin. (b) (4)

The effect of a neprilysin inhibitor on Aβ in the CNS will depend on its ability to cross the BBB and it appears that a very small amount (0.3%) of LCZ696 crosses the BBB. It is unclear if this is sufficient to significantly elevate Aβ in the CNS. The Phase 1 PK/PD study suggests that LCZ696 may elevate some forms of Aβ in the CSF and plasma in the short-term, but the clinical significance of these findings is unclear. The effects of chronic administration of LCZ696 on Aβ in the CNS are unknown. However, it should be stressed that even if elevations of Aβ should occur with LCZ696, it is not known if these elevations would impact the risk of developing AD. It has become increasingly evident that disturbances in amyloid regulation are but one of a number of complex pathophysiologic changes that occur in AD. Co-morbidities such as cardiovascular disease can also contribute significantly to the onset of dementia in patients with AD pathology. As patients with HF frequently have some degree of cognitive impairment, it is even theoretically possible that LCZ696 could have a positive benefit on the vascular contributions to dementia that may balance or outweigh the potential risk of increasing Aβ.

A signal for dementia risk was not identified for the (b) (4) study; however, the study was not designed to assess dementia or cognitive outcomes. As noted in the Clinical review, dementia and cognitive impairment were captured as adverse events but were not identified as Adverse Events of Special Interest so there is a possibility that these events may be underreported. Additionally, a median follow-up of 27 months would not be long enough to capture a significant number of incident cases of AD which can have a long latency period. Although there were limitations in the study design for ascertainment of dementia, this was a large study with approximately half of the patients age ≥65 years who are at risk of developing dementia by virtue of age. There was not an imbalance in events seen between the treatment groups in either narrow or broad SMQ analyses for dementia to suggest a signal for increased risk of dementia or cognitive impairment with LCZ696.

At this point there is no clinical evidence to suggest that there is a risk for increasing development of AD or cognitive impairment with use of LCZ696 in this population of HF patients with low ejection fraction. The Sponsor's plan to further evaluate the (b) (4) study and a cognitive test battery and (b) (4) PET imaging (b) (4) study are reasonable as additional steps for assessing any impact of LCZ696 on cognition and amyloid pathology.

[2] Vodovar et al. Eur Heart J. 2015;36:902-5.
[3] http://www.alzforum.org/news/research-news/inhibiting-neprilysin-good-heart-what-about-brain. Accessed June 30, 2015
[4] Xingzhi et al. J Neurol Sci 2014; 346:6-10.

DCRP Questions

1. **Dr. Link (DCRP pharmacology-toxicology reviewer) reviewed the evidence that neprilysin breaks down beta amyloid (see attached). Do you agree with his assessment of the evidence that neprilysin breaks down beta amyloid?**

   We agree with Dr. Link's view that the evidence supports a role for neprilysin as one of the primary Aβ degrading enzymes (of more than a dozen enzymes identified to date) that are involved in clearance of Aβ from the brain. However, other important Aβ clearance mechanisms include phagocytosis, transport across the blood-brain barrier, and transport into the CSF. One recent report estimated that these latter two mechanisms may each account for about 25% of Aβ clearance out of the CNS *(Roberts KF et al., 2014, Annals of Neurology 76(6):837-844)*.

2. **How strong is the science supporting the amyloid hypothesis in the etiology of Alzheimer's disease?**

   The veracity of the amyloid cascade hypothesis in Alzheimer's disease (AD), which posits that accumulation of the beta-amyloid peptide (specifically the abnormal Aβ42 form) in brain parenchyma initiates a sequence of events that ultimately leads to dementia, is the subject of a great deal of scientific uncertainty and debate. Disruptions of amyloid processing are commonly involved in some manner in the pathophysiology of AD. However, the exact nature of their role in the development of clinical disease has yet to be determined. It has also become increasingly evident that disturbances in amyloid regulation are but one of a number of complex pathophysiologic changes that occur in AD. In addition, over the past decade a series of development programs have evaluated drugs that have sought to lower levels of amyloid in the brain. While many of these drugs have demonstrated target engagement, they have all uniformly failed to confer any clinical benefit to patients with dementia. The reasons for these seemingly discordant results are uncertain and, no doubt, complicated. However, they further highlight the lack of understanding as to the part that amyloid plays in the disease process.

   The fact that the rare early-onset autosomal-dominant forms of AD involve mutations in genes that are directly involved in amyloid processing lends support to the amyloid hypothesis. However, the relevance to the far more common sporadic forms of the disease is not immediately obvious. For example, evidence suggests that the autosomal dominant forms of AD may result from amyloid over-production, while the sporadic forms potentially involve disruptions in clearance. Timing of pathology may also be important as some authors propose that amyloid may trigger a downstream series of events, but then become less directly relevant over time. It must be stressed that this view is also highly theoretical at the present time. The past decade of scientific research and clinical trials in AD have revealed our substantial lack of understanding as to how the commonly observed pathophysiologic changes in AD ultimately manifest in clinical disease. It is clear, however, that the processes involved are complex. As a result, the clinical impact of the disruption of a single aspect of this environment in isolation would be extremely uncertain.

3. How do you interpret the CSF findings in the preclinical and clinical studies? What is the likely clinical significance of these findings?

Young female cynomolgus monkeys (2.5-4 years old) given oral LCZ696 50 mg/kg once daily for 16 days showed significant increases in CSF exposures to newly generated Aβ38, Aβ40, Aβ42, and total Aβ (Day 14/15 AUC) compared to vehicle controls; however, no changes were observed in cortex or hippocampus levels of Aβ40 or Aβ42 (Study 1270586; Aβ38 levels were below the limit of quantitation). These observations suggest that sufficient levels of LBQ657 (the active moiety produced by esterase metabolism of the sacubitril component of LCZ696 after oral administration) reached the CNS to inhibit neprilysin, but that other Aβ clearance mechanisms, including transport into the CSF, compensated such that no net increase in brain Aβ was apparent at steady state.

The dose of 50 mg/kg was described as "clinically relevant," since the mean LBQ657 CSF Day 15 Cmax (19.8 ng/mL) was similar to the mean LBQ657 CSF Day 14 Cmax (19.2 ng/mL) observed in healthy volunteers given LCZ696 400 mg QD (Study A2126; the target dose for LCZ696 is 200 mg BID); however, the mean LBQ657 CSF $AUC_{0\text{-}24\ hr}$ was 387 ng*hr/mL in humans vs. 128 ng*hr/mL in monkeys. Higher doses should have been explored to allow assessment of CNS exposures several-fold greater than those expected in humans at the maximum recommended dose.

These results suggest that drug-induced changes in Aβ CSF levels may not reliably reflect steady state changes in Aβ brain levels because of the complex and potentially compensatory mechanisms involved in Aβ clearance from the CNS. Furthermore, these effects observed in 2.5-4 year old monkeys may not accurately predict effects that might occur in elderly humans, since cynomolgus monkeys do not typically have measurable cerebral amyloid pathology until middle age. Diffuse amyloid plaques were observed in cynomolgus monkeys aged 18-19 years in one study *(Kodama et al., 2010, Toxicologic Pathology 38:303-311)*, while classic dense core senile plaques were observed in another study in cynomolgus monkeys aged 29-30 years *(Darusman et al., 2014, Frontiers in Aging 6:313)*. Humans typically accumulate amyloid pathology starting at age 45-65 years (depending on ApoE genotype).

Study A2126, which analyzed the PD effects of LCZ696 on CSF Aβ, demonstrated BBB penetration of approximately 0.3%. Over a two week period there was an increase in $Aβ_{1\text{-}38}$ in the CSF and $Aβ_{1\text{-}40}$ in the plasma, but no increases were seen in the more pathologic $Aβ_{1\text{-}42}$ in either CSF or plasma. The clinical significance of these findings is not known. This was also a short study and it is not known how LCZ696 may impact Aβ levels with chronic use. Moreover, it is unknown whether increasing levels of any form of Aβ in the CSF may ultimately increase the risk of developing Alzheimer's disease.

The Sponsor's plan for a (b) (4) study that will include neurocognitive tests and (b) (4) PET imaging is reasonable as an additional step for assessing any impact of LCZ696 on cognition (b) (4). However, there is no *a priori* basis at the present time to conclude that the pattern of results observed in the CSF would necessarily suggest that LCZ696 would convey a high likelihood of an increased risk for Alzheimer's disease.

4. How do you interpret the brain tissue findings in the 39-week monkey study as relates to the risk of LCZ696 causing Alzheimer's disease?

In Study 0670621, 2-4 year old cynomolgus monkeys given 300 mg/kg LCZ696 once daily via oral gavage for 39 weeks showed no changes in Aβ42 immunostaining in brain (parenchymal or vascular) compared to vehicle controls. Plasma LBQ657 exposures were approximately 2-fold (Cmax) and 9-fold (AUC) those observed in humans given LCZ696 200 mg BID. These results are not very informative about the risk of AD, since amyloid deposition does not occur spontaneously in non-human primates until at least middle age, as noted above (see response to Question 3). A study in aged monkeys, measuring levels of soluble and insoluble Aβ in brain homogenates as well as immunoreactive Aβ, may have provided more relevant information.

5. See Table 77 of the FDA Clinical Review. Do you think the approach that was taken to analyze the AE data in PARADIGM-HF was reasonable? If not, how do you think the data should be analyzed?

The analyses that were performed using broad and narrow range SMQs for dementia appear to be appropriate. The incidence of dementia AEs under the dementia narrow SMQ are quite low. As noted in the Clinical review by Dr. McDowell and Smith, there was no prospective assessment of dementia or cognitive impairment in the PARADIGM-HF study so there may be underreporting of dementia and cognitive impairment. Despite this limitation, there does not appear to be any imbalance of dementia adverse events between the two treatment arms. Given the low reported rates of dementia AEs, additional analyses are not likely to be informative.

6. Are you aware of any PMRs to assess the risk of Alzheimer's disease? If so, can you provide additional information on the design of these studies?

We are not aware of any PMRs to assess the risk of AD.

Summary Comment: As expressed in our responses to the consult questions above, certain aspects of the studies in the monkey limit the extent to which they could fully investigate the effect of LCZ696 on amyloid pathology. However, these limitations must also be viewed in the context of the sponsor's overall development program as well as the current scientific understanding of the pathophysiology of AD. Based on the totality of the data available at this time, we do not believe that they suggest a high likelihood of an increased risk of developing AD with the use of LCZ696.

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/s/

NICHOLAS A KOZAUER
07/01/2015

TERESA J BURACCHIO
07/01/2015

DAVID B HAWVER
07/01/2015

LOIS M FREED
07/01/2015

WILLIAM H Dunn
07/02/2015

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo

NDA: 207620 Sacubitril plus valsartan (Entresto) for reducing the risk of cardiovascular mortality and (b) (4) hospitalization in patients with chronic heart failure.

Sponsor: Novartis

Review date: 22 June 2015

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

This memo conveys the Division's recommendation to issue an "Approval" letter for this application.

This application has been the subject of reviews of CMC (Banerjee, McLamore-Hines, Kurtyka, Mello, Li, Bloom, Wilson-Lee; 15 May 2015), pharmacology/toxicology (Link; 15 May 2015), clinical pharmacology (Sabarinath, Zhuang; 15 May 2015), clinical effectiveness and safety (Marciniak; 29 December 2014, Smith; 15 May 2015, and McDowell; 15 May 2015), and statistics (Lawrence; 20 May 2015). There is also a CDTL memo (Thompson; 12 June 2015), with which I am in agreement.

Entresto is the 1:1 combination of valsartan, an angiotensin receptor blocker, and sacubitril, which would be the first approved neprilysin inhibitor. The latter's effects include vasodilation, natreuresis, aldosterone antagonism, and elevation of CSF levels of beta-amyloid in cynomogus monkeys and man.

Entresto would be marketed as tablets of (sacubitril/valsartan) 24/26 mg, 49/51 mg, and 97/103 mg. (b) (4) There is a 24-month expiry. Facility inspections are *not* complete.

There are no unresolved issues with pharmacology/toxicology. Hydrocephalus and reduced survival were seen in rabbit pups. CSF levels of beta-amyloid are elevated short-term, but, in a 2-year study in monkeys, beta-amyloid levels were not elevated in brain parenchyma. Given the typical lifespan of a patient with heart failure, I find the available data adequately reassuring with regard to the potential of Entresto to cause cognitive decline.

Sacubitril is at least 60% bioavailable. Valsartan is somewhat more bioavailable from Entresto than as monotherapy. Sacubitril is subject to esterase activity, but neither sacubitril nor valsartan is subject to other metabolism. Entresto inhibits transporters OATP1B1 and B3.

Entresto was (b) (4) Although the review team is not unanimous in the policy decision we made, we did say that one did not need to satisfy the combination policy if one could demonstrate an effect on mortality or irreversible morbidity, and this decision led to the heart failure development program.

The sole study supporting approval for heart failure is PARADIGM, a randomized, double-blind study comparing enalapril to a single regimen of Entresto. Subjects with stable NYHA Class II-IV heart failure and reduced ejection fraction (HFrEF) underwent sequential several-week run-in phases on enalapril and Entresto before being randomized, resulting in about 10% withdrawal rates in each run-in phase, a feature that complicates description of study results.

PARADIGM was stopped after the third of three planned interim analyses. Results are summarized in the table below:

Endpoint	Enalapril N=4212	Entresto N=4187	RR (95% CI)	Alpha	P-value
Primary: Heart failure hospitalization or CV death	26.5%	21.8%	0.80 (0.73, 0.87)	0.002	0.0000002
HF Hospitalization	15.6%	12.8%	0.79 (0.71, 0.89)	--	--
CV death	16.5%	13.3%	0.80 (0.71, 0.89)	--	--
All-cause mortality	19.8%	17.0%	0.84 (0.76, 0.93)	0.0016	0.0009

All of the effect on all-cause mortality appears to be the effect on cardiovascular mortality; this finding merely reassures me that there are not other, important adverse mortal effects of Entresto. Inclusion of all-cause mortality as a formal end point was probably harmless in this study, but I do not think its inclusion is ever smart.

There was a second secondary end point attributed 20% of the alpha: the Kansas City Cardiomyopathy Questionnaire (KCCQ), a widely used 23-item patient-reported, symptom assessment. Although there was an effect, (b) (4) the review team notes and I concur that the effect is much smaller than is generally regarded as clinically relevant, (b) (4)

Subsequent secondaries for time to new onset atrial fibrillation or a 50% reduction in eGFR showed no nominally statistically significant effects.

Expected adverse effects were hypotension, which was generally adequately managed without study drug discontinuation, and hyperkalemia, which was nominally worse on enalapril.

Angioedema was a major problem with omapatrilat, a drug with ACE inhibitor and neprilysin inhibitor properties. As with ACE inhibitors alone, rates of angioedema were several-fold higher in Blacks. Several severe cases with airway compromise occurred in the omapatrilat development program, and it was never approved. In the Entresto heart failure program, no cases with airway compromise were reported. Rates were 0.1% in each run-in period, but then showed the expected amplification in the randomized period: 0.2% on enalapril and 0.5% on Entresto. The program also showed the expected increased risk in Blacks, few though there were in the study—0.5% on enalapril and 2.4% on Entresto. There is discussion of a post-marketing requirement to obtain further data on angioedema, particularly in US Blacks, but I do not recommend a PMR, in part because I believe we already know the risk well enough and in part because our pharmacovigilance tools are likely better than anything we could get Novartis to do.

There is a third clinical review, by Dr. Marciniak, not mentioned in the CDTL memo. Dr. Marciniak was not part of the review team. He cites “flaws” in the case report forms for PARADIGM “that challenge the validity of its data”, but then he concludes the issues “are not severe enough to reject outright the trial results”, and in that conclusion I certainly concur. Dr. Marciniak describes the 27 lung cancers in the Entresto group vs. 22 on enalapril as a “modest increased risk”, but makes little of other trends—all solid

tumors 122 vs 118[1], all brain 6 vs 7, all hematologic 10 vs 10—and he dismisses as unreliable the biggest observed difference, in non-melanoma skin—11 vs 29. In my view, there is no cancer finding here of the least concern.

I concur with the entire review team in recommending approval. I also want to acknowledge the entire review team's diligence in producing their reviews well in advance of user fee goal dates for a priority review. I particularly wish to acknowledge leadership by Drs. Wilson-Lee and Thompson.

[1] *Entresto vs enalapril*

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/s/

NORMAN L STOCKBRIDGE
06/22/2015

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207620
Priority or Standard	Priority
Submit Date(s)	December 17, 2014
Received Date(s)	December 17, 2014
PDUFA Goal Date	August 26, 2015
Division / Office	Division of Cardiovascular and Renal Products/ODEI
Reviewer Name(s)	Tzu-Yun McDowell (safety) Kimberly Smith (efficacy)
Review Completion Date	May 15, 2015
Established Name	Sacubitril/valsartan
(Proposed) Trade Name	Entresto
Therapeutic Class	Angiotensin receptor neprilysin inhibitor
Applicant	Novartis Pharmaceuticals Corporation
Formulation(s)	50, 100, and 200 mg film-coated tablets
Dosing Regimen	Initial dose of 100 mg twice daily with titration to a target dose of 200 mg twice daily. Initial dose of 50 mg daily for patients not currently taking an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker, or on low doses.
Indication(s)	Treatment of heart failure (NYHA class II–IV) (b) (4) (b) (4)
Intended Population(s)	Adults

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

LCZ696 should be approved for the treatment of heart failure (NYHA class II-IV) (b) (4)

1.2 Risk Benefit Assessment

Chronic heart failure is a serious disease affecting millions of adults in the United States. Despite current pharmacologic and device-based therapies, the morbidity and mortality of heart failure remains high. Heart failure is the primary diagnosis in over one million hospitalizations annually with 25% of patients rehospitalized within one month of discharge (Yancy, 2013). Ultimately, approximately 50% of patients die within five years of diagnosis. Hence, despite current therapy, there remains significant unmet medical need for better treatments for this condition.

LCZ696 is a dual angiotensin receptor neprilysin inhibitor (ARNi) that dissociates into valsartan, an angiotensin receptor (AT_1) blocker (ARB), and the pro-drug sacubitril (AHU377) following oral administration. Sacubitril is rapidly hydrolyzed in vivo to the active neprilysin inhibitor LBQ657. Novartis developed LCZ696 for the treatment of heart failure (NYHA class II–IV) (b) (4)

In support of this indication, Novartis conducted PARADIGM-HF, a randomized, double-blind, active-controlled, outcomes trial in which 8,442 subjects with chronic heart failure and a reduced ejection fraction were randomized to treatment with LCZ696 or enalapril. In sequential single-blind run-in periods, subjects received enalapril 10 mg bid, followed by LCZ696 100 mg bid, increasing to 200 mg bid. Subjects who successfully completed the run-in periods were randomized to LCZ696 200 mg bid or enalapril 10 mg bid. The primary endpoint was cardiovascular death or first heart failure hospitalization. The trial was terminated for efficacy following the third interim analysis on the recommendation of the trial's independent data monitoring committee. LCZ696 reduced the risk of the primary composite endpoint based on a time-to-event analysis with a hazard ratio (HR) of 0.80 (95% confidence interval [95% CI] 0.73, 0.87; 1-sided p=0.0000002), with LCZ696 subjects experiencing both fewer first heart failure hospitalizations (537 [12.8%] vs. 658 [15.6%]) and fewer cardiovascular deaths as the first event (377 [9.0%] vs. 459 [10.9%]) compared with enalapril subjects. Although not pre-specified or adjusted for multiplicity, the applicant analyzed the components of the primary endpoint separately as the time to first heart failure hospitalization and time to cardiovascular death, including deaths preceded by a heart failure hospitalization. Both endpoints achieved nominal statistical significance favoring LCZ696 (first heart failure hospitalization HR 0.79; 95% CI 0.71, 0.89; cardiovascular death HR 0.80; 95% CI 0.71, 0.89). In addition, LCZ696 reduced the risk of the secondary endpoint of all-cause mortality with a HR of 0.84 (95% CI 0.76, 0.93; 1-sided p=0.0005), an effect driven entirely by a reduction in cardiovascular causes of death.

The important risks identified during the safety review are angioedema, hypotension, renal impairment, and hyperkalemia. The most concerning of these risks is angioedema, although the overall incidence during the double-blind period was low (19 [0.5%] LCZ696 vs. 10 [0.2%] enalapril subjects) and none of these events involved airway compromise or required airway support. We note, however, that the incidence was higher for black subjects (5 [2.4%] LCZ696 vs. 1 [0.5%] enalapril subjects) including black subjects enrolled in the United States (3/54 [5.6%] LCZ696 vs. 0/57 [0%] enalapril subjects). Given that only 5% of PARADIGM-HF subjects were black, there is substantial uncertainty in these risk estimates. LCZ696 was also associated with an increased risk of hypotension-related adverse events compared with enalapril (HR 1.4, 95% CI 1.3, 1.5), although most events either did not require intervention or were managed by dose adjustment. LCZ696 and enalapril had similar risks of hyperkalemia and renal impairment.

It is important to note that estimates of risk derived from the double-blind period of PARADIGM-HF may underestimate the true risk of LCZ696. To be eligible for randomization, PARADIGM-HF subjects were required to be tolerant to an angiotensin converting enzyme inhibitor (ACEi) or ARB at screening. In addition, all had to successfully complete sequential enalapril and LCZ696 run-in periods during which subjects were excluded for hypotension, renal impairment, hyperkalemia, or angioedema. Although there is uncertainty in the true incidence of these risks, we believe they can be adequately managed through clinical monitoring and dose titration. In addition, PARADIGM-HF subjects underwent a 36-hour washout period between ACEi and LCZ696 dosing to reduce the risk of angioedema, and we believe it is important to include this washout period in the label.

Neprilysin is involved in the clearance of amyloid-β from the brain and cerebrospinal fluid and, therefore, LCZ696 could lead to accumulation of amyloid-β in the brain and result in cognitive impairment. In preclinical studies and a two-week study of healthy volunteers, LCZ696 resulted in an increase in amyloid-β in the cerebrospinal fluid. In a 39-week study in monkeys, there was no accumulation of amyloid-β in the brain. The clinical significance of these findings is unclear. There was no imbalance in dementia-related adverse events in PARADIGM-HF, although such events were not specified as adverse events of interest and may have gone unnoticed or underreported. Although the risk of cognitive impairment is uncertain, we do not believe it would be reasonable to delay approval given the magnitude of the benefit observed in PARADIGM-HF.

LCZ696 is considered a fixed-dose combination drug; therefore, according to the Agency's regulations for such products outlined in 21 CFR 300.50, each component must contribute to the effect. As designed, PARADIGM-HF cannot establish the independent contribution of valsartan and sacubitril so it is necessary to consider other available data. Valsartan is known to have efficacy in HFrEF based on the results of the Valsartan Heart Failure Trial (Val-HeFT; Cohn, 2001), which enrolled a population similar to PARADIGM-HF, patients with NYHA class II-IV heart failure and an LVEF <40%. Val-HeFT's primary goal was to examine the effect of valsartan when added to an ACEi so, unlike PARADIGM-HF, 93% of subjects were also taking an ACEi. There were two primary endpoints: all-cause mortality and heart failure morbidity, the latter defined as all-cause mortality, sudden death with resuscitation, hospitalization for heart failure, and the need for intravenous inotropic or vasodilatory drugs for at least four hours. Valsartan did not show a mortality benefit but did reduce heart failure morbidity; however, this

result was largely driven by the 7% of subjects not on an ACEi, the population most similar to PARADIGM-HF. In this subpopulation, valsartan reduced both mortality and heart failure hospitalizations. Enalapril is also known to reduce mortality and heart failure hospitalizations in HFrEF based on the results of the SOLVD-Treatment and CONSENSUS trials (SOLVD Investigators, 1991; CONSENSUS Trial Study Group, 1987). Although no studies have directly compared the efficacy of valsartan and enalapril in HFrEF, ACEi and ARBs are generally regarded as equivalent therapies for heart failure and it seems highly unlikely that valsartan alone would outperform enalapril to the degree shown in PARADIGM-HF. If anything, we might expect enalapril to have greater efficacy since the favorable findings in Val-HeFT were driven by a subgroup of the overall trial population. Therefore, we believe it is likely that sacubitril contributed to the treatment effect. It is also possible that sacubitril alone was responsible for the full benefit of LCZ696 and the valsartan component was unnecessary. However, the applicant notes that treatment with sacubitril alone leads to increases in angiotensin II, which is detrimental in heart failure, and sacubitril should therefore not be administered without concomitant blockade of the renin-angiotensin-aldosterone system. Finally, and perhaps most importantly, LCZ696 demonstrated an effect on mortality even compared with an active control that itself has a mortality benefit. It seems unlikely that additional studies to determine the independent contributions of sacubitril and valsartan would be feasible.

In conclusion, the benefits of LCZ696 outweigh the risks. LCZ696 reduces the risk of cardiovascular death and heart failure hospitalization. We believe the key risks of hypotension, renal impairment, hyperkalemia, and angioedema can be adequately managed through clinical monitoring and dose titration.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

We believe a post marketing study is necessary to better characterize the risk of serious angioedema in the black population treated with LCZ696 in the United States. At the mid-cycle communication, we recommended that the applicant investigate claims and observational databases that might be suitable to evaluate this risk in the post marketing setting. A database should include reliable ascertainment of race and an ability to identify cases of serious angioedema. Alternatively, or in addition, the Agency could conduct such a study.

We do not believe a post marketing study is necessary to characterize the risk of cognitive impairment in the HFrEF population. We note that the applicant is planning to (1) (b) (4) and (2) conduct a stand-alone trial ((b) (4)) in a patient population similar to (b) (4), which will include additional neurocognitive testing. Both may provide further insight into the theoretical risk of amyloid-β deposition in the brain.

2 Introduction and Regulatory Background

Chronic heart failure affects millions of adults in the United States with over 650,000 new cases diagnosed annually. Heart failure due to left ventricular systolic dysfunction, referred to as Heart Failure with reduced Ejection Fraction (HFrEF), accounts for half of these cases with the remainder having a preserved ejection fraction (HFpEF). Despite current pharmacologic and device-based therapies, the morbidity and mortality of heart failure remains high. Heart failure is the primary diagnosis in over one million hospitalizations annually with 25% of patients rehospitalized within one month of discharge (Yancy, 2013). Ultimately, approximately 50% of patients die within five years of diagnosis. Hence, despite current therapy, there remains significant unmet medical need for better treatments for this condition.

2.1 Product Information

LCZ696 is a dual angiotensin receptor neprilysin inhibitor (ARNi). The proposed proprietary name is Entresto. Following oral administration, LCZ696 dissociates into valsartan and the pro-drug sacubitril (AHU377) in a 1:1 molar ratio. The first component, valsartan, is an angiotensin II type 1 (AT_1) receptor antagonist (ARB) approved in 1996. The second component, sacubitril, is rapidly hydrolyzed in vivo to the active neprilysin inhibitor LBQ657. There are no approved neprilysin inhibitors. Sacubitril is a new molecular entity.

The proposed indication is:

(b) (4)

The applicant has proposed a starting dose of 100 mg bid as a film-coated tablet. For patients not taking an ACEi or ARB, the applicant proposes a starting dose of 50 mg bid.
The target dose is 200 mg bid.

2.2 Tables of Currently Available Treatments for Proposed Indications

Approved Therapies
Several pharmacologic agents are approved for the treatment of HFrEF as outlined in Table 1. The basis for approval has most often, but not always, been reductions in mortality and/or hospitalizations. Some agents such as carvedilol are approved for subjects with a reduced ejection fraction following acute myocardial infarction, a slightly different population. Diuretics, including loop diuretics, thiazide and thiazide-like diuretics, and potassium-sparing diuretics are approved to treat volume overload in chronic heart failure.

Table 1: Approved treatments for chronic heart failure

Drug	Heart Failure Indication[1]
Angiotensin Converting Enzyme Inhibitors	
Enalapril	Treatment of symptomatic congestive heart failure, usually in combination with diuretics and digitalis. In these patients, enalapril maleate improves symptoms, increases survival, and decreases the frequency of hospitalization. *Comment: According to the* Clinical Pharmacology: Pharmacodynamics and Clinical Effects *section of the label, survival claim was based on reduced all-cause mortality.*
Lisinopril	Adjunctive therapy in the management of heart failure in patients who are not responding adequately to diuretics and digitalis. *Comment: According to the* Clinical Pharmacology: Pharmacodynamics and Clinical Effects *section of the label, indication was based on improved heart failure signs and symptoms.*
Captopril	Treatment of congestive heart failure usually in combination with diuretics and digitalis. *Comment: According to the* Clinical Pharmacology: Pharmacodynamics, *section of the label, indication was based on reduced all-cause mortality, cardiovascular mortality, and heart failure hospitalizations.*
Fosinopril	Management of heart failure as adjunctive therapy when added to conventional therapy including diuretics with or without digitalis *Comment: According to the* Clinical Pharmacology: Pharmacodynamics and Clinical Effects *section of the label, indication was based on reduced heart failure hospitalizations, signs, and symptoms.*
Quinapril	Management of heart failure as adjunctive therapy when added to conventional therapy including diuretics with or without digitalis. *Comment: According to the* Clinical Pharmacology: Pharmacodynamics and Clinical Effects *section of the label, indication was based on reduced heart failure signs and symptoms.*
Angiotensin Receptor Blockers	
Candesartan	Treatment of heart failure (NYHA class II-IV); ATACAND reduces cardiovascular death and heart failure hospitalization.
Valsartan	Treatment of heart failure (NYHA class II-IV); Diovan significantly reduced hospitalization for heart failure. *Comment: See Section 6 for a discussion of data supporting the efficacy of valsartan.*

Drug	Heart Failure Indication[1]
Beta-blockers	
Carvedilol, Carvedilol CR	To reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of ≤40% (with or without symptomatic heart failure) *Comment: According to Section 14 of the label, the cardiovascular mortality indication was based on an all-cause mortality endpoint where nearly all deaths were cardiovascular.*
Metoprolol succinate extended release	Treatment of stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin…In this population, metoprolol succinate extended-release tablets decreased the rate of mortality plus hospitalization, largely through a reduction in cardiovascular mortality and hospitalizations for heart failure. *Comment: According to Section 14 of the label, the mortality indication was based on an all-cause mortality endpoint.*
Aldosterone Antagonists	
Eplerenone	Improve survival of stable patients with left ventricular systolic dysfunction (ejection fraction ≤40%) and clinical evidence of congestive heart failure after an acute myocardial infarction. *Comment: According to Section 14 of the label, survival claim was based on reduced all-cause mortality.*
Spironolactone	Severe heart failure (NYHA class III-IV): To increase survival, and to reduce the need for hospitalization for heart failure when used in addition to standard therapy. *Comment: According to the Clinical Studies section of the label, survival claim was based on reduced all-cause mortality.*
Other	
Hydralazine and isosorbide dinitrate	Treatment of heart failure as an adjunct therapy to standard therapy in self-identified black patients to improve survival, prolong time to hospitalization for heart failure and to improve patient-reported functional status. *Comment: According to Section 14 of the label, survival claim was based on reduced all-cause mortality.*
Digoxin	Treatment of mild to moderate heart failure in adults. Digoxin increases left ventricular ejection fraction and improves heart failure symptoms as evidenced by improved exercise capacity and decreased heart failure-related hospitalizations and emergency care, while having no effect on mortality.
Ivabradine	Reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

[1]Does not include indications related to asymptomatic left ventricular dysfunction, acute heart failure, or acute myocardial infarction.

Reviewer's comment: Although there are inconsistencies, drugs with favorable effects on an all-cause mortality endpoint are most often indicated to "improve/increase survival" (e.g., enalapril, eplerenone, spironolactone, and hydralazine/isosorbide dinitrate). In contrast, carvedilol is indicated to reduce cardiovascular mortality based on an all-cause mortality endpoint where nearly all deaths were cardiovascular, and metoprolol is indicated to reduce "the rate of mortality." Similarly, there are inconsistencies in referring to heart failure subgroups as "symptomatic" (e.g., enalapril, ivabradine) or NYHA class II-IV (e.g., candesartan, valsartan).

Standard Therapies for Heart Failure
The standard therapy for HFrEF in the United States is an ACEi or an ARB, if ACEi-intolerant, and a beta-blocker. Aldosterone antagonists are generally recommended for patients with an EF ≤35% and persistent symptoms. Hydralazine/isosorbide dinitrate is recommended for self-identified black patients (b) (4). Diuretics and digitalis are added as needed. Ivabradine was approved most recently and is indicated for patients with a heart rate of ≥ 70 beats per minute despite maximally tolerated doses of beta-blockers.

In addition to pharmacotherapy, device treatment of HFrEF includes implantable cardioverter-defibrillators (ICD) and cardiac resynchronization therapy devices (CRT), which are generally recommended in the following groups (Yancy, 2013):

- ICD therapy for primary prevention of sudden cardiac death to reduce mortality in selected patients at least 40 days post-myocardial infarction on guideline-directed medical therapy (GDMT) with a reasonable expectation of meaningful survival for more than one year and:
    - An LVEF of ≤ 30% and NYHA class I symptoms
    - An LVEF of ≤ 35% and NYHA class II or III symptoms
- CRT for patients who have an LVEF of ≤ 35%, sinus rhythm, left bundle-branch block (LBBB) with a QRS duration of ≤ 150 ms, and NYHA class II, III, or ambulatory class IV symptoms on GDMT.

2.3 Availability of Proposed Active Ingredient in the United States

Sacubitril is a new molecular entity and is not marketed in the United States or in other countries. There are no approved neprilysin inhibitors or dual angiotensin receptor neprilysin inhibitors.

Valsartan is currently approved for the following indications (NDAs 20665 and 21283):

- Treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
- Treatment of heart failure (NYHA class II-IV); Diovan significantly reduced hospitalization for heart failure.
- Reduction of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction.

2.4 Important Safety Issues with Consideration to Related Drugs

Angiotensin Receptor Blockers
Angiotensin receptor blocker labels carry a boxed warning for fetal injury or death because of actions on the renin-angiotensin-aldosterone system (RAAS). Additional key safety considerations include hypotension, impaired renal function, and hyperkalemia.

Neprilysin Inhibitors
Omapatrilat is a combined ACEi and neprilysin inhibitor that has been developed for the treatment of hypertension (b) (4) but is not approved in the United States. Based on the omapatrilat experience, a key safety consideration is angioedema.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

There were a number of interactions with the Agency over the course of development; a summary of key regulatory milestones, agreements, and advice is provided in Table 2. (b) (4)

Table 2: Summary of key regulatory milestones, agreements, and advice

Source	Advice from Agency
April 22, 2009 Pre-IND meeting	Sponsor requested meeting to discuss their overall development plan for a heart failure indication. The Division agreed with the sponsor's proposal to perform a pharmacokinetic study in the heart failure population followed by a phase 3 outcome study. *Active Control* Agency agreed that enalapril was a relevant comparator for superiority in an outcome study in heart failure with reduced systolic function. Sponsor proposed enalapril 10 mg bid based on the SOLVD-Treatment trial. Agency recommended titration of subjects to 20 mg bid. *Combination Policy* Agency stated that LCZ696 was considered a combination product for which the contribution of each component to the beneficial effect must be demonstrated and recommended adding a valsartan arm to the study. *Background Therapy* Agency recommended documentation that approved treatments for heart failure are employed at adequate dosages including beta blockers and, for classes III-IV, spironolactone. *Primary Endpoint* Agreement was obtained on the composite primary endpoint of cardiovascular mortality and hospitalization for heart failure. *Safety* Agency stated that the phase 3 trial must include at least 300 African

Source	Advice from Agency
	Americans because of an increased susceptibility to angioedema.
July 16, 2009 Request for Special Protocol Assessment (SPA) - No agreement	*Active Control* Agency stated that the dose of enalapril was inadequate since the labeling directed titration of enalapril to 20 mg bid as tolerated. *Combination Policy* Agency stated that the study needed to assess whether one of the components of the combination product is sufficient for the entirety of the benefit and suggested comparison with valsartan. *Secondary Endpoints* Agency (SEALD) stated that the KCCQ (b) (4) *Inclusion Criteria* Agency indicated that beta blockers should be limited to metoprolol extended release and carvedilol, the agents approved for heart failure.
August 20, 2009 SPA follow-up meeting	*Combination Policy* Agency stated that demonstrating the contribution of each component of LCZ696 would not be necessary if the effect is on non-reversible events (e.g., mortality, myocardial infarction, and stroke). *Endpoints* Regarding renal endpoints, discussed need to identify an unequivocal clinically important effect and to exclude acute hemodynamic effects. Agency indicated that a positive KCCQ finding would be interpreted as indicating a difference in treatment (b) (4)
October 1, 2009 IND application submitted	IND 104628 for LCZ696 was opened in the United States for the treatment of heart failure. IND-opening study was pivotal phase 3 study in patients with heart failure with reduced ejection fraction (PARADIGM-HF).
November 6, 2009 IND advice letter	*Endpoints* Agency (SEALD) (b) (4) recommended development of an instrument that measures the signs and symptoms of heart failure. Regarding renal endpoints, recommended a combined endpoint of doubling of serum creatinine and ESRD.
January 21, 2010 Type C guidance meeting	*Endpoints* Sponsor requested meeting to discuss use of the KCCQ Clinical Summary Score. Agency (SEALD) (b) (4)

Source	Advice from Agency
	(b) (4) *Labeling Claims* Agency noted that an efficacy claim could result if LCZ696 beats an active control (P=0.05) (b) (4)
April 20, 2011 Advice letter	(b) (4)
April 1, 2014	Sponsor notified Agency that the PARADIGM-HF Data Monitoring Committee recommended early closure of the trial for compelling efficacy following a pre-specified interim analysis.
June 13, 2014 Pediatric Study Plan – Initial Agreement	Initial agreement on waiver of pediatric studies of LCZ696 for the treatment of heart failure because the causes and mechanisms of heart failure in children and adults are different.
June 23, 2014	Granted fast track designation and rolling review.
June 25, 2014 Pre-NDA meeting	*Labeling Claims* Agency stated that, provided data are supportive, a suitable indication might read TRADE NAME is indicated to reduce the (b) (4) of cardiovascular death and heart failure hospitalization in patients with reduced ejection fraction heart failure (b) (4) NYHA classes II-IV)" and that any description of the superiority to enalapril is likely to appear in the Clinical Trials section. Although the first protocol amendment (b) (4) if a sizable portion of subjects were enrolled in this subgroup before the amendment and the results for the primary endpoint were generally consistent with the overall population. *Statistical Analysis Plan* Agency agreed that all-cause mortality could be removed from the testing chain in the secondary endpoints prior to database lock. Agency asked sponsor to propose a way to analyze the primary efficacy endpoint by change in systolic blood pressure over the treatment period to help understand whether blood pressure reduction contributed to the efficacy findings.

Source	Advice from Agency
	Safety Agency stated that the sponsor should address the theoretical safety concerns of neurological disease secondary to possible β-amyloid accumulation in CNS tissues.
September 22, 2014 Top-line results meeting	Agency agreed that the content and technical aspects discussed appeared to be adequate to support an NDA filing. *Labeling Claims* Agency indicated that if LCZ696 were to be approved, the design and results of PARADIGM-HF would be described in Section 14; however, the indication statement would not include language regarding superiority to enalapril. Agency stated that the sponsor should include (b) (4) in the application and provide a rationale for the clinical meaningfulness of the effect size. *Safety* Agency indicated that a REMS is unlikely to be necessary. Sponsor proposed a (b) (4) and Agency agreed with the idea. Sponsor proposed to incorporate (b) (4) into the (b) (4) (b) (4) Agency stated that further review and discussion was required.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was well organized and sufficiently complete to support review of the application.

3.2 Compliance with Good Clinical Practices

FDA Inspections
Clinical investigator sites are being inspected to assess the quality, integrity, and acceptability of the data submitted in support of the application and the adequacy of the protection of the rights

and welfare of human research subjects. Four international sites were selected based on a high risk ranking as determined by the GCP Site Selection Tool, primarily because of enrollment of large numbers of study subjects and favorable efficacy findings. The results of these audits are not yet available; however, no single site is driving the efficacy findings and so removal of a single site from efficacy analyses based on inspection findings is unlikely to alter the regulatory outcome.

Audits Conducted by Applicant
During the course of the trial, the applicant employed groups independent of those involved in the conduct, monitoring, and quality control of the trial to perform site audits to assess compliance with global and local regulatory requirements, protocols, and internal standard operating procedures. The audit of site 0096 identified serious GCP violations and the applicant closed this site permanently. During routine monitoring, serious GCP violations were also identified at sites 0030 and 1009. In addition to the applicant's audits, 13 sites were inspected by local health authorities. In Germany, site 2321 was closed after the health authority's inspection identified inconsistencies with signatures on informed consent forms. In total, these four sites enrolled 37 subjects (23, 2, 10, and 2 subjects, respectively). Due to concerns with data integrity, the applicant elected prospectively to exclude all 37 subjects from efficacy analyses but to include them in safety analyses.

Protocol Deviations
A total of 505 (12.0%) LCZ696 subjects and 500 (11.8%) enalapril subjects had one or more protocol deviations. The most common deviations were a lab test performed by the central lab that was not required by the protocol or recommended by the investigator (100 [2.4%] LCZ696, 92 [2.2%] enalapril) and failure to undergo the required washout period between stopping ACEi and starting LCZ696 (99 [2.4%] LCZ696, 88 [2.1%] enalapril). Of note, 36 (0.9%) LCZ696 and 58 (1.4%) enalapril subjects used open-label ACEi or ARBs during the study concomitant with study medication. Four (0.1%) LCZ696 and 2 (0.1%) enalapril subjects were "misrandomized," defined as a patient failing the run-in period for whom IVRS randomization calls were erroneously performed but who never received study medication. These six subjects were prospectively excluded from efficacy analyses.

3.3 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators in PARADIGM-HF. The applicant reported receiving statements from 1,146 of 1,179 (97%) investigators in the United States and 4,157 of 4,174 (99%) non-U.S. investigators. The applicant was unable to obtain financial disclosure information for 50 individuals involved in study conduct. The total number of subjects enrolled at sites where one or more individuals did not complete disclosure forms was 152 (1.8%) of randomized subjects. The submission contains a description of the process used to collect financial disclosure information, and, based on this description, the applicant appears to have acted with due diligence to obtain the required information.

As shown in Table 3, none of the investigators were full or part-time employees of Novartis Pharmaceuticals Corporation. Two investigators reported disclosable financial interests, specifically "significant payments of other sorts" as outlined in Table 4.

Table 3: Clinical investigator financial disclosure information for PARADIGM-HF

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 5,353		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from applicant)

Table 4: Disclosable financial arrangements

Investigator	Center Number	Location	Number of Subjects	Amount Disclosed	Disclosure
Dr. (b) (6)	(b) (6)	(b) (6)	(b) (6)	$100,000	Unrestricted grant to the (b) (6) for nonproprietary clinical research
Dr. (b) (6)	(b) (6)	France	(b) (6)	Over $25,000	Consulting fee

The applicant addressed steps taken to minimize the potential for bias resulting from these interests and arrangements including the design of PARADIGM-HF as a randomized, double-

blind, controlled trial; each individual site contributing a relatively small proportion of subjects to the overall trial population; and independent data monitoring by the applicant.

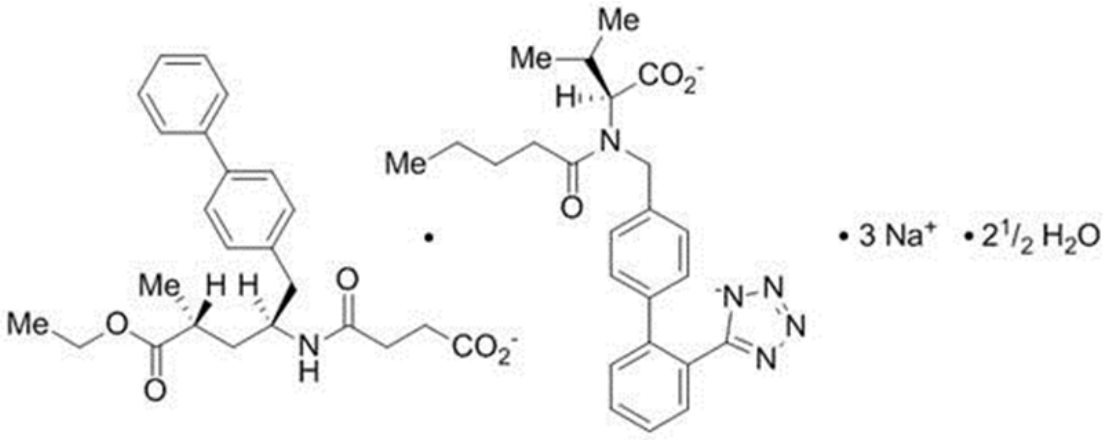
Reviewer's comment: Given the number of subjects enrolled at these sites, it is unlikely that these financial arrangements could have biased the study findings.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

LCZ696 contains the anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5 respectively. Its schematic structural formula is shown in Figure 1.

Figure 1: LCZ696 schematic structural formula



Source: Applicant's proposed labeling.

The applicant has proposed to manufacture film-coated tablet strengths of 50, 100, and 200 mg [redacted] (b) (4). The Agency, however, considers valsartan and sacubitril to be the drug substances and the [redacted] co-crystal the drug product. As the drug product is considered a fixed-dose combination, the applicant was advised to label the drug product strength based on the fixed dose combination with the free acid/base of both drug substances as the basis for strength expression. A revised proposal is pending.

The CMC review is not yet complete. To date, no other significant issues have been identified that would affect the clinical interpretation of the safety or efficacy data.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

This section provides a brief summary of key findings from the applicant's preclinical evaluation of LCZ696. Please refer to Dr. William Link's pharmacology/toxicology review for details.

4.3.1 Preclinical Pharmacology

LCZ696 comprises sacubitril (AHU377, a new-molecular entity) and valsartan. Following oral administration, LCZ696 dissociates into valsartan and the pro-drug AHU377, which is further metabolized to the NEP inhibitor LBQ657.

The primary and secondary pharmacology studies demonstrated that LCZ696 had cardiac, renal, and vascular protective effects and effectively reduces arterial pressure in multiple animal models of hypertension. In addition, no meaningful effects of AHU377, LBQ657 and valsartan were observed on a broad range of receptors, transporters, enzymes and ion channels. LCZ696 is not considered to pose a risk to cardiovascular, respiratory, or neuro-behavioral system in safety pharmacology studies in various species of animals at the highest doses tested (100-2000 mg/kg/day).

The applicant also conducted additional studies assessing angioedema risk with AHU377 and valsartan using rat models of bradykinin (BK) activity. Neither the individual treatment of AHU377 or valsartan nor their combined use potentiated BK actions. In contrast, the comparator ACEi (enalapril) and omapatrilat potentiated the BK response in the rate models.

4.3.2 Preclinical Toxicology

The toxicity profile of LCZ696 has been characterized through a combined program of studies performed with LCZ696, studies with sacubitril (AHU377) and studies supporting the original marketing application for valsartan. The main toxicity issues from these studies are described below:

<u>Reproductive toxicity findings</u>
LCZ696 and AHU377 had no effect on fertility in rats. LCZ696 is teratogenic in rabbits and is associated with increased embryo-fetal toxicity including hydrocephaly and embryo-fetal lethality; the latter was also confirmed in rats. The adverse embryo-fetal effects of LCZ696 are attributed to valsartan. There was no pre and post natal development studies performed with LCZ696. However, pup development and survival were reduced in pre-and post natal development studies with valsartan in rats.

Reviewer's comment: Based on reproductive toxicity data and toxicity for agents that act directly on RAAS, LCZ696 presents a potential risk of fetal harm during pregnancy in humans. LCZ696 should be contraindicated in pregnancy. The proposed warning for fetal toxicity, similar to valsartan labeling, is adequate.

Renal findings
Renal effects (juxtaglomerular hypertrophy/hyperplasia) were observed in all toxicology studies in monkey at various doses and in a 2-weel toxicology study in rat at doses ≥ 200 mg/kg. Juxtaglomerular hypertrophy was not observed in the studies with AGU377 alone. These findings are attributed to the pharmacology of valsartan and subsequent increases in renin production.

β-amyloid findings in Cerebrospinal Fluid
The theoretical risk of β-amyloid accumulation in the CNS was studied in cynomolgus monkeys receiving 50 mg/kg/day of LCZ696 for 2 weeks. In this study, there were increases in cerebrospinal fluid (CSF) β-amyloid 1-38 1-40 and 1-42; there were no corresponding elevations in β-amyloid levels in brain (Table 5).

Table 5: Increases in CSF β-amyloid levels in monkeys receiving 50 mg/kg/day of LCZ696

	β-amyloid 1-42	β-amyloid 1-40	Total β-amyloid[a]	β-amyloid 1-38[a]
Day 1	20.4%			
Day 15	34.7%[b]	23.4%[b]	50.45%	64%

[a] newly synthesized
[b] increases in plasma were also observed
Reviewer's table, Source: Dr.Link's review/mid-cycle slide

Gastric findings
Gastrointestinal effects with LCZ696 in the repeat-dose toxicity studies were characterized by microscopic focal erosion and inflammation of stomach in rat and mouse. Table 6 shows the threshold dose where these findings were observed. No lesions were observed in monkey in studies with a duration of 2, 13, and 39 weeks or in marmosets in a 52-week study.

Table 6: Threshold dose (mg/kg/day) where gastric lesions were observed in rat and mouse

Duration (weeks)	LCZ696	AHU377
2	rat: 200, mouse:200	No findings
13	rat: 100, mouse 50	No findings
26	rat: 100	No findings

Reviewer's table, Source: Dr.Link's review/mid-cycle slide

Reviewer's Comments: Although the applicant stated in their toxicology summary report that gastritis was attributed primarily to local irritant effects of orally administered AHU377, Dr. Link concluded that the pre-clinical data suggest valsartan is required for the gastrointestinal effect but do not rule out a possible synergistic effect of AHU377. Gastric effects in rats are (b) (4) *than what was studied with LCZ696.*

Genotoxicity and carcinogenicity
The carcinogenic studies (2 year studies at Carcinogenicity Assessment Committee-approved doses) in mice and rats showed no evidence of any carcinogenic potential with AHU377 and valsartan. Mutagenicity and clastogenicity studies conducted with LCZ696, AHU377, and valsartan did not reveal any genotoxic.

Juveniles
The applicant studied the effect of AHU377 in neonatal and juvenile rats to address the theoretical risk of neprilysin inhibition leading to skeletal overgrowth and malformed bones. Slightly decreases in bone length and decreases in bone mass were observed in these studies. These adverse events were most apparent in neonatal rats (corresponding to ~2 years of age in human) and were not observed in an adult rat study.

4.4 Clinical Pharmacology

The Office of Clinical Pharmacology has reviewed the clinical pharmacology and biopharmaceutics information. The clinical pharmacology review is not yet complete. To date, no significant issues have been identified that would affect the clinical interpretation of the safety or efficacy data. Clinical pharmacology attributes pertinent to the current application are highlighted below. For a discussion of the rationale supporting dose selection, see Section 6.1.8.

4.4.1 Mechanism of Action

Following oral administration, the LCZ696 co-crystal dissociates into valsartan and the pro-drug sacubitril (AHU377). Valsartan is an angiotensin II type 1 (AT_1) receptor antagonist that inhibits the action of angiotensin II and angiotensin II-dependent aldosterone release. Sacubitril is metabolized by esterases to form the active neprilysin inhibitor LBQ657. The effects of sacubitril in heart failure are believed to be mediated through increases in peptides normally degraded by neprilysin such as natriuretic peptides. Natriuretic peptides activate membrane-bound guanylyl cyclase-coupled receptors, resulting in increased concentrations of the second messenger cyclic guanosine monophosphate (cGMP), thereby promoting vasodilation, natriuresis and diuresis, increased glomerular filtration rate and renal blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity, and anti-hypertrophic and anti-fibrotic effects.

4.4.2 Pharmacodynamics

LCZ696 subjects had increases in cGMP levels (LCZ696A2102), presumably mediated through neprilysin inhibition, and decreased aldosterone levels, presumably mediated through inhibition of the AT_1 receptor. LCZ696 was associated with reduced blood pressure (see Section 7.4.3).
(b) (4)

4.4.3 Pharmacokinetics

The oral absolute bioavailability of sacubitril is at least 60%. The bioavailability of valsartan from LCZ696 is at least 50% higher than valsartan administered alone so the valsartan in 400 mg LCZ696 (203 mg valsartan) is equivalent to 320mg of valsartan alone.

Sacubitril is converted to LBQ657 by plasma esterases; LBQ657 is not further metabolized into any major metabolites. In a mass balance study, 52-68% of sacubitril, primarily as LBQ657, is

excreted in the urine and 37-47% in the feces. Approximately 20% of the valsartan dose is recovered as metabolites with approximately 13% of valsartan and its metabolites excreted in urine and 86% in feces. The mean elimination half-life was 1.4 hours, 11.5 hours, and 9.9 hours for sacubitril, LBQ657, and valsartan, respectively. The LCZ696 components are highly protein bound at 97% for sacubitril and LBQ657 and 94% for valsartan.

Exposures to LBQ657 increased by 2X and 2.7X in subjects with mild/moderate renal impairment (Creatinine clearance 30 to 80 mL/min) and severe renal impairment (Creatinine clearance <30 mL/min), respectively. Exposures to valsartan and sacubitril were not significantly altered. Based on the clinical experience in PARADIGM-HF, clinical pharmacology does not recommend dose adjustment for subjects with mild/moderate renal impairment. Patients with severe renal impairment were excluded from PARADIGM-HF. Based on the expected increase in exposure, clinical pharmacology is recommending a starting dose of 50 mg bid in these patients.

In subjects with mild hepatic impairment (Child-Pugh Class A), exposure to sacubitril, LBQ657 and valsartan increased by approximately 53, 48, and 19%, respectively. With moderate hepatic impairment (Child-Pugh Class B), exposure to sacubitril, LBQ657 and valsartan increased by approximately 245, 90 and 109%, respectively. As a result, clinical pharmacology recommends a starting dose of 50 mg bid in patients with moderate hepatic impairment. No studies were conducted in subjects with severe hepatic impairment (Child-Pugh Class C).

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

In support of the proposed indication, the applicant conducted PARADIGM-HF (CLCZ696B2314), a phase 3, randomized, double-blind, active-controlled trial. PARADIGM-HF is described in detail in Section 5.3. The applicant also conducted TITRATION (CLCZ696B2228), a randomized, double-blind comparison of two different upward dose titration regimens. TITRATION is described in Section 6.1.8. In total, the applicant conducted an additional 30 phase 1 and 2 clinical pharmacology studies to evaluate the pharmacokinetics and pharmacodynamics of LCZ696 including studies of subjects with renal or hepatic impairment, drug-drug interaction studies, a food effect study, a thorough QTc study, and a study of cerebrospinal fluid amyloid-β concentrations in healthy subjects. See Section 4.4 and the clinical pharmacology review by Drs. Sreedharan Sabarinath and Luning Zhuang for additional detail regarding the phase 1 and 2 clinical pharmacology studies. See Section 7 for an overview of the studies submitted in support of safety.

5.2 Review Strategy

This was a joint review. Dr. Smith focused on the data supporting efficacy and Dr. McDowell focused on the data supporting safety.

5.3 Discussion of Individual Studies/Clinical Trials

In support of the proposed indication, the applicant submitted the results of a single phase 3 trial (CLCZ696B2314) titled "A multicenter, randomized, double-blind, double-dummy, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure and reduced ejection fraction" referred to as PARADIGM-HF. The trial was conducted at 984 sites in 47 countries worldwide.

Initial Protocol and Amendments
The original protocol was issued on September 10, 2009 and was amended four times on December 15, 2010, June 14, 2011, March 7, 2013, and March 26, 2014. The overview provided in this section is based on the original protocol with amendments as noted.

Important Trial Dates
The trial was initiated on December 8, 2009 (first patient first visit) and was terminated early on March 31, 2014 for efficacy. This decision was based on a March 28, 2014 recommendation of the trial's independent data monitoring committee following their review of the third pre-specified interim analysis. March 31, 2014, the study termination date, was used as the cut-off date for efficacy analyses. The last patient visit occurred on May 21, 2014. Database lock and unblinding of the trial occurred sequentially on July 18, 2014.

Trial Administrative Structure
Executive Committee:
An Executive Committee participated in the trial's design and conduct and regularly met with the applicant. The applicant submitted minutes for meetings of the Executive Committee.

Reviewer's comment: Executive Committee deliberations pertaining to trial design and protocol amendments are discussed in the relevant sections of this review. The meeting minutes did not raise any additional concerns regarding trial conduct.

Data Monitoring Committee:
An independent Data Monitoring Committee (DMC) regularly reviewed accumulating study data and the results of pre-specified interim analyses. The committee membership and responsibilities were defined by a written charter and included cardiology, nephrology, and statistical expertise. The applicant submitted minutes for meetings of the DMC.

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

Independent Statistician and Programmer:
An external independent statistician and programmer performed analyses and generated reports for the DMC according to a pre-specified analysis plan.

Clinical Endpoint Committee:
An independent Clinical Endpoint Committee (CEC) received reports of all potential endpoint events occurring on or before the study termination date of March 31, 2014. The CEC classified the cause of all deaths and determined whether pre-specified endpoint criteria were met for

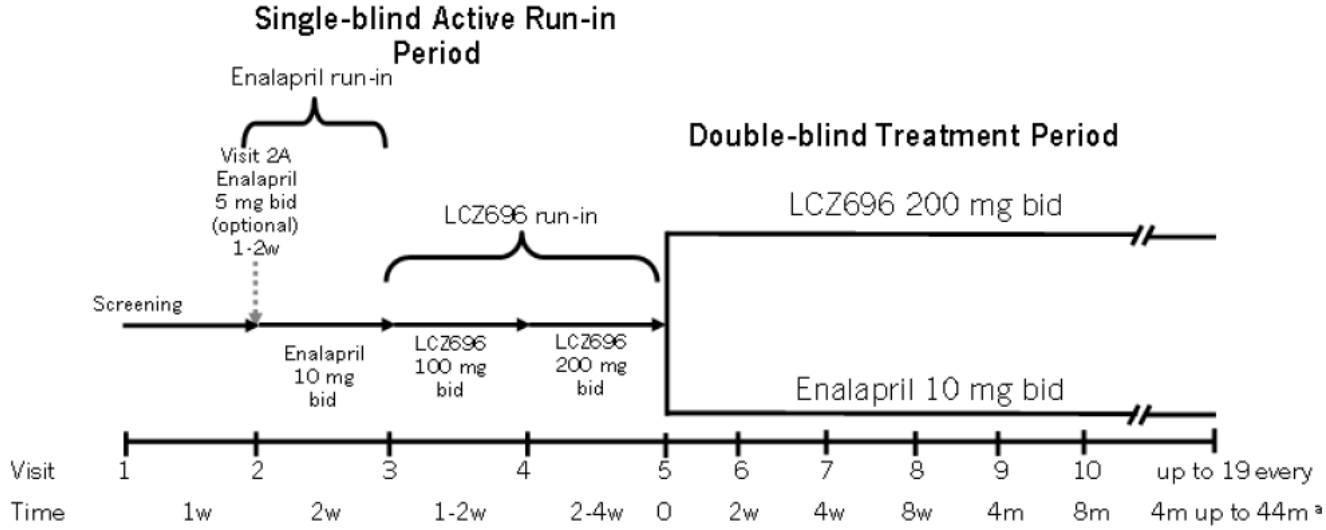
non-fatal events. Potential endpoint events were each assigned to two reviewers for adjudication and discordant decisions were presented to the CEC with the final decision made by the Chairman and/or Co-Chairman. The committee was governed by a Clinical Endpoint Committee Manual of Operations first issued December 9, 2009 with one revision dated July 1, 2011.

Angioedema Adjudication Committee:
An independent Angioedema Adjudication Committee (AAC) adjudicated all potential angioedema events and determined the severity as specified in an Angioedema Adjudication Manual. The first manual version was issued April 24, 2009 and was modified five times on October 1, 2009, December 7, 2009, August 17, 2010, August 31, 2010, and June 6, 2014. The applicant submitted minutes for meetings of the AAC.

Reviewer's comment: AAC deliberations are discussed in Section 7.3.5.1.

Study Design
PARADIGM-HF was a randomized, double-blind, double-dummy, parallel group, active-controlled trial comparing LCZ696 with enalapril in patients with chronic heart failure (NYHA class II-IV) and a reduced ejection (LVEF ≤ 40%; changed to ≤ 35% per Protocol Amendment 1). An overview of the study design is shown in Figure 2.

Figure 2: PARADIGM-HF study design



Source: Applicant, PARADIGM-HF Clinical Study Report, Figure 9-1.

Run-in Periods:
Subjects first entered sequential single-blind enalapril and LCZ696 run-in periods lasting six to ten weeks total. All subjects started with enalapril 10 mg bid or, at the investigator's discretion, enalapril 5 mg bid for subjects treated with an ARB or lower dose ACEi at screening. After one to two weeks, subjects initially started on enalapril 5 mg bid were increased to 10 mg bid. Subjects tolerating enalapril 10 mg bid for two weeks were then eligible for the LCZ696 run-in period starting with LCZ696 100 mg bid. Subjects continued on this dose for one to two weeks

at the investigator's discretion. Subjects tolerating 100mg bid were then titrated to 200 mg bid for two to four weeks, again at the investigator's discretion. Subjects tolerating LCZ696 200 mg bid for at least two weeks were eligible for randomization. Each drug and dose had a different size, shape, and color so, during the single-blind run-in period, subjects took both an active treatment tablet and a placebo tablet matching the opposite treatment twice daily.

Subjects had to meet all eligibility criteria (see below) at each decision point (i.e., before the enalapril run-in, before the LCZ696 run-in, and before randomization). If necessary, investigators could reduce or discontinue concomitant medications during the run-in period in response to adverse events (e.g., hyperkalemia, hypotension, or renal dysfunction) to facilitate meeting eligibility criteria (Protocol Amendment 1). This included disease-modifying drugs such as beta-blockers, aldosterone antagonists, or hydralazine/isosorbide dinitrate, if, in the opinion of the investigator, they were believed to be the cause of the adverse event.

Between the enalapril and LCZ696 run-in periods and before starting randomized study drug, subjects underwent a wash-out period of approximately 36 hours to minimize the potential risk of angioedema with overlapping ACE and neprilysin inhibition.

Randomized Double-blind Period:
Following successful completion of the run-in period, eligible subjects were randomized 1:1 to LCZ696 200 mg bid or enalapril 10 mg bid.

Schedule of Study Procedures (see Section 7.2 for safety assessments)
During the first four months of the double-blind treatment period, subjects were to return to the study site every two to eight weeks. After the first four months, visits were to be scheduled every four months. In addition, subjects could be seen anytime throughout the study at the discretion of the investigator to follow-up laboratory abnormalities or adverse events. All subjects including those who discontinued study medication prematurely were expected to attend visits until study termination. Subjects unwilling or unable to attend visits were contacted by phone to assess endpoints.

Complete laboratory assessments (serum chemistry, hematology, and urine parameters) and 12-lead ECGs were performed at randomization, months 12, 24, and 36, and at the end of the study. Serum chemistries and liver tests were performed at the end of the enalapril run-in period and at two and four months into the double-blind treatment period (Protocol Amendment 2). Potassium, BUN, and creatinine were measured at all visits. The Kansas City Cardiomyopathy Questionnaire (KCCQ) and EuroQol-5D (EQ-5D) questionnaires were administered at the start of the double-blind treatment period, at months 4, 8, 12, 24, and 36, and at the end of the study. According to the original protocol, patients without a valid translation of the KCCQ available in their language were exempt from completing the instrument.

Study Objectives
The primary objective was to test if LCZ696 is superior to enalapril in delaying the time to first occurrence of the composite endpoint of cardiovascular death or heart failure hospitalization.

The secondary study objectives were to test whether LCZ696:

- Is superior to enalapril in delaying the time to all-cause mortality;
- Improves the clinical summary score for heart failure symptoms and physical limitations, as assessed by the KCCQ at 8 months, compared to enalapril;
- Is superior to enalapril in delaying time to new onset atrial fibrillation (Protocol Amendment 3); and
- Is superior to enalapril in delaying the time to first occurrence of either:
  (1) A 50% decline in estimated glomerular filtration rate (eGFR) relative to baseline;
  (2) A >30 mL/min/1.73 m^2 decline in eGFR relative to baseline to a value below 60 mL/min/1.73 m^2 (Protocol Amendment 1); or
  (3) End stage renal disease (ESRD).

Study Population

Key Inclusion Criteria:

1. Aged ≥ 18 years.
2. Chronic heart failure (NYHA class II-IV) with an LVEF ≤ 40% (changed to ≤35% per Protocol Amendment 1).
3. B-type natriuretic peptide (BNP) ≥ 150 pg/ml (N-terminal prohormone B-type natriuretic peptide [NT-proBNP] ≥ 600 pg/ml) **or** BNP ≥ 100 pg/mL (NT-proBNP ≥ 400 pg/ml) and a hospitalization for heart failure within the last 12 months.
4. On an ACEi or ARB at a stable dose of at least 10 mg/day of enalapril or a protocol-defined equivalent agent for at least four weeks before screening.
5. On a beta-blocker, unless contraindicated or not tolerated, at a stable dose for at least four weeks before screening (reason should be documented for patients not on target doses for heart failure per local guidelines).
6. An aldosterone antagonist should be considered in all patients taking into account renal function, serum potassium, and tolerability (Protocol Amendment 1). If given, subjects must be on a stable dose for at least four weeks before screening.
7. Other therapy should be considered for selected patients per guideline recommendations including implantation of cardiac resynchronization therapy (CRT) and/or implantable cardioverter defibrillator (ICD) devices (Protocol Amendment 1).

Reviewer's comment: Although subjects were expected to be on a beta-blocker, unless contraindicated or not tolerated, specific agents and doses were not specified.

Key Exclusion Criteria:

1. A history of hypersensitivity or allergy to study drugs or drugs of similar chemical classes.
2. Previous intolerance to recommended target doses of ACEi or ARB.
3. History of angioedema.
4. Current acute decompensated heart failure.
5. Symptomatic hypotension and/or a systolic blood pressure of <100 mmHg at screening or <95 mmHg during run-in.
6. Estimated GFR <30 mL/min/1.73 m^2 (MDRD) at screening or during run-in or >25% decline in eGFR (changed to >35% by Protocol Amendment 1) between screening visit and end of enalapril or end of LCZ696 run-in periods.
7. Serum potassium >5.2 mmol/L at screening or >5.4 mmol/L during the run-in period.

8. Acute coronary syndrome, stroke, transient ischemic attack, cardiac/carotid/major cardiovascular surgery, percutaneous coronary intervention, or carotid angioplasty within three months before screening.
9. Coronary or carotid artery disease likely to require intervention within six months after screening.
10. Implantation of CRT pacemaker or CRT defibrillator within three months before screening or intent to implant.
11. Implantation of conventional pacemaker or ICD or revision of device leads within one month of screening.
12. Heart transplant or on transplant list.
13. Ventricular assist device or intent to implant.
14. History of severe pulmonary disease.
15. Diagnosis of peripartum or chemotherapy-induced cardiomyopathy within twelve months of screening.
16. Untreated ventricular arrhythmia with syncopal episodes within three months of screening.
17. Symptomatic bradycardia or second or third degree heart block without a pacemaker.
18. Hemodynamically significant mitral and/or aortic valve disease or obstructive lesions of left ventricular outflow tract (e.g., aortic and sub-aortic stenosis) except mitral regurgitation secondary to left ventricular dilatation.
19. Bilateral renal artery stenosis (Protocol Amendment 1).
20. Presence of any other disease with an anticipated life expectancy of < 5 years.

In addition to the listed criteria, patients were excluded for surgical or medical conditions that might significantly alter the absorption, distribution, metabolism, or excretion of study drug including active inflammatory bowel disease during the twelve months before screening; duodenal or gastric ulcers during the three months before screening; evidence of hepatic disease with an AST or ALT > 2x upper limit of normal (ULN) at screening or a history of hepatic encephalopathy, esophageal varices, or portacaval shunt; and treatment with cholestyramine or colestipol resins (Protocol Amendment 1). Finally, the protocol excluded pregnant or nursing (lactating) women and women of child-bearing potential unless they agreed to use two methods of contraception.

Patients who failed the initial screening or run-in period were eligible for rescreening a maximum of two times at a minimum of two weeks apart, for patients never exposed to study medication, or four weeks apart, for patients exposed to study medication during the run-in period (Protocol Amendment 2).

Study Procedures

Randomization:

Randomization occurred via an interactive voice response system (IVRS) or web-based system that had the same functionalities as the IVRS. A randomization list was produced by the IVRS provider using a system that automated the random assignment of patient numbers to randomization numbers. These randomization numbers were linked to the two treatment arms, which in turn were linked to medication numbers. Randomization was stratified by site only.

Trial treatments:

Dose titration: Subjects who successfully completed the run-in period were randomized and started on the target dose of enalapril 10 mg bid or LCZ696 200 mg bid. LCZ696 was available in tablet strengths of 50, 100, and 200 mg and enalapril was available in tablet strengths of 2.5, 5, and 10 mg. This allowed for titration of doses at the investigator's discretion based on safety and tolerability. Investigators were provided the following instructions for dose titration:

- The investigator should first consider whether non-disease modifying medications (e.g., calcium channel blockers, nitrates, or alpha-blockers) could be reduced to rectify the situation.
- If this is insufficient, the investigator should consider whether disease-modifying drugs (e.g., beta-blockers, aldosterone antagonists, or hydralazine/isosorbide dinitrate) could be adjusted if it is believed they are the most likely cause of the adverse effect (Protocol Amendment 1).
- If this does not alleviate the concern, study drug could be down-titrated to the next lower level for one to four weeks or, if needed, to lower levels or stopped.
- After tolerating a reduced level for one to four weeks, the patient could be re-challenged with the next higher dose at the investigator's discretion.
- Study drug should be reintroduced for subjects who temporarily discontinue therapy as soon as medically justified in the opinion of the investigator.

Reviewer's comment: The 50 mg dose of LCZ696 was not available for upward dose titration during the LCZ696 run-in period. It was only available to investigators for downward dose titration during the double-blind treatment period.

If down titration was required, the investigator indicated this when calling the IVRS to obtain subsequent supplies of study drug. They entered the dose level to dispense: level 1 - LCZ696 50 mg or enalapril 2.5 mg bid; level 2 - LCZ696 100 mg or enalapril 5 mg bid; level 3 - LCZ696 200 mg or enalapril 10 mg bid; or no study drug in the case of study drug withdrawal. Investigators were to keep the patient on the highest dose of study drug possible for as long as possible. All randomized subjects were to continue to receive double-blind treatment, including subjects experiencing health events, until the trial was terminated.

At the time of study drug discontinuation, either prematurely during the double-blind period or at the end of study visit, investigators were told that subjects must have a 36-hour study drug-free period before starting an open-label ACEi. Similarly, a 36-hour washout was required for subjects discontinuing open-label ACEi and restarting study drug.

Compliance: Investigators assessed compliance at each visit using history and pill counts. Subjects with compliance below 80% received counseling.

Concomitant medications: In self-identified black subjects, the use of hydralazine/isosorbide dinitrate was "to be considered." Diuretics could be started or adjusted throughout the study as needed.

Subjects were prohibited from taking an open-label ACEi, ARB, or renin inhibitor while receiving study medication. Bile acid sequestering agents were prohibited to avoid interference with drug absorption (Protocol Amendment 1). Investigators were instructed to use potassium-sparing

diuretics, potassium supplements, aldosterone antagonists, or other medications known to raise potassium levels "with caution" and were encouraged to regularly assess potassium levels in subjects receiving these medications. Investigators were instructed to use phosphodiesterase-5 inhibitors "with caution" because of the possibility of hypotension (Protocol Amendment 1). Finally, investigators were instructed to start nesiritide and intravenous nitrates at lower doses and to monitor blood pressure carefully (Protocol Amendment 1).

Blinding:
The study was designed to be double-dummy with subjects taking their assigned active treatment tablet and a placebo tablet matching the opposite treatment twice daily.

Reviewer's comment: The applicant submitted samples of each tablet and matching placebo and they are identical in packaging, labeling, and appearance.

Semi-blinded data (e.g., Treatment 1 and Treatment 2) were available only to the DMC and the independent statisticians and programmers performing analyses for the DMC. The study bioanalytical monitor and bioanalyst at the bioanalytical site were unblinded to facilitate pharmacokinetic analysis (Protocol Amendment 2).

Reviewer's comment: Although the DMC was initially semi-blinded, they voted to fully unblind the data at their August 2, 2010 meeting because of imbalances in safety parameters. The unblinded data favored LCZ696 and the study was allowed to proceed.

Endpoints
Primary Endpoint:
The primary endpoint was the time to first occurrence of a composite endpoint of cardiovascular death or heart failure hospitalization.

Secondary Endpoints:
The secondary endpoints were:

- Time from randomization to all-cause death;
- Change from baseline (randomization visit) in the clinical summary score for heart failure symptoms and physical limitations (as assessed by KCCQ) at 8 months;
- Time from randomization to new onset of atrial fibrillation (Protocol Amendment 3);
- Time from randomization to first occurrence of:
    - A 50% decline in eGFR relative to baseline;
    - A >30 mL/min/1.73 m^2 decline in eGFR relative to baseline to a value below 60 mL/min/1.73 m^2; or
    - ESRD.

Identification of Potential Endpoint Events:
Potential endpoint events were reported by investigators at the study sites. Renal events involving decreases in eGFR relative to baseline were to be confirmed by two central laboratory values at least 30 days apart. Additional events could be identified during the adjudication process by the individuals preparing the adjudication packages or the adjudicators. In addition, the Novartis study team regularly reviewed reported SAEs and patient retention data and could call events to the attention of the investigator for reporting, if appropriate. Finally, the Novartis

study team reviewed all central laboratory eGFR values to flag drops in eGFR relative to baseline.

Adjudication of Potential Endpoint Events:
The CEC adjudicated all reported deaths, unplanned hospitalizations for heart failure, non-fatal myocardial infarctions/unplanned hospitalizations for myocardial ischemia, non-fatal strokes, resuscitated sudden deaths, new onset atrial fibrillation, new onset diabetes mellitus, ESRD, and worsening renal function events occurring during the run-in and randomized periods. A Clinical Endpoint Committee Manual of Operations specified the adjudication criteria for primary and secondary endpoint events as follows:

Death:
Cardiovascular death included death categorized as one of the following:

1. *Fatal myocardial infarction* for one of the following scenarios:
    a. Occurred within 14 days of a documented myocardial infarction with no conclusive evidence of another cause of death.
    b. Autopsy evidence showed a recent infarct with no other conclusive cause of death.
    c. Abrupt death with characteristics of acute infarct:
        i. Acute ischemic symptoms
        ii. AND one of following:
            1. ECG changes indicative of acute injury
            2. Abnormal cardiac biomarkers
            3. Evidence of new ventricular wall motion abnormality
2. *Pump failure* if death occurred:
    a. In the context of clinically worsening symptoms and/or signs of heart failure without another cause of death.
    b. As a complication of ventricular assist device placement, cardiac transplant, or other surgery for refractory heart failure.
    c. After referral to hospice for progressive heart failure.
3. *Sudden death* if death occurred suddenly in an otherwise stable subject and the subject was last seen alive <24 hours before.
4. *Presumed sudden death* if death occurred suddenly in an otherwise stable subject and the subject was last seen alive ≥ 24 hours before.
5. *Presumed cardiovascular death* if death was likely from a cardiovascular cause in which the data were insufficient to support a more specific cause.
6. *Fatal stroke* if death occurred as a result of a documented stroke.
7. *Fatal pulmonary embolism* if death occurred as a direct result of a documented pulmonary embolism.
8. *Procedure-related death* if death occurred during a cardiovascular procedure or from procedural complications, usually within 14 days.
9. *Other* if death resulted from another specific cardiovascular cause.

Non-cardiovascular death included deaths with an unequivocal and documented non-cardiovascular cause. Non-cardiovascular deaths were further classified as infection, malignancy, pulmonary, gastrointestinal, renal, accidental, suicide, or other.

Unknown death included deaths for which insufficient data were available to make a reasonable differentiation between cardiovascular and non-cardiovascular causes.

Hospitalization for Heart Failure:
A hospitalization for heart failure event required presentation to an acute care facility (i.e., hospital, emergency room, or observation unit) with a change in calendar day from presentation to discharge for an exacerbation of heart failure meeting the following criteria:

1. *Symptoms and signs of heart failure*
    a. One or more symptoms:
        i. Worsening dyspnea
        ii. Worsening orthopnea
        iii. Paroxysmal nocturnal dyspnea
        iv. Increasing fatigue/worsening exercise tolerance
        v. Worsening edema/anasarca.

    AND

    b. Two or more signs:
        i. Rapid weight gain
        ii. Pulmonary edema or rales
        iii. Elevated jugular venous pressure
        iv. Radiologic signs of heart failure
        v. Peripheral edema
        vi. Increasing abdominal distension or ascites
        vii. S_3 gallop
        viii. Hepatojugular reflux
        ix. Elevated BNP or NT pro-BNP above most recent baseline

AND

2. *Treatment*
    Initiation or intensification (doubling) of oral diuretics or treatment with intravenous diuretics, intravenous vasodilators, intravenous inotropes, mechanical fluid removal (e.g., ultrafiltration or dialysis), or insertion of an intra-aortic balloon pump.

New Onset Atrial Fibrillation:
New onset atrial fibrillation was defined as atrial fibrillation identified on a 12-lead electrocardiogram in a subject not previously known to have atrial fibrillation.

Renal Composite Endpoint:

1. *End Stage Renal Disease* was defined as meeting one of the following:
    a. Initiation of dialysis (e.g., hemodialysis, peritoneal dialysis, or continuous veno-venous hemodialysis) continuing for ≥ 30 days.
    b. Initiation of dialysis with death before 30 days.
    c. Kidney transplantation.
    d. A physician recommendation for renal replacement therapy (dialysis and/or transplant) with subject refusal of therapy.
2. *Worsening renal function* was defined as meeting one of the following criteria as determined by two post-baseline central laboratory measurements separated by ≥30 days:
    a. A 50% reduction in eGFR.
    b. A 30 mL/min/1.73m^2 reduction in eGFR to a value <60 mL/min/1.73m^2.

Protocol Amendments
An overview of the four amendments to the protocol is shown in Table 7. The amendments were issued after accrual of 39 (1.9%), 177 (8.7%), 1302 (64.1%), and 2024 (99.7%) of 2031 total primary endpoint events.

Table 7: Overview of protocol amendments

Amendment # and Date	Summary of Changes
#1 December 15, 2010	*Entry Criteria* • Reduced the LVEF inclusion criterion from ≤ 40% to ≤ 35%. • Added inclusion criteria instructing investigators to consider the use of mineralocorticoid receptor antagonists and other evidence-based therapies for heart failure (e.g., CRT or ICD placement). • Excluded patients with bilateral renal artery stenosis. • Allowed patients with a reduction in eGFR of ≤ 35% rather than 25% to continue the run-in period. *Concomitant Medications* • Allowed for reduction in the dose of disease-modifying drugs such as beta-blockers or aldosterone antagonists during the run-in and double-blind periods to facilitate maintenance of study drug if, in the investigator's opinion, they were believed to be the cause of an observed adverse effect. • Prohibited concomitant administration of renin inhibitors to reduce risk of hyperkalemia and bile acid sequestering agents to avoid decreased absorption of study drug. • Cautioned against concomitant administration of phosphodiesterase-5 inhibitors, nesiritide, and intravenous nitrates to reduce the risk of hypotension. *Efficacy Analyses* • Modified the renal composite endpoint component of a >30 mL/min/1.73m^2 decline in eGFR to include "to a value below 60 mL/min/1.73m^2." • Added a third interim efficacy analysis at half of primary events and changed from Fleming-O'Brien to Peto-Peto boundaries for early trial termination. • Excluded subjects who were "misrandomized" from efficacy analyses, meaning subjects who had failed the run-in period, were mistakenly randomized, and did not receive study drug. *Unblinding Adverse Events* • Modified instructions for the unblinding of SUSARs to avoid unblinding efficacy endpoint events.
#2 June 14, 2011	• Changed from an abbreviated chemistry panel to a complete serum chemistry panel including liver tests at the end of the enalapril run-in period and two and four months into the double-blind treatment period. • Required fractionated bilirubin measurement for total bilirubin value >2x ULN. • Stated that appropriate follow-up of adverse events and laboratory

Amendment # and Date	Summary of Changes
	abnormalities may require additional testing as determined by the investigator or the study's medical monitor. • Modified follow-up procedures during the double-blind period to reduce loss to follow-up by instructing investigators to maintain regular phone contact according to the visit schedule for patients unable to attend study visits. Stated that data could also be obtained from health care providers, public or medical records, or other sources. • Specified that a patient could be rescreened twice at a minimum of two weeks apart for patients never exposed to study medication or four weeks apart for patients exposed to run-in study medication. • Stated that a bioanalytical monitor and bioanalyst at the bioanalytical site would be unblinded to facilitate PK analysis.
#3 March 7, 2013	• Elevated the exploratory objective of new onset atrial fibrillation to a secondary objective based on results from the PARAMOUNT study (CLCZ696B2214) in patients with HFpEF.
#4 March 26, 2014	• In Czech Republic only, implemented procedures requested by the health authority to evaluate cognitive function every six months during study and for one year after discontinuation of study drug.

Reviewer's comment: According to the Executive Committee meeting minutes, the applicant provided two main reasons for reducing the LVEF entry criterion to ≤35% (1) an analysis of the characteristics of patients with a screening LVEF between 35 and 40% showed that they may be more similar to patients with HFpEF than HFrEF relative to those with an LVEF <30%, raising concern for "EF creep" over time and (2) anticipation that the use of aldosterone antagonists would increase over the course of the trial based on newly published results. As a result, they recommended decreasing the LVEF requirement to ensure an adequate event rate. The rationale is reasonable and the protocol amendment was submitted after accrual of only 39 (1.9%) primary endpoint events.

Statistical Analysis Plan

The initial statistical analysis plan (SAP) was issued on October 10, 2012 (951 [46.8%] primary endpoint events accrued) and was amended on April 9, 2014, July 7, 2014, and October 20, 2014. The overview provided in this section is based on the original SAP with amendments as noted. A summary of amendments to the SAP, all of which occurred following termination of the trial, is shown in Table 8.

Table 8: Overview of statistical analysis plan amendments

Amendment # and Date	Summary of Changes
#1 April 9, 2014	• Defined "study completer" as a subject who died or had vital status available after the study close-out date. • Removed several subgroups from disposition and treatment exposure analyses. • Added an analysis plan for new onset atrial fibrillation, which was elevated to

Amendment # and Date	Summary of Changes
	a secondary endpoint by Protocol Amendment 3. • Added sensitivity analyses for the KCCQ endpoint including (1) considering data missing following death, and (2) imputing a score of 0 for death and imputing other missing values using multiple imputation with penalty factors for data missing following a heart failure hospitalization
#2 July 7, 2014	• Stated that KCCQ analyses would include patients with at least one double-blind KCCQ score at a protocol scheduled KCCQ data collection visit • Exempted patients from completion of the KCCQ and excluded them from analyses if a valid translation was not available in their language (as per original protocol). • Defined March 31, 2014 as the cut-off date for efficacy analyses and stated that analyses would include all available adjudicated data up to this date. • Stated that the overall alpha level used for the final primary and secondary endpoint analyses would be 0.001 (one-sided) based on the level used for the third interim analysis.
#3 October 20, 2014	• Added efficacy subgroups based on weight, renal function, U.S. enrollment, Western Europe enrollment excluding Israel and South Africa, and beta-blocker, diuretic, and digoxin use. • Added several *post hoc* analyses: the effect of blood pressure on the primary endpoint; subjects with a five point improvement or decline in KCCQ; the distribution of change in KCCQ from baseline to month eight; the change in NYHA class from baseline categorized as improved, unchanged, or worsened; a composite endpoint of 50% decline in eGFR or ESRD; the slope of eGFR decline; and the time to first non-CV hospitalization.

Reviewer's comment: Although all SAP amendments occurred after study termination, it seems unlikely that any of the changes would influence interpretation of the study's key efficacy findings. Amendment #3 was driven primarily by the Agency's recommendations at the top-line results meeting held on September 22, 2014. Of note, change in NYHA class was not a pre-specified endpoint but was a post hoc *analysis specified after unblinding of the trial data.*

Datasets:
The SAP defined the following key datasets:

- *Screened set:* All patients who signed the informed consent. Re-screened patients assigned different patient IDs are counted as separate patients.
- *Enalapril run-in set:* All patients who received at least one dose of run-in enalapril.
- *LCZ696 run-in set:* All patients who received at least one dose of run-in LCZ696.
- *Randomized set:* All patients who received a randomization number.
- *Full analysis set (FAS):* All randomized patients excluding misrandomized patients who did not qualify for randomization but were inadvertently randomized and did not receive study drug. Further exclusions could be justified in exceptional circumstances (e.g., serious GCP violations).
- *Per protocol set*: A subset of the FAS including all patients who received at least one dose of study drug during the double-blind period and had no major protocol deviations.

- *Safety set:* All randomized patients who received at least one dose of study drug during the double-blind period.

Primary Efficacy Analysis:
The primary efficacy analysis was based on the FAS and included all positively adjudicated events occurring between randomization and the analysis cut-off date of March 31, 2014, including those that occurred before this date but were reported after termination of the trial. The data were analyzed using the Cox proportional hazards model with treatment and region as fixed-effect factors. The overall type I error rate was to be controlled at 2.5% (one-sided), adjusted for the interim efficacy analyses as described below.

Secondary Efficacy Analyses:
The applicant specified that the KCCQ endpoint would be based on a calculated Clinical Summary Score (CSS). First, a subject's response to each question was assigned an ordinal value from 1 to 5 or 7, depending on number of response options, with 1 assigned to the response implying the lowest level of function (see Section 9.4 for the full set of questions). Of 15 total KCCQ questions, eight were grouped into the following three domains used to calculate the CSS:

- Physical Limitation = question 1 (6 items)
- Symptom Frequency = questions 3, 5, 7, and 9
- Symptom Burden = questions 4, 6, and 8

Domain scores were then calculated by taking the mean of the individual question scores and transforming the result to a 0 to 100 scale, where a score of 100 represents perfect health and a score of 0 represents dead. The domain scores were then used to calculate summary scores:

- Total Symptom Score = mean of the Symptom Frequency and Symptom Burden Scores
- CSS = mean of the Physical Limitation and Total Symptom Scores.

Reviewer's comment: Seven KCCQ questions in the following domains were not included in calculation of the CSS:

- *Symptom Stability = question 2*
- *Self-efficacy = questions 10 and 11*
- *Social Limitation = questions 15 (4 items)*
- *Quality of Life = questions 12, 13, 14*

Investigators often report a KCCQ Overall Summary Score (OSS), which includes the Physical Limitation, Total Symptom, Social Limitation, and Quality of Life domains. The applicant's more limited CSS includes the domains more likely to be influenced by LCZ696 and is therefore generally reasonable.

As noted in Section 2.5, the Agency (SEALD) [redacted] (b) (4)

The primary analysis of the KCCQ CSS endpoint was a repeated measures 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 analysis included subjects with at

least one double-blind KCCQ score and excluded subjects for whom a valid instrument was not available in their language (SAP Amendment 2).

Reviewer's comment: During the February 12, 2010 Type C meeting, the Agency recommended that, instead of evaluating a minimally important difference in group means, the applicant evaluate responders defined by pre-defined changes in individual patient scores over a specified time period. The applicant did not elect to specify this as the primary KCCQ analysis but added these analyses post hoc *to the SAP in an amendment dated October 20, 2014.*

Time to all-cause death, new onset atrial fibrillation, and the composite renal endpoint were analyzed using the Cox proportional hazards model with treatment and region as fixed-effect factors.

Adjustment for Multiplicity:
The secondary null hypotheses were to be tested only if the primary null hypothesis was rejected. The sequentially rejective multiple test procedure was used to control the overall type 1 error rate at the same level as the adjusted alpha used for the final primary efficacy analysis. Initially, 0.2α was allocated to the KCCQ and 0.8α to all-cause mortality. If both hypotheses were rejected, the full α was to be allocated to new onset atrial fibrillation. If that hypothesis was rejected, the full α was to be allocated to the renal composite endpoint. If only one of the initial hypotheses was rejected (KCCQ or all-cause mortality), the α allocated to the rejected hypothesis would then be allocated to new onset atrial fibrillation. If new onset atrial fibrillation was rejected, the α would be allocated to the renal composite endpoint.

Reviewer's comment: Since the study was terminated following the third interim analysis, the alpha of 0.001 allocated to the third interim analysis was allocated to testing the secondary hypotheses.

At the June 25, 2014 pre-NDA meeting, the Agency stated that it has advised applicants in the past not to include all-cause mortality in the testing chain and agreed that the applicant could modify the analysis plan to remove all-cause mortality. The applicant did not elect to do so.

Subgroup Analyses:
The pre-specified efficacy subgroups were age (<65, ≥65; <75, ≥75 years), gender, race (Caucasian, black, Asian, other), region, NYHA class (I/II, III/IV), LVEF (≤median, >median), LVEF (≤35%, >35%), time since diagnosis of heart failure (≤1 year, 1-5 years, >5 years), prior heart failure hospitalization (Y/N), hypertension (Y/N), diabetes (Y/N), atrial fibrillation (Y/N), prior use of ACEi (Y/N), prior use of ARB (Y/N), aldosterone antagonist (Y/N), systolic blood pressure (≤median, >median), NT-proBNP (≤median, >median), and eGFR (<60, ≥ 60 mL/min/1.73 m^2). The third amendment to the SAP added the additional subgroups of weight by tertile, eGFR (30 to <60, 60 to <90, ≥90 mL/min/1.73m^2), beta-blocker (Y/N), diuretic (Y/N), digoxin (Y/N), and U.S. site of enrollment.

Missing Data:
For time-to-event endpoints the following censoring rules were applied for efficacy analyses:

- For all-cause death, censoring occurred at the earliest of the following dates: date of withdrawal of consent, last known alive date, or analysis cutoff date.

- For cardiovascular death, censoring occurred at the earliest of the following dates: date of withdrawal of consent, last known alive date, analysis cutoff date, or date of death from non-CV causes.
- For non-mortality, non-composite endpoints, censoring occurred at the earliest of the following dates: date of withdrawal of consent, lost to follow-up date, analysis cutoff date, or date of death.
- For composite endpoints, censoring occurred at the earliest censoring date of the components.

For the KCCQ, the worst score of zero was imputed for all subsequent visits for patients who died. An algorithm specified in the original SAP guided the handling of missing KCCQ item responses. If no responses were available for a time point, the data were considered missing at random and excluded from analyses. Sensitivity analyses included (1) considering deaths missing, and thereby excluding those subjects, rather than imputing a score of zero, and (2) imputing a score of zero for visits following death as was done with the main analysis but imputing other missing data using a multiple imputation approach and applying various penalty factors for data missing following a heart failure hospitalization (SAP Amendment 1).

For all other endpoints, missing data were imputed using the last outcome carried forward method.

Interim Analyses:
The initial protocol specified two interim efficacy analyses at one third and two thirds of primary endpoint events using the O'Brien-Fleming type of boundary with Lan-DeMets alpha spending function. The first protocol amendment added a third interim analysis at one half of information time and stated that the interim analyses would use the Peto-Peto type of boundary.

The original SAP defined three formal interim efficacy analyses at approximately 1/3, 1/2, and 2/3 of information time (i.e., approximately 804, 1205, and 1607 patients with a primary endpoint event) and stated that the Haybittle-Peto type of boundary would be used to assess superiority with a one-sided alpha of 0.0001 spent on the first interim analysis and 0.001 each on the second and third interim analyses. Total cardiovascular deaths were also assessed at each interim analysis. The study was to be terminated early only if *both* the primary composite and cardiovascular death endpoints met the specified boundary.

Sample Size Calculations:
The trial was designed to have 80% power to detect a 15% reduction in cardiovascular mortality, assuming a 7% annual cardiovascular death rate in the enalapril group, an enrollment period of 18 to 22 months, and a minimum follow-up of 21 months. The projected sample size was 7,980 patients to obtain 1,229 cardiovascular deaths. This resulted in 97% power to detect a 15% reduction in the primary composite endpoint, assuming a 14.5% annual primary event rate in the enalapril group. This corresponds to a projected 2,410 primary events during the trial.

Baseline for Double Blind Period:
The baseline for the double blind period for most variables was defined as the last available measurement during the LCZ696 *run-in* phase including the time of randomization. Specifically,

the baseline for the following parameters was assessed at the randomization visit: NYHA class, heart failure signs and symptoms, vital signs, eGFR, safety laboratory values, endpoints, ECG, KCCQ scores, and EQ-5D assessments. The baseline for the following parameters was assessed at screening: height/weight, heart failure and cardiovascular medications, histories (cardiovascular disease, heart failure, and medical), demographics, and inclusion/exclusion criteria.

6 Review of Efficacy

Efficacy Summary

In support of the proposed indication, Novartis conducted PARADIGM-HF, a randomized, double-blind, active-controlled, outcomes trial in which 8,442 subjects with chronic heart failure and a reduced ejection fraction were randomized to treatment with LCZ696 or enalapril. In sequential single-blind run-in periods, subjects received enalapril 10 mg bid, followed by LCZ696 100 mg bid, increasing to 200 mg bid. Subjects who successfully completed the run-in periods were randomized to LCZ696 200 mg bid or enalapril 10 mg bid. The primary endpoint was cardiovascular death or first heart failure hospitalization, an endpoint that is well-established in heart failure trials.

The trial was terminated for efficacy following the third interim analysis on the recommendation of the trial's independent data monitoring committee. LCZ696 reduced the risk of the primary composite endpoint based on a time-to-event analysis (HR 0.80; 95% CI 0.73, 0.87; 1-sided p=0.0000002), with LCZ696 subjects experiencing both fewer first heart failure hospitalizations (537 [12.8%] vs. 658 [15.6%]) and fewer cardiovascular deaths as the first event (377 [9.0%] vs. 459 [10.9%]) compared with enalapril subjects. Although not pre-specified or adjusted for multiplicity, the applicant analyzed the components of the primary endpoint separately as the time to first heart failure hospitalization and time to cardiovascular death, including deaths preceded by a heart failure hospitalization. Both endpoints achieved nominal statistical significance favoring LCZ696 (first heart failure hospitalization HR 0.79; 95% CI 0.71, 0.89; cardiovascular death HR 0.80; 95% CI 0.71, 0.89). The reduction in cardiovascular deaths was driven primarily by a lower incidence of sudden death, death from pump failure, and presumed cardiovascular death in the LCZ696 arm. Missing vital status data were minimal and the primary efficacy results were robust to sensitivity analyses. The results were largely consistent across subgroups based on demographics, medical history, concomitant heart failure treatment, vital signs, and laboratory parameters.

Combination Policy

LCZ696 is considered a fixed-dose combination drug; therefore, according to the Agency's regulations for such products outlined in 21 CFR 300.50, each component must contribute to the effect. As designed, PARADIGM-HF cannot establish the independent contribution of valsartan and sacubitril so it is necessary to consider other available data. Valsartan is known to have efficacy in HFrEF based on the results of the Valsartan Heart Failure Trial (Val-HeFT; Cohn, 2001), which enrolled a population similar to PARADIGM-HF, patients with NYHA class II-IV heart failure and an LVEF <40%. Val-HeFT's primary goal was to examine the effect of valsartan when added to an ACEi so, unlike PARADIGM-HF, 93% of subjects were also taking

an ACEi. There were two primary endpoints: all-cause mortality and heart failure morbidity, the latter defined as all-cause mortality, sudden death with resuscitation, hospitalization for heart failure, and the need for intravenous inotropic or vasodilatory drugs for at least four hours. Valsartan did not show a mortality benefit but did reduce heart failure morbidity; however, this result was largely driven by the 7% of subjects not on an ACEi, the population most similar to PARADIGM-HF. In this subpopulation, valsartan reduced both mortality and heart failure hospitalizations. Enalapril is also known to reduce mortality and heart failure hospitalizations in HFrEF based on the results of the SOLVD-Treatment and CONSENSUS trials (SOLVD Investigators, 1991; CONSENSUS Trial Study Group, 1987). Although no studies have directly compared the efficacy of valsartan and enalapril in HFrEF, ACEi and ARBs are generally regarded as equivalent therapies for heart failure and it seems highly unlikely that valsartan alone would outperform enalapril to the degree shown in PARADIGM-HF. If anything, we might expect enalapril to have greater efficacy since the favorable findings in Val-HeFT were driven by a subgroup of the overall trial population. Therefore, we believe it is likely that sacubitril contributed to the treatment effect. It is also possible that sacubitril alone was responsible for the full benefit of LCZ696 and the valsartan component was unnecessary. However, the applicant notes that treatment with sacubitril alone leads to increases in angiotensin II, which is detrimental in heart failure, and sacubitril should therefore not be administered without concomitant blockade of the renin-angiotensin-aldosterone system. Finally, and perhaps most importantly, LCZ696 demonstrated an effect on mortality even compared with an active control that itself has a mortality benefit. It seems unlikely that additional studies to determine the independent contributions of sacubitril and valsartan would be feasible.

Claim of Superiority to Enalapril

The applicant is seeking a claim of superiority to enalapril. As such, it is important to consider that the target enalapril dose of 10 mg bid is half of the maximum labeled dose for heart failure of 20 mg bid. In contrast, the dose of the valsartan component of LCZ696 is equivalent to 160 mg bid, the maximum labeled dose of valsartan for heart failure. For this reason, the Agency previously recommended a dose of enalapril 20mg bid and this, in fact, was one reason for failure to reach agreement on a Special Protocol Assessment. The dose of 10 mg bid was based on the target dose used in the SOLVD-Treatment trial, which enrolled a population similar to PARADIGM-HF. The CONSENSUS trial targeted a dose of 20 mg bid, but only 22% of subjects actually achieved this dose because of tolerability, although the trial enrolled only NYHA class IV subjects who may have been less tolerant to higher doses. It is not clear whether increasing the target dose of enalapril from 10 to 20 mg in PARADIGM-HF would have improved the efficacy of enalapril or simply led to a higher rate of adverse events and study drug discontinuations in the control arm, thereby complicating interpretation of the results. In the face of these unknowns and the SOLVD-Treatment data, the enalapril dose was reasonable; however, it is uncertain whether LCZ696 would have demonstrated efficacy of a similar magnitude compared with a higher dose, raising questions about granting a claim of superiority to enalapril. We believe enalapril should be referenced in Section 14 of the label when describing the design of PARADIGM-HF but a claim of superiority should not be included in the indication statement.

Generalizability to United States Population

Although only 5% of subjects were randomized in the United States, the trial population was generally representative of the U.S. heart failure population. One exception is that, compared

with the prevalence of heart failure in the U.S. black population, black patients were underrepresented in PARADIGM-HF. The point estimate for black subjects (HR 0.81; 95% CI 0.57, 1.15), however, was consistent with that of the overall trial. A second exception is that ICD use in the overall trial population (15%) was substantially lower than that of subjects enrolled in the United States (60%) or a large U.S. heart failure registry (50%). There is no reason to believe that patients with an ICD would not derive the same benefit from LCZ696. In fact, the point estimate for subjects enrolled in the United States (HR 0.66, 95% CI 0.47, 0.92), and for subjects with an ICD (HR 0.85, 95% CI 0.68, 1.06) and without (HR 0.79, 95% CI 0.72, 0.87), were consistent with the overall trial.

Indicated Population
The applicant is seeking an indication for patients with (b) (4) NYHA class II-IV heart failure. The original entry criterion specified an LVEF <40%, which was later modified to ≤35% by the first protocol amendment in an effort to ensure an adequate event rate. Overall, 11% of subjects were enrolled with an LVEF of >35%. The point estimate favored LCZ696 for both the ≤35% (HR 0.79, 95% CI 0.72, 0.86) and >35% subgroups (HR 0.90, 95% CI 0.69, 1.17). It is reasonable to indicate LCZ696 for patients with an LVEF <40%.

The data are limited in NYHA class IV since the majority of PARADIGM-HF subjects were NYHA class II (70%) or III (24%) at randomization and less than 1% were NYHA class IV. The reason for this is likely multifactorial: (1) it is likely that the trial's entry criteria eliminated many NYHA class IV subjects at the screening stage (e.g., need for a stable medication regimen; adequate blood pressure and renal function; and no intent to place a VAD or list the subject for heart transplant); (2) subjects with NYHA class IV heart failure were more likely than other NYHA classes to fail the run-in period (see Section 7); and (3) NYHA class improved somewhat during the run-in period so some subjects who were NYHA class IV at screening were no longer NYHA class IV at randomization. The latter highlights the fact that NYHA class is a subjective and relatively fluid classification system. We have no reason to believe that the mechanistic pathways through which LCZ696 is hypothesized to provide clinical benefit are not relevant to NYHA class IV patients. Ultimately, for subjects with *symptomatic* heart failure (NYHA classes II-IV) who met the eligibility criteria and tolerated both enalapril and LCZ696 during the run-in period, the efficacy results favored LCZ696.

Secondary Endpoints
The effect of LCZ696 on the pre-specified secondary endpoints was mixed. The 1-sided alpha of 0.001 used for the final primary efficacy analysis was first allocated to testing all-cause mortality at an alpha of 0.0008 and the KCCQ endpoint at an alpha of 0.0002. LCZ696 reduced the risk of all-cause mortality (HR 0.84, 95% CI 0.76, 0.93; 1-sided p-value = 0.0005) driven entirely by a reduction in cardiovascular causes of death. For the KCCQ, the least squares mean of the difference in the Clinical Summary Score from baseline to month 8 between the LCZ696 and enalapril groups was 1.6 points (95% CI 0.6, 2.7) on a scale ranging from 0 to 100, favoring LCZ696; however, the one-sided p-value of 0.0007 did not meet the pre-specified significance threshold of 0.0002. The alpha of 0.0008 from the all-cause mortality endpoint was then allocated to testing new onset atrial fibrillation. LCZ696 did not reduce the occurrence of new onset atrial fibrillation. Since the atrial fibrillation endpoint was not successful, the renal composite endpoint was not to be formally tested according to the pre-specified statistical

analysis plan. Regardless, there was no difference in the time to the first component of the renal composite endpoint.

Kansas City Cardiomyopathy Questionnaire-based (b) (4)
Although the KCCQ secondary endpoint did not achieve statistical significance based on the pre-specified statistical analysis plan, some have questioned whether it is necessary from a statistical perspective to carry down the more stringent alpha of 0.001 from the third interim analysis to testing of the secondary endpoints. With a less stringent threshold, the KCCQ would have achieved statistical significance. From a clinical perspective, however, it is not clear what represents a clinically important difference in the CSS as defined by the applicant. In general, a five point change in the KCCQ Overall Summary Score (OSS), which incorporates additional KCCQ domains, is generally considered a small but clinically meaningful difference (Spertus, 2005; Kosiborod, 2007). Changes of <5 points have been reported as background variation in subjects who are considered clinically stable. For example, Green (2002) reported a mean change in CSS (called a "KCCQ functional status score" by Green) of 1.4 over a three month period; Spertus (2005) reported a change in OSS of 1.3 over six weeks; and, in subject with more advanced heart failure, Hauptman (2004) reported a change in OSS of 4.1 over six weeks. Therefore, the between-group difference in CSS of 1.6 (95% CI 0.6, 2.7) observed in PARADIGM-HF falls within the range of background variation for subjects considered clinically stable. Furthermore, this difference is attenuated when the CSS is considered missing rather than 0 following death (0.98; 95% CI 0.30, 1.66), suggesting that the difference in CSS is being driven, at least in part, by differential mortality between the treatment arms. (b) (4)

(b) (4)

(b) (4)

. All were exploratory analyses and not analyzed in a way that controls type-I error (b) (4) it is reassuring to note that the reduction in heart failure hospitalizations seen with LCZ696 does not appear to come at the expense of hospitalizations for other causes and this should be noted in the label.

6.1 Indication

The proposed indication is:

(b) (4)

6.1.1 Methods

In support of the proposed indication, the applicant submitted the results of PARADIGM-HF, a multicenter, randomized, double-blind, active-controlled phase 3 trial conducted in 8,442 patients aged ≥ 18 years with NYHA class II-IV chronic heart failure and an LVEF ≤ 40% (≤ 35% per Protocol Amendment 1). The following sections describe the efficacy findings for PARADIGM-HF. See Section 5.3 for an overview of trial design.

6.1.2 Demographics

Baseline demographics were similar in the two treatment arms (Table 9). The mean age was 64 years (range 18 to 96) with 19% of subjects aged 75 years or older. The majority of subjects were male (78%). Overall, 66% of subjects were white, 18% Asian, and 5% black. Sites in the United States represented only 5% of subject enrollment.

Table 9: Baseline demographics[1]

	Enalapril (N=4233) n (%)	**LCZ696 (N=4209) n (%)**
Male	3274 (77)	3321 (79)
Age (range)	64 (21-96)	64 (18-96)
≥65	2056 (49)	2087 (50)
≥75	783 (19)	786 (19)
Race		
White	2799 (66)	2780 (66)
Asian	750 (18)	760 (18)
Black[2]	215 (5)	213 (5)
Native American/Pacific Islander	89 (2)	84 (2)
Other	380 (9)	372 (9)
Hispanic Ethnicity	778 (18)	777 (19)
Region[3]		
Central Europe	1439 (34)	1398 (33)
Western Europe	1028 (24)	1029 (24)
Asia/Pacific/Other	742 (18)	746 (18)
Latin America	732 (17)	726 (17)
North America	292 (7)	310 (7)
United States	209 (5)	225 (5)

Source: Reviewer's analysis of applicant's datasets (*dmg, aident*).
[1]Assessed at screening.
[2]Enrollment region: 115 (27%) North America, 160 (37%) Latin America, 153 (36%) Europe.
[3]North America: United States, Canada; Latin America: Argentina, Brazil, Chile, Columbia, Dominican Republic, Ecuador, Guatemala, Mexico, Panama, Peru, Venezuela; Western Europe: Belgium, Denmark, Finland, France, Germany, Iceland, Italy, Netherlands, Portugal, Spain, Sweden, Israel, South Africa, United Kingdom; Central Europe: Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Rep of Slovakia, Romania, Russia, Turkey; Asia/Pacific/Other: China, Hong Kong, India, Republic of Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand.

Baseline characteristics were well balanced between the treatment arms (Table 10). Overall, 71% of subjects had a history of hypertension, 35% diabetes, and 60% had an ischemic etiology of heart failure. At screening, the mean enalapril equivalent dose was 15 mg per day. Device use was reported in 17% of subjects overall and in 60% of subjects enrolled in the United States. A total of 963 subjects (11%) were enrolled with an EF of >35% before the protocol was amended to reduce the EF criterion to ≤ 35% (Protocol Amendment 1).

Table 10: Baseline characteristics[1]

	Enalapril (N=4233) n (%)	**LCZ696 (N=4209) n (%)**
Medical history		
Hypertension	2990 (71)	2980 (71)
Diabetes	1459 (35)	1457 (35)
Atrial fibrillation by history	1587 (38)	1524 (36)
Myocardial infarction	1823 (43)	1828 (43)
Ischemic heart failure etiology	2540 (60)	2518 (60)
Prior heart failure hospitalization	2679 (63)	2620 (62)
ACEi/ARB use		
ACEi	3281 (78)	3279 (78)
ARB	969 (23)	938 (22)
Enalapril equivalent daily dose (mean [SD] mg)	15 (8.2)	15 (8.4)
Device Use		
Any ICD (including CRT-D)	622 (15)	624 (15)
CRT-P	70 (2)	80 (2)
Ejection fraction (mean [SD] %)	29.4 (6.3)	29.6 (6.1)
≤35%	3742 (88)	3736 (89)
BNP (median [IQR] pmol/L)[2]	72 (44, 134)	74 (45, 137)
NT proBNP (median [SD] pmol/L)[3]	188 (105, 389)	193 (105, 373)

Source: Reviewer's analysis of applicant's datasets (*ahis, aident*).
[1]Assessed at screening.
[2]Enalapril n=4199, LCZ696 n=4183.
[3]Enalapril n=4224, LCZ696 n=4204.

Concomitant heart failure therapy was well-balanced between the treatment arms at baseline (Table 11). Overall, 93.4% of subjects were taking a beta-blocker at randomization, most often carvedilol immediate release (36%), bisoprolol (27%), or metoprolol (22%). Of note, available data cannot distinguish immediate and extended release metoprolol formulations. Beta-blocker use did not change during the run-in period between screening and randomization. Overall, 56% of subjects were taking an aldosterone antagonist at randomization with most taking sprinolactone. Aldosterone antagonist use decreased slightly in both treatment arms during the run-in period between screening and randomization. As noted in Section 5.3, investigators could reduce or discontinue concomitant medications during the run-in period in response to adverse events (e.g., hyperkalemia, hypotension, or renal dysfunction) to facilitate continuation of study drug. Beta-blocker and aldosterone antagonist doses were generally similar in the two

treatment arms (see Section 9.5, Table 90 and Table 91). At randomization, 80% of subjects were on a diuretic and 30% were on digoxin.

Table 11: Baseline heart failure medication use (safety set[1])

	Enalapril (N=4229)		LCZ696 (N=4203)	
	Screening	Randomization	Screening	Randomization
	n (%)	n (%)	n (%)	n (%)
Beta-blocker	3974 (94)	3946 (93)	3958 (94)	3928 (94)
Carvedilol[2]	1677 (40)	1663 (39)	1654 (39)	1637 (40)
Immediate release	1537 (36)	1521 (36)	1529 (36)	1504 (36)
Extended release	44 (1)	43 (1)	44 (1)	44 (1)
Other	96 (2)	99 (2)	81 (2)	89 (2)
Bisoprolol	1114 (26)	1116 (26)	1119 (27)	1120 (27)
Metoprolol[3]	917 (22)	900 (21)	939 (22)	925 (22)
Nebivolol	152 (4)	156 (4)	129 (3)	128 (3)
Atenolol	72 (2)	69 (2)	85 (2)	79 (2)
Other	58 (1)	56 (1)	53 (1)	57 (1)
Aldosterone Antagonist	2530 (60)	2416 (57)	2400 (57)	2291 (55)
Spironolactone	2331 (55)	2217 (52)	2224 (53)	2113 (50)
Eplerenone	172 (4)	173 (4)	154 (4)	158 (4)
Canrenone/Canrenoate	29 (1)	28 (1)	24 (1)	22 (1)

Source: Reviewer's analysis of applicant's datasets (*aident*). Applicant's analyses (*Response to Information Request – Clinical* dated February 17, 2015).
[1]Safety set excludes 4 subjects randomized to enalapril and 6 to LCZ696 who were never treated. Full analysis set excludes 21 enalapril and 22 LCZ696 subjects who were misrandomized (2 and 4, respectively) or were from sites excluded because of serious GCP violations.
[2]Investigator's did not report whether carvediol was immediate or extended release. For the purposes of this table, applicant considered carvedilol to be immediate release for reported total daily doses of 3.125, 6.25, 12.5, 25 and 50 mg and extended release for total daily doses of 10, 20, 40 and 80 mg. "Other" includes doses not captured under those categories.
[3]Applicant is unable to distinguish immediate from extended release metoprolol formulations.

Baseline NYHA class, vital signs, and selected laboratory parameters were similar in the two treatment arms (Table 12). NYHA class improved somewhat in both treatment arms during the run-in period and, by the time of randomization, most subjects were NYHA class II (70%) or III (24%). Only 4.7% of subjects were NYHA class I and less than 1% were NYHA class IV. During the run-in period, systolic and diastolic blood pressure decreased by approximately 7 and 4 mmHg, respectively. The mean heart rate was in the low 70s in both treatment arms at both screening and randomization. The mean eGFR was 68 mL/min/1.73m^2 with approximately one-third of subjects having an eGFR <60 mL/min/1.73m^2. The mean potassium was 4.5 mmol/L in both treatment arms and did not change during the run-in period.

Table 12: Baseline heart failure characteristics, vital signs, and selected laboratory parameters

	Enalapril (N=4233) n (%)		LCZ696 (N=4209) n (%)	
	Screening	**Randomization**	**Screening**	**Randomization**
NYHA class I[1,2]	15 (0.4)	213 (5)	14 (0.3)	183 (4)
II	2704 (64)	2930 (69)	2748 (65)	3007 (71)
III	1452 (34)	1056 (25)	1374 (33)	979 (23)
IV[3]	60 (1.4)	27 (0.6)	66 (1.6)	33 (0.8)
Systolic BP (mean[SD] mmHg)	128 (17)	121 (15)	129 (17)	122 (15)
Diastolic BP (mean[SD] mmHg)	78 (11)	74 (10)	78 (11)	74 (10)
Heart rate (mean [SD])	74 (13)	73 (12)	73 (13)	72 (12)
eGFR (mean [SD] mL/min/1.73m^2)[4]	68 (20)	68 (20)	68 (19)	68 (20)
eGFR <60 mL/min/1.73m^2 (n [%])[4]	1527 (36)	1530 (36)	1449 (34)	1552 (37)
Potassium (mean [SD] mmol/L)[5]	4.5 (0.4)	4.5 (0.5)	4.5 (0.4)	4.5 (0.5)

Source: Reviewer's analysis of applicant's datasets (*vsn, avsn, alrs1, alrs2, alrs3, alrs4, alrs5, aident*).
[1]Screening: enalapril n=4231, LCZ696 n=4202. Randomization: enalapril n=4226, LCZ696 n=4202.
[2]Nineteen subjects were NYHA class I at both screening and randomization (protocol violation); one subject with a missing NYHA class at screening was NYHA class I at randomization (protocol violation); and 376 subjects improved to NYHA class I during the run-in period.
[3]Of the 60 NYHA class IV subjects at randomization, 21 were enrolled in Russia and 19 in Bulgaria. Only four were enrolled in the United States.
[4]eGFR = 175 × (standardized serum creatinine in mg/dL)$^{-1.154}$ × (age in years)$^{-0.203}$ × (0.742 if female) × (1.212 if black).
[5]Screening: enalapril n=4199, LCZ696 n=4165. Randomization: enalapril n=4155, LCZ696 n=4130.

Reviewer's comment: The baseline characteristics of the PARADIGM-HF trial population overall are generally similar to the 5% of subjects randomized in the U.S. and to patients enrolled in a large U.S. registry of outpatient cardiology patients with HFrEF (Fonarow, 2010) with a few exceptions (see Section 9.6):

- *Similar to other heart failure trials, the trial population was slightly younger and had fewer female subjects than the registry cohort. Age and gender-based subgroup analyses are shown in Section 6.1.7.*
- *Compared with the prevalence of heart failure in the U.S. black population, black patients were underrepresented in PARADIGM-HF. This issue will be discussed in greater detail in Section 7 in the context of the risk of angioedema.*
- *The prevalence of comorbidities in the trial was similar to the registry cohort with the exception of hypertension, which was more common in the trial population. In addition, screening systolic and diastolic blood pressures were higher in the trial population compared with the registry cohort. This is not unexpected since subjects with lower blood pressures were excluded at several points during the screening and run-in periods of PARADIGM-HF. This issue will be discussed in greater detail in Section 7 in the context of the risk of hypotension.*
- *Beta-blocker and aldosterone antagonist use in the trial exceeded that observed in the U.S. registry cohort suggesting that subjects were on a reasonable heart failure regimen at baseline.*

- *ICD use in the U.S. trial subset and registry cohort markedly exceeded that of the overall trial population (60, 50, and 15%, respectively). See Section 6.1.7 for an analysis of efficacy by subgroups of device use.*
- *Despite the fact that "low BNP/NT-pro BNP" was the most common reason for screen failure (see Section 6.1.3), the median BNP of trial subjects was still lower than that of the registry cohort.*

6.1.3 Subject Disposition

Screening Period
Of 18,071 screened patients, 10,537 (58%) were eligible for the run-in period (Table 13). For ineligible patients, investigators indicated the reason(s) on the case report form using the checkboxes listed in Table 13. The most common reasons were low BNP/NT-pro-BNP (25.8%), hyperkalemia (8%), and "Other" (3%). Based on the brief accompanying statements, the most common reasons marked "Other" were (1) patient issues with the visit schedule or inability to complete enrollment within the protocol-specified time period, and (2) inadequate baseline heart failure treatment or need to adjust medication doses.

Table 13: Subject disposition – screening period

	Subjects n (%)
Subjects screened[1]	18071 (100)
Subjects eligible for run-in	10537 (58.3)
Attended initial run-in visit, never treated	16 (0.1)
Screen failures[2]	7534 (41.7)
Low BNP/NT-pro BNP	4661 (25.8)
Potassium > 5.2 mmol/L	1436 (8.0)
Other	535 (3.0)
Patient withdrew consent	446 (2.5)
eGFR <30 mL/min/1.73 m^2	414 (2.3)
Did not meet diagnostic/severity criteria	281 (1.6)
Unacceptable laboratory value (other than potassium, serum creatinine, or eGFR)	279 (1.5)
Unacceptable past medical history/concomitant diagnosis	103 (0.6)
Symptomatic hypotension and/or SBP < 100 mmHg	102 (0.6)
Unacceptable test procedure result	93 (0.5)
Intercurrent medical event	61 (0.3)
Unacceptable use of excluded medication/therapy	43 (0.2)
Unknown/No reason provided	15 (0.1)

Source: Reviewer's analysis of applicant's dataset (*scr*).
[1]Includes 1274 re-screens.
[2]Includes three subjects who died.

Run-in Period
A total of 10,521 subjects entered the single-blind run-in period, 10,513 (99.9%) starting with enalapril and eight starting with LCZ696 (protocol violation) (Table 14). Overall, 1,102 subjects

failed the enalapril run-in and 982 failed the LCZ696 run-in, 10.5% and 10.4% of subjects entering each run-in, respectively. In total, 2,084 (19.8%) subjects failed the run-in period.

Table 14: Subject disposition – run-in period

	Subjects[1] (n=10521) n (%)
Enalapril run-in	10513 (99.9)
Run-in failure	1102 (10.5)
Death[2]	55 (0.5)
LCZ696 run-in	9419 (89.5)
Run-in failure	982 (9.3)
Death[3]	63 (0.6)
Total run-in failures	2084 (19.8)
Misrandomized[4]	6 (0.1)
Subjects eligible for randomization	8437 (80.2)
Not randomized	1 (0)

Source: Reviewer's analysis of applicant's datasets (*aident*).
[1]Eight run-in subjects did not take enalapril but took LCZ696.
[2]Includes six enalapril run-in subjects who discontinued treatment for another primary reason and subsequently died.
[3]Includes sixteen LCZ696 run-in subjects who discontinued treatment for another primary reason and subsequently died.
[4]Subjects who failed the run-in period for whom IVRS randomization calls were erroneously performed but who never received study medication.

Reasons for Run-in Failure:

For subjects who failed the run-in period, investigators indicated the primary reason for discontinuation using the checkboxes listed in Table 15. The most common reason for failure during both the enalapril and LCZ696 run-in periods was an adverse event, most often renal dysfunction, hyperkalemia, or hypotension, which were all protocol-specified reasons for discontinuation (see Section 7 for additional discussion). The adverse event was categorized as "Other" for 102 (1.0%) enalapril and 132 (1.4%) LCZ696 subjects. Only three "other" adverse events were reported for more than five subjects during either run-in period: cardiac failure (6 enalapril, 14 LCZ696), dizziness (8 enalapril, 11 LCZ696), and angioedema (12 enalapril, 10 LCZ696). Investigators indicated "Other" as the primary reason for run-in failure for 81 (0.8%) subjects who failed the enalapril run-in and 65 (0.7%) who failed the LCZ696 run-in. Based on the brief accompanying statements, "Other" was most often used for subjects who declined further participation, were nonadherent with study drug or visits, or no longer met specific eligibility criteria (e.g., renal function, potassium, disease severity).

Table 15: Primary reason for run-in failure

	Enalapril Run-in (N=10513) n (%)	**LCZ696 Run-in (N=9419) n (%)**
Run-in failures	1102 (10.5)	982 (10.4)
Adverse Event[1]	591 (5.6)	551 (5.9)
Renal dysfunction	181 (1.7)	174 (1.8)
Hyperkalemia	174 (1.7)	125 (1.3)
Hypotension	146 (1.4)	164 (1.7)
Other	102 (1.0)	132 (1.4)
Cough	49 (0.5)	15 (0.2)
Subject withdrew consent	171 (1.6)	100 (1.1)
Protocol deviation	79 (0.8)	92 (1.0)
Other	81 (0.8)	65 (0.7)
Abnormal laboratory value(s) (other than potassium, serum creatinine, or eGFR)	55 (0.5)	50 (0.5)
Death	49 (0.5)	47 (0.5)
Lost to follow-up	39 (0.4)	26 (0.3)
Administrative problems	20 (0.2)	29 (0.3)
Abnormal test procedure results(s)	11 (0.1)	9 (0.1)
Unsatisfactory therapeutic effect	4 (0)	10 (0.1)
Subject's condition no longer requires study drug	1 (0)	2 (0)
Missing	1 (0)	1 (0)

Source: Reviewer's analysis of applicant's datasets (*aident, acmp, aaev*).
[1]Investigators could indicate more than one adverse event.

Randomized Period

A total of 8,442 subjects were randomized, 4,233 (50.1%) to enalapril and 4,209 (49.9%) to LCZ696 (Table 16). All but ten were treated with study drug. Overall, 79.8% of enalapril and 81.8% of LCZ696 subjects were on treatment at the time of either study termination or death. A total of 35 (0.4%) subjects did not complete study follow-up because of withdrawal of consent or being lost to follow-up. Vital status was unknown for 20 (0.2%) subjects.

Table 16: Subject disposition during randomized period

	Enalapril (n=4233) n (%)	**LCZ696 (n=4209) n (%)**
Randomized	4233 (100)	4209 (100)
Not treated	4 (0.1)	6 (0.1)
Misrandomized[1]	2 (0.1)	4 (0.1)
Other	2 (0.1)	2 (0.1)
Primary efficacy population (full analysis set)	4212 (99.5)	4187 (99.5)
Excluded	21 (0.5)	22 (0.5)
Misrandomized[1]	2 (0.1)	4 (0.1)
Site excluded for GCP violations	19 (0.5)	18 (0.4)
Completed study on treatment	3379 (79.8)	3441 (81.8)
Alive at study termination	2869 (67.8)	3011 (71.5)
Died during double-blind period	510 (12.1)	430 (10.2)
Prematurely discontinued study treatment	815 (19.3)	729 (17.3)
Alive at study termination	481 (11.4)	435 (10.3)
Died during double-blind period	334 (7.9)	294 (7.0)
Did not complete study	18 (0.4)	17 (0.4)
Withdrew consent	13 (0.3)	15 (0.4)
Vital status known[2]	9 (0.2)	6 (0.1)
Vital status unknown	4 (0.1)	9 (0.2)
Lost to follow-up (vital status unknown)	5 (0.1)	2 (0.1)

Source: Reviewer's analysis of applicant's datasets (*aident , cmp*). Applicant's analyses (*Response to Information Request – Clinical* dated February 27, 2015).
[1]Subjects who failed the run-in period for whom IVRS randomization calls were erroneously performed but who never received study medication.
[2]Three enalapril subjects with vital status listed as unknown in *cmp* dataset were identified as dead in *aident* dataset.

At the time of treatment discontinuation, either prematurely during the double-blind period or at study termination, investigator's completed an "End of Treatment" summary indicating the last known date the subject took study drug and checking the primary reason for discontinuation. The primary reasons for premature discontinuation, excluding death, are listed in Table 17. "Other" was indicated as the primary reason for treatment discontinuation for 81 enalapril and 72 LCZ696 subjects. Based on the brief accompanying statements, the most common reason checked as "Other" related to the early termination of the trial, which other investigators likely checked as "Patient completed study".

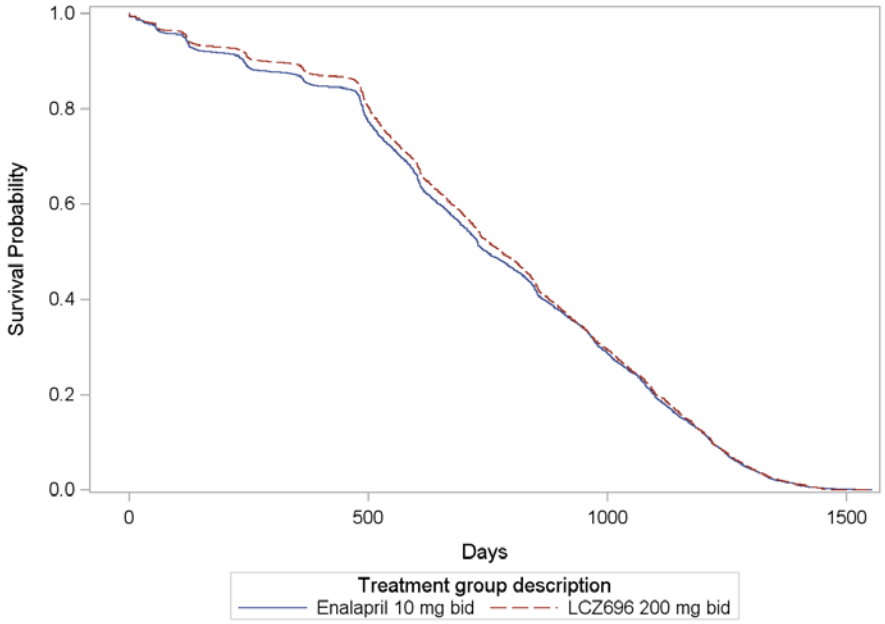
Table 17: Primary reason for premature treatment discontinuation during double-blind period (FAS)

	Enalapril (n=4212) n (%)	**LCZ696 (n=4187) n (%)**
Premature treatment discontinuations	833 (19.8)	746 (17.8)
Adverse event(s)	508 (12.1)	436 (10.4)
Patient's request	219 (5.2)	208 (5.0)
Other	81 (1.9)	71 (1.7)
Lost to follow-up[1]	7 (0.2)	8 (0.2)
Abnormal laboratory value(s)	6 (0.1)	7 (0.2)
Administrative problems	4 (0.1)	8 (0.2)
Protocol deviation	3 (0.1)	5 (0.1)
Condition no longer requires study drug	4 (0.1)	3 (0.1)
Unsatisfactory therapeutic effect	1 (0)	0 (0)

Source: Reviewer's analysis of applicant's datasets (*cmp*).
[1]As indicated by investigator on the "End of Treatment" summary. Numbers are greater than those in Table 16, which only lists subjects for whom no additional follow-up data was available after treatment discontinuation.

As an assessment of adequacy of follow-up, Figure 3 shows the time to last follow-up, defined as the last clinic visit at which a pulse was recorded. The number of days of follow-up appears similar between the treatment arms.

Figure 3: Days of follow up based on pulse data



Source: Reviewer's analysis of applicant's datasets (*avsn*).

6.1.4 Analysis of Primary Endpoint(s)

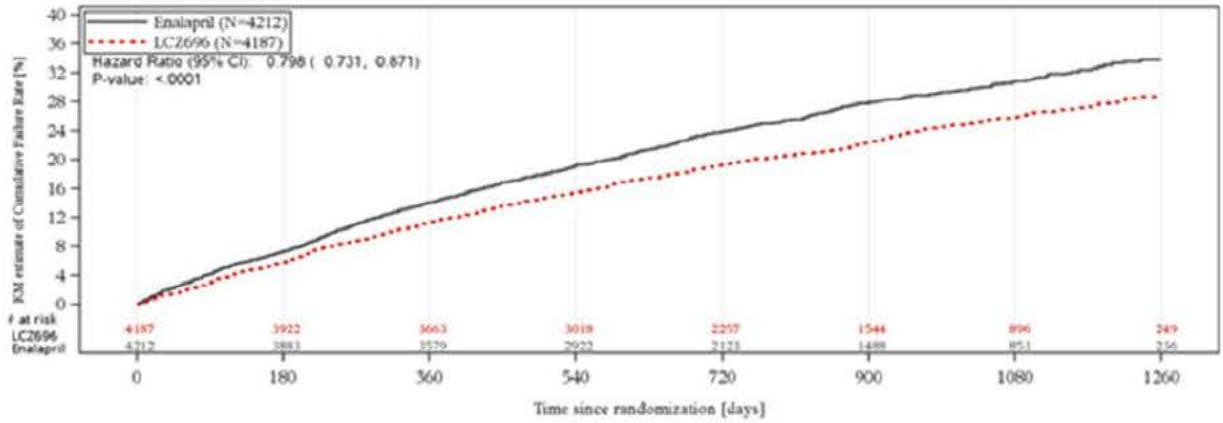
The primary endpoint was a composite of cardiovascular death or first heart failure hospitalization. Subjects in the LCZ696 arm experienced fewer primary endpoint events with both components of the composite favoring LCZ696 (Table 18). The Kaplan-Meier curve separated early and the treatment effect persisted for the duration of the trial (Figure 4).

Table 18: Primary efficacy analysis (FAS)[1]

	Enalapril (n=4212) n (%)	LCZ696 (n=4187) n (%)	Hazard Ratio (95% CI; 1-sided p-value)
Primary composite endpoint	1117 (26.5)	914 (21.8)	0.80 (0.73, 0.87; 0.0000002)
CV death	459 (10.9)	377 (9.0)	
HF Hospitalization	658 (15.6)	537 (12.8)	

Source: Applicant, PARADIGM-HF CSR Table 11-5.
[1]Analysis shown is time to first component of primary composite endpoint. Analysis confirmed by statistical reviewer.

Figure 4: Kaplan-Meier plot for first primary endpoint event (FAS) BEST AVAILABLE COPY



Source: Applicant, PARADIGM-HF CSR Figure 11-1.

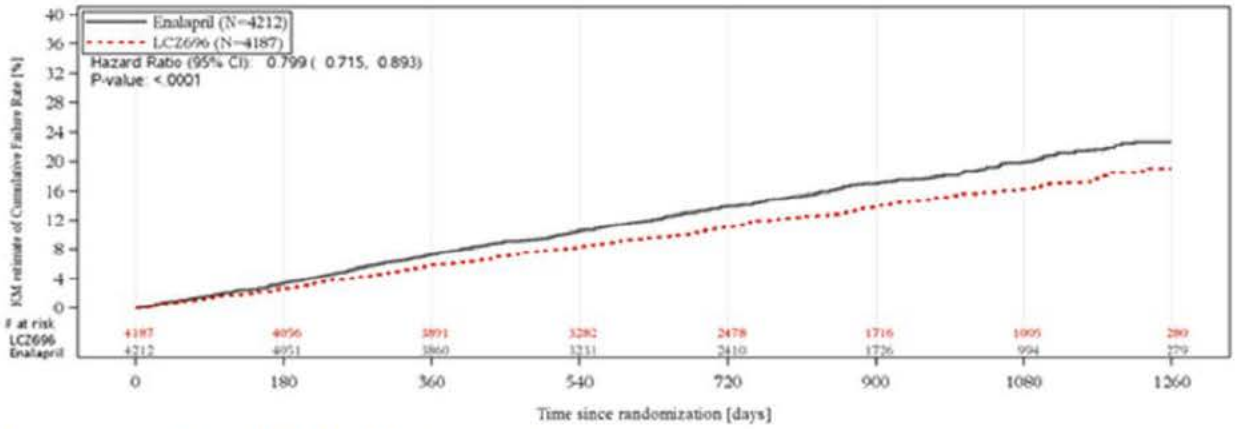
LCZ696 subjects experienced fewer cardiovascular deaths during the randomized period and fewer first heart failure hospitalizations with both achieving nominal statistical significance (Table 19). The Kaplan-Meier curves for both separated early and the treatment effect persisted for the duration of the trial (Figure 5, Figure 6).

Table 19: Results for total cardiovascular deaths and first heart failure hospitalization

	Enalapril (n=4212) n (%)	LCZ696 (n=4187) n (%)	Hazard Ratio (95% CI; 1-sided p-value)
Cardiovascular death	693 (16.5)	558 (13.3)	0.80 (0.71, 0.89; 0.00004)
First heart failure hospitalization	658 (15.6)	537 (12.8)	0.79 (0.71, 0.89; 0.00004)

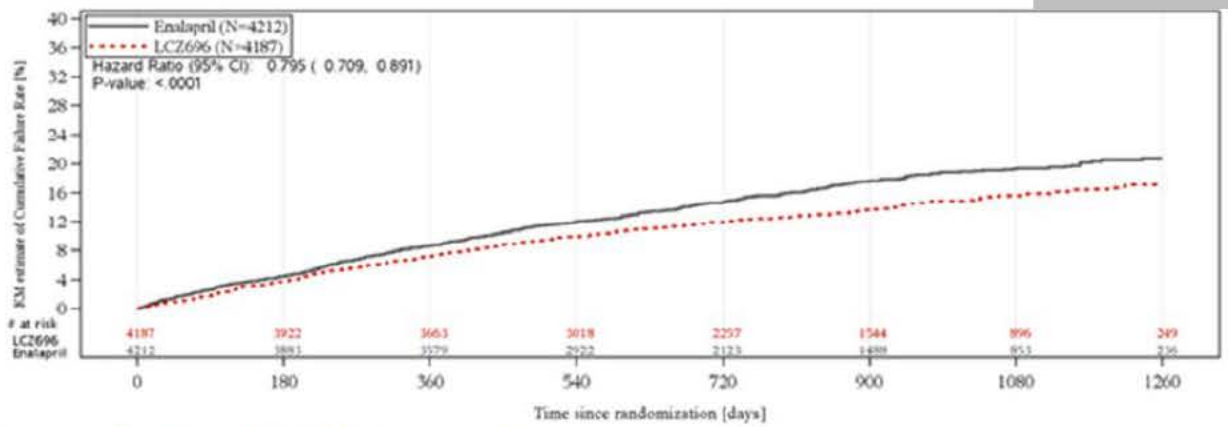
Source: Applicant, PARADIGM-HF CSR Table 11-5.

Figure 5: Kaplan-Meier plot for cardiovascular death (FAS)



Source: Applicant, PARADIGM-HF CSR Figure 11-2.

Figure 6: Kaplan-Meier plot for first hospitalization for heart failure (FAS)



Source: Applicant, PARADIGM-HF CSR Figure 11-3.

Reviewer's comment: The applicant did not pre-specify analyses of total cardiovascular deaths or first heart failure hospitalizations and these endpoints were not included in plans to control type I error; however, these analyses are not unreasonable to understand the contribution of the individual components to the composite endpoint result.

The effect on cardiovascular death was driven by fewer sudden deaths, deaths from pump failure, and presumed cardiovascular deaths (Table 20).

Table 20: Causes of cardiovascular death

	Enalapril (n=4212) n (%)	**LCZ696 (n=4187) n (%)**
Sudden death	311 (7.4)	250 (6.0)
Pump failure	184 (4.4)	147 (3.5)
Presumed CV death	95 (2.3)	67 (1.6)
Fatal stroke	34 (0.8)	30 (0.7)
Ischemic	24 (0.6)	22 (0.5)
Hemorrhagic	9 (0.2)	5 (0.1)
Unknown	1 (0)	3 (0.1)
Fatal myocardial infarction	33 (0.8)	24 (0.6)
Presumed sudden death	23 (0.5)	26 (0.6)
CV procedural	4 (0.1)	3 (0.1)
Other cardiovascular death[1]	6 (0.1)	7 (0.2)
Pulmonary embolism	3 (0.1)	4 (0.1)

Source: Reviewer's analysis of applicant's datasets (*aident, aenp*).
[1]Includes fatal arrhythmia, peripheral arterial disease, cardiac tamponade, and abdominal aortic dissection.

With each interim analysis, the p-values for the primary endpoint and total cardiovascular deaths became increasingly significant (see Section 9.7, Table 93). The primary endpoint reached the pre-specified stopping threshold at the second interim analysis and total cardiovascular deaths at the third. As a result, the study was terminated early for efficacy following the third interim analysis.

Sensitivity Analyses
The applicant conducted several sensitivity analyses of the primary efficacy endpoint including analyses of:

- An endpoint of confirmed death due to cardiovascular *or unknown cause* or first heart failure hospitalization.
- A per-protocol dataset excluding 46 enalapril and 43 LCZ696 subjects with pre-specified major protocol deviations.
- Only on-treatment occurrence of primary endpoint events, defined as events occurring up to 28 days after study drug discontinuation.
- All site-reported events, both CEC confirmed and non-confirmed.
- Adjustment for time-varying systolic blood pressure using a Cox regression model with treatment and region as fixed factors and systolic blood pressure as the time-dependent covariate.

The treatment effect was maintained in all sensitivity analyses (Table 21).

Table 21: Sensitivity analyses related to the primary efficacy endpoint

	Enalapril (n=4212) n (%)	LCZ696 (n=4187) n (%)	Hazard Ratio (95% CI; 2-sided p-value)
Primary composite endpoint including unknown cause of death	1148 (27.3)	946 (22.6)	0.80 (0.74, 0.88; <0.001)
Per protocol dataset	1112 (26.6)	905 (21.7)	0.79 (0.73, 0.87; <0.001)
On-treatment events	973 (23.1)	800 (19.1)	0.80 (0.72, 0.87; <0.001)
Site-reported events	1213 (28.8)	1044 (24.9)	0.84 (0.77, 0.91; <0.001)
Adjusted for time-varying systolic blood pressure	1117 (26.5)	914 (21.8)	0.78 (0.71, 0.85; <0.001)

Source: Applicant, PARADIGM-HF CSR, Tables 14.2-1.1.1, 14.2-1.2, 14.2-1.6, 14.2-1.1.post.11

Events occurring after March 31, 2014, the specified cut-off date for inclusion in efficacy analyses, were not systematically adjudicated; however, there were few such events overall and their inclusion is unlikely to influence the results (Table 22).

Table 22: Events occurring after March 31, 2014 cut-off date

	Enalapril (n=4212) n (%)	LCZ696 (n=4187) n (%)
Primary composite endpoint	15 (0.4)	19 (0.5)
Cardiovascular death	7 (0.2)	7 (0.2)
First hospitalization for heart failure	10 (0.2)	14 (0.3)
All cause death	13 (0.3)	17 (0.4)

Source: Applicant, PARADIGM-HF CSR, Table 14.2-1.1.post.23.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints were:

- Change from baseline (randomization) in the clinical summary score for heart failure symptoms and physical limitations as assessed by KCCQ at 8 months;
- Time from randomization to all-cause death;
- Time from randomization to new onset of atrial fibrillation;
- A renal composite of time from randomization to first occurrence of either:
    - A 50% decline in eGFR relative to baseline,
    - A >30 mL/min/1.73 m^2 decline in eGFR relative to baseline to a value below 60 mL/min/1.73 m^2, or
    - ESRD.

Since the primary endpoint was successful, the secondary endpoints were tested using a sequentially rejective multiple test procedure to control the overall type 1 error rate at the alpha used for the final primary efficacy analysis (1-sided alpha 0.001). As discussed in Section 5.3, 0.2α (1-sided alpha 0.0002) was initially allocated to the KCCQ endpoint and 0.8α (1-sided alpha 0.0008) to all-cause mortality.

Kansas City Cardiomyopathy Questionnaire
The pre-specified secondary endpoint related to the KCCQ was the change in the KCCQ Clinical Summary Score (CSS) from baseline (randomization) to month 8. As discussed in Section 5.3, a subject's KCCQ item responses were used to calculate Physical Limitation, Symptom Frequency, and Symptom Burden domain scores, which were then combined to produce a Total Symptom score (mean of the Symptom Frequency and Symptom Burden scores) and CSS (mean of Total Symptom and Physical Limitation scores). Subjects who died were assigned a CSS of zero for all subsequent visits. Other missing data were considered missing at random and the secondary endpoint analysis only included subjects with data available at baseline and month 4 and/or 8.

The CSS and its individual components declined less in the LCZ696 treatment arm than the enalapril treatment arm (Table 23). The least squares mean (LSM) of the difference in the change from baseline between the LCZ696 and enalapril groups was 1.6 points (95% CI 0.6 - 2.7, 2-sided p=0.001), favoring LCZ696; however, the one-sided p-value of 0.0007 did not meet the pre-specified significance threshold of 0.0002. See Section 6.1.10 for exploratory analyses related to the KCCQ.

Table 23: Change in KCCQ Clinical Summary Score and component scores from baseline to month 8

	Enalapril		LCZ696		LSM of difference[1] (95% CI; 2-sided p-value)
	n (%)	LSM of CFB[2] (SE)	n (%)	LSM of CFB[2] (SE)	
Clinical Summary Score[3]	3638 (94)	-4.6 (0.4)	3643 (95)	-3.0 (0.4)	1.6 (0.6, 2.7; 0.001[4])
Physical Limitation	3586 (93)	-4.1 (0.4)	3588 (94)	-2.6 (0.4)	1.5 (0.5, 2.6; 0.005)
Total Symptom	3635 (94)	-5.2 (0.4)	3640 (95)	-3.3 (0.4)	1.9 (0.8, 3.0; 0.001)
Symptom Frequency	3632 (94)	-5.2 (0.4)	3637 (95)	-3.0 (0.4)	2.2 (1.1, 3.3; <0.001)
Symptom Burden	3635 (94)	-5.3 (0.4)	3640 (95)	-3.6 (0.4)	1.7 (0.6, 2.8; 0.003)

Source: Applicant, PARADIGM-HF CSR Table 11-7.
[1]LSM of difference = LSM of (CFB [LCZ696] - CFB [Enalapril]).
[2]CFB=change from baseline.
[3]Subject numbers represent subjects in the full analysis set with a KCCQ CSS score at both baseline and month 8 and subjects who died. An additional 171 subjects with data available at month 4 but not month 8 are included in the secondary endpoint analysis.
[4]One-sided p-value = 0.0007.

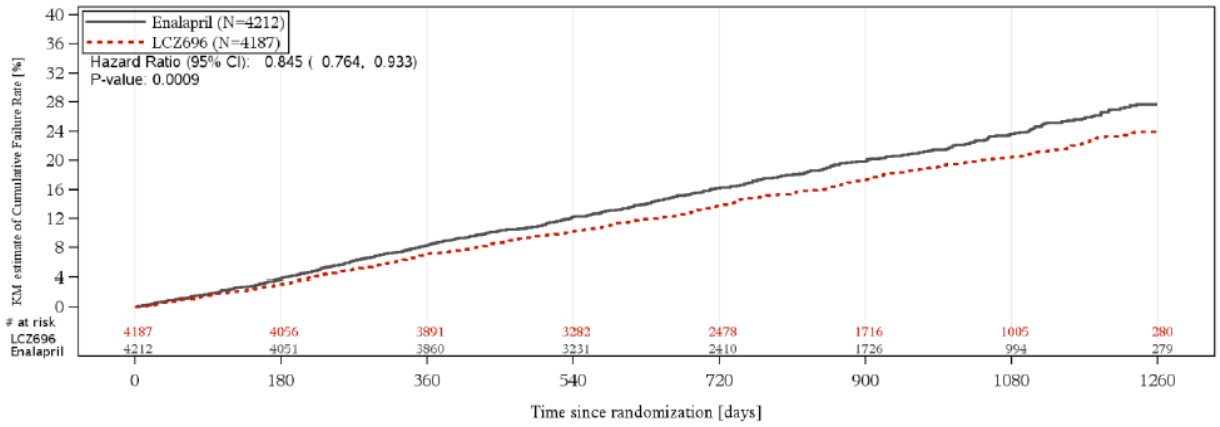
All-Cause Mortality
Subjects in the LCZ696 treatment arm had a reduced risk of death with a hazard ratio of 0.84 (95% CI 0.76-0.93; 2-sided p-value <0.001) driven entirely by a reduction in cardiovascular causes of death (Table 24). The Kaplan-Meier curves separated early and the treatment effect persisted for the duration of the trial (Figure 7).

Table 24: Secondary efficacy analysis for all-cause mortality (FAS)[1]

	Enalapril (N=4212) n (%)	LCZ696 (N=4187) n (%)	Hazard Ratio (95% CI; 2-sided p-value)
All-cause death	835 (19.8)	711 (17.0)	0.84 (0.76, 0.93; <0.001[2])
Cardiovascular death	693 (16.5)	558 (13.3)	
Non-cardiovascular death	109 (2.6)	120 (2.9)	
Unknown	33 (0.8)	33 (0.8)	

Source: Reviewer's analysis of applicant's dataset (*aendpt*).
[1]Analysis shown is time to event.
[2]1-sided p-value = 0.0005 met the pre-specified threshold of ≤0.0008.

Figure 7: Kaplan-Meier plot for all-cause mortality (FAS)



Source: Applicant, PARADIGM-HF CSR Figure 11-4.

New-Onset Atrial Fibrillation

Since the null hypothesis for all-cause mortality was rejected, the 0.8α (one-sided alpha 0.0008) initially allocated to all-cause mortality was reallocated to the new onset atrial fibrillation endpoint. There was no difference in the time to new onset atrial fibrillation (Table 25).

Table 25: Secondary efficacy analysis for new onset of atrial fibrillation (FAS)[1]

	Enalapril (N=2638[2]) n (%)	LCZ696 (N=2670[2]) n (%)	Hazard Ratio (95% CI; 1-sided p-value)
Time to first new onset atrial fibrillation	83 (3.2)	84 (3.2)	0.97 (0.72, 1.31; 0.42)

Source: Applicant, PARADIGM-HF CSR Table 11-9.
[1]Analysis shown is time to event.
[2]Analysis based on subset of FAS without a history of atrial fibrillation before randomization.

Decline in Renal Function

Since the null hypothesis for new-onset atrial fibrillation was not rejected, the renal composite endpoint was not to be formally tested according to the pre-specified statistical analysis plan. For completeness, the results for this endpoint are shown in Table 26. There was no difference in the time to the first component of the renal composite endpoint. Numerically fewer subjects in

the LCZ696 arm experienced a 50% decline in eGFR or progression to ESRD compared with the enalapril arm, but more experienced a >30 mL/min/1.73m^2 decline in eGFR to a value <60 mL/min/1.73m^2.

Table 26: Secondary efficacy analysis for renal endpoint composite event and components (FAS)[1]

	Enalapril (N=4212) n (%)	LCZ696 (N=4187) n (%)	Hazard Ratio (95% CI; 1-sided p-value)
Renal endpoint event	108 (2.6)	94 (2.3)	0.86 (0.65, 1.13; 0.14)
50% decline in eGFR	42 (1.0)	32 (0.76)	0.75 (0.48, 1.19; 0.11)
>30 mL/min/1.73m^2 decline in eGFR to value <60 mL/min/1.73m^2	69 (1.6)	77 (1.8)	1.1 (0.80, 1.53; 0.73)
ESRD	16 (0.4)	8 (0.2)	0.50 (0.21, 1.16; 0.053)

Source: Applicant, PARADIGM-HF CSR Table 11-9.
[1]Analysis shown is time to first component of composite endpoint.

6.1.6 Other Endpoints

(b) (4).

Hospitalizations
LCZ696 subjects experienced fewer first hospitalizations for any cause, for cardiovascular causes, and for non-cardiovascular causes compared with enalapril subjects (Table 27).

Table 27: Exploratory analyses of hospitalizations

	Enalapril (N=4212) n (%)	LCZ696 (N=4187) n (%)	Hazard Ratio[1] (95% CI; 2-sided p-value)
First all-cause hospitalization	1827 (43.4)	1660 (39.7)	0.88 (0.82, 0.94; 0.0001)
First cardiovascular hospitalization	1344 (31.9)	1210 (28.9)	0.88 (0.81, 0.95; 0.0008)
First non-cardiovascular hospitalization	931 (22.1)	833 (19.9)	0.87 (0.80, 0.96; 0.0047)

Source: Applicant, PARADIGM-HF CSR Table 11-11.
[1]Analysis performed using Cox-regression model with treatment and region as fixed effect factors.

The rate ratio for hospital admissions for heart failure per patient per year for LCZ696 relative to enalapril was 0.77 (95% CI 0.67-0.89; p=0004), indicating that LCZ696 subjects had a reduced "total heart failure hospitalization rate" (Table 28). The results were similar for the total number of hospitalizations from any cause.

Table 28: Exploratory analyses of heart-failure and all-cause hospitalization rates

	Enalapril (N=4212)	LCZ696 (N=4187)	Rate ratio LCZ696:enalapril (95% CI; 2-sided p-value)
Hospitalizations for heart failure			
Total admissions	1079	851	
Total years in study	9235	9308	
Unadjusted rate	0.09	0.12	
Adjusted rate[1]	0.11	0.14	0.77 (0.67, 0.89; 0.0004)
Hospitalizations for any cause			
Total admissions	4053	3564	
Total years in study	9235	9308	
Unadjusted rate	0.44	0.38	
Adjusted rate[1]	0.50	0.42	0.85 (0.78, 0.91; <0.0001)

Source: Applicant, PARADIGM-HF CSR Table 14.2-3.5.
[1]Estimated from negative binomial regression model adjusted for treatment and region.

Reviewer's comment: The reduction in heart failure hospitalizations seen with LCZ696 does not appear to come at the expense of hospitalizations for other causes.

NYHA Class
The applicant conducted an exploratory *post hoc* analysis of change in NYHA class from randomization to month 8 categorizing subjects as improved, unchanged, or worsened. Subjects were included if they had an NYHA class at both baseline and month 8 or had died. Subjects who died were categorized as worsened (NYHA class V). The majority of subjects were unchanged but slightly more subjects improved and fewer worsened in the LCZ696 arm compared with enalapril (Table 29).

Table 29: Exploratory analysis of change in NYHA class from randomization to month 8

	Enalapril (N=4072) n (%)	LCZ696 (N=4041) n (%)
Improved	569 (14.0)	639 (15.8)
Unchanged	2990 (73.4)	2989 (74.0)
Worsened	513 (12.6)	413 (10.2)

Source: Applicant, PARADIGM-HF CSR Table 11-16.

Reviewer's comment: Categorizing death as the worst possible outcome, in this case "worsened", favors LCZ696 given the difference in mortality observed by month 8.

6.1.7 Subpopulations

Demographics
Results for the primary efficacy endpoint were consistent across subgroups based on gender, age, race, and region and for subjects enrolled in the United States (Table 30).

Table 30: Primary efficacy endpoint by demographic subgroups

Subgroup		% of population	% with Endpoint		Hazard Ratio (95% CI)
			Enalapril	LCZ696	
Gender	Male	78.2	27.7	22.9	0.80 (0.73, 0.89)
	Female	21.8	22.6	18.0	0.77 (0.62, 0.94)
Age quartiles	<57	24.3	24.9	21.3	0.82 (0.68, 0.98)
	57 to 63	22.7	26.5	19.8	0.73 (0.61, 0.88)
	63 to 71	25.8	25.3	21.1	0.82 (0.68, 0.97)
	>71	27.2	29.1	24.6	0.82 (0.70, 0.96)
Race	Caucasian	66.0	25.8	21.6	0.81 (0.73, 0.90)
	Black	5.1	33.5	27.2	0.81 (0.57, 1.15)
	Asian	18.0	27.2	23.6	0.85 (0.70, 1.04)
	Other	10.9	26.6	17.5	0.64 (0.48, 0.85)
Region	Central Europe	33.6	27.5	22.8	0.79 (0.68, 0.92)
	Western Europe	24.4	23.3	21.2	0.89 (0.74, 1.07)
	Asia/Other	17.7	26.7	23.0	0.85 (0.69, 1.04)
	North America	7.2	35.3	24.8	0.67 (0.50, 0.90)
United States	No	94.8	26.0	21.6	0.81 (0.74, 0.89)
	Yes	5.2	36.8	25.8	0.66 (0.47, 0.92)

Source: Reviewer's analysis of applicant's dataset (*aendpt*).

Medical History
Results for the primary efficacy endpoint were consistent across subgroups based on medical and heart failure history (Table 31).

Table 31: Primary efficacy endpoint by baseline medical history

Subgroup		% of population	% with Endpoint		Hazard Ratio (95% CI)
			Enalapril	LCZ696	
Diabetes	No	65.5	24.0	19.0	0.77 (0.69, 0.87)
	Yes	34.5	31.4	27.2	0.83 (0.73, 0.95)
Atrial fibrillation	No	63.2	24.1	20.7	0.83 (0.74, 0.94)
	Yes	36.8	30.5	23.9	0.75 (0.66, 0.86)
Hypertension	No	29.3	24.4	20.1	0.79 (0.67, 0.93)
	Yes	70.7	27.4	22.5	0.80 (0.72, 0.89)
Etiology of heart failure	Non-ischemic	40.0	25.0	20.2	0.78 (0.67, 0.90)
	Ischemic	60.0	27.5	22.9	0.81 (0.73, 0.91)
Prior heart failure hospitalization	No	37.2	22.5	16.6	0.71 (0.61, 0.84)
	Yes	62.8	28.8	25.0	0.84 (0.76, 0.94)
Time since heart failure diagnosis	<=1 year	30.0	19.2	15.8	0.81 (0.67, 0.97)
	1-5 year	38.5	27.7	24.2	0.86 (0.75, 0.98)
	>5 years	31.5	31.8	24.8	0.73 (0.64, 0.85)
	Yes	14.8	28.2	24.6	0.85 (0.68, 1.06)

Source: Reviewer's analysis of applicant's dataset (*aendpt*).

Concomitant Heart Failure Therapy
Results for the primary efficacy endpoint were consistent across subgroups based on concomitant heart failure treatment at baseline, including for subjects with and without an ICD (Table 32).

Table 32: Primary efficacy endpoint by baseline heart failure therapy

Subgroup		% of population	% with Endpoint		Hazard Ratio (95% CI)
			Enalapril	LCZ696	
Aldosterone antagonist[1]	No	44.4	27.3	20.8	0.74 (0.65, 0.84)
	Yes	55.6	26.0	22.7	0.85 (0.76, 0.96)
Beta-blocker[1]	No	7.0	37.0	24.0	0.61 (0.45, 0.82)
	Yes	93.0	25.7	21.7	0.82 (0.75, 0.90)
ACEi[2]	No	22.2	26.0	24.0	0.92 (0.76, 1.10)
	Yes	77.8	26.7	21.2	0.77 (0.69, 0.85)
ARB[2]	No	77.5	26.7	21.2	0.77 (0.69, 0.85)
	Yes	22.5	26.1	24.0	0.92 (0.76, 1.10)
Any ICD (including CRT-D)	No	85.2	26.2	21.4	0.79 (0.72, 0.87)
	Yes	14.8	28.2	24.6	0.85 (0.68, 1.06)

Source: Reviewer's analysis of applicant's dataset (*aendpt*).
[1]Assessed at randomization.
[2]Assessed at screening.

Baseline Measures
Results for the primary efficacy endpoint were consistent across quartiles of ejection fraction, blood pressure, heart rate, and selected laboratory parameters (Table 33).

Table 33: Primary efficacy endpoint by selected baseline measures

Subgroup		% of population	% with Endpoint		Hazard Ratio (95% CI)
			Enalapril	LCZ696	
Ejection fraction quartiles (%)	<26	28.2	30.5	25.6	0.82 (0.70, 0.96)
	26 to 30	25.8	27.3	21.3	0.77 (0.65, 0.91)
	31 to 34	21.1	24.1	19.0	0.75 (0.61, 0.92)
	>34	25.0	23.2	20.7	0.86 (0.71, 1.03)
Ejection fraction (%)	≤ 35	88.5	26.8	21.8	0.79 (0.72, 0.86)
	>35	11.4	24.1	21.8	0.90 (0.69, 1.17)
SBP quartiles[1] (mmHg)	<116[2]	23.9	29.6	22.1	0.71 (0.60, 0.84)
	116 to 127	25.0	27.5	24.0	0.87 (0.74, 1.03)
	128 to 139	24.2	25.8	21.2	0.79 (0.66, 0.94)
	>139	26.9	23.5	20.2	0.84 (0.70, 1.00)
Heart rate quartiles[3]	<65	27.6	24.3	19.4	0.78 (0.65, 0.93)
	65 to 71	22.6	24.8	19.5	0.76 (0.62, 0.92)
	72 to 79	23.6	27.9	22.2	0.77 (0.64, 0.91)
	>79	26.2	29.0	26.3	0.89 (0.76, 1.04)
BNP quartiles[1] (pmol/L)	<45	25.4	16.1	12.4	0.74 (0.59, 0.93)
	45	24.2	21.4	16.4	0.74 (0.61, 0.91)
	73	24.8	27.6	22.8	0.80 (0.67, 0.95)
	>=1	25.0	41.9	35.5	0.83 (0.72, 0.95)
eGFR quartiles[3] (mL/min/1.73m^2)	<54	23.9	33.8	28.3	0.80 (0.68, 0.94)
	54 to 66	25.8	27.9	22.1	0.78 (0.66, 0.93)
	67 to 79	24.8	22.5	19.6	0.85 (0.70, 1.02)
	>79	25.4	22.2	17.7	0.78 (0.64, 0.94)

Source: Reviewer's analysis of applicant's dataset (*aendpt*).
[1]Assessed at screening.
[2]Eligibility criteria specified a SBP >100mmHg at screening.
[3]Assessed at randomization.

Results for the primary efficacy endpoint favored LCZ696 for NYHA classes II-IV, the classes for which the applicant is seeking an indication (Table 34). The pre-specified baseline for NYHA class was the value at randomization; however, as was shown in Section 6.1.2, NYHA class shifted in some subjects during the run-in period between screening and randomization. When analyzed using NYHA class at screening, the point estimates vary somewhat for NYHA classes I and IV but, given the small numbers, the confidence intervals are wide.

Table 34: Primary efficacy endpoint by NYHA class

Subgroup		% of population	% with Endpoint		Hazard Ratio (95% CI)
			Enalapril	LCZ696	
NYHA class at randomization	I	4.6	16.7	18.3	1.07 (0.66, 1.72)
	II	70.5	25.4	19.3	0.74 (0.66, 0.82)
	III	24.0	31.4	30.1	0.93 (0.79, 1.09)
	IV	0.7	40.7	30.3	0.75 (0.32, 1.77)
NYHA class at screening	I	0.3	7.1	28.6	2.07 (0.21, 20.95)
	II	64.7	23.1	17.7	0.75 (0.66, 0.84)
	III	33.4	32.7	29.4	0.87 (0.76, 0.99)
	IV	1.5	37.3	36.5	1.03 (0.57, 1.85)

Source: Reviewer's analysis of applicant's dataset (*aendpt*).

As shown in Table 34, although LCZ696 subjects who were NYHA class III at randomization experienced fewer primary endpoint events than enalapril subjects, the hazard ratio of 0.93 (95% CI 0.79 to 1.09) was less favorable than that of NYHA class II and IV subjects. When the components of the primary endpoints are evaluated separately, LCZ696 subjects who were NYHA class III at randomization experienced numerically more first heart failure hospitalizations but had fewer cardiovascular deaths than enalapril subjects (Table 35). Using NYHA class at screening, however, the difference in heart failure hospitalizations is no longer apparent. LCZ696 subjects who were NYHA class IV at randomization experienced fewer first heart failure hospitalizations and total cardiovascular deaths, differences that are no longer apparent when using NYHA class at screening.

Table 35: First heart failure hospitalization and total cardiovascular death by NYHA class

Subgroup		% of population	% with Endpoint		Hazard Ratio (95% CI)
			Enalapril	LCZ696	
NYHA class at randomization					
First heart failure hospitalization	I	4.6	10.0	7.2	0.70 (0.35, 1.41)
	II	70.5	15.7	11.3	0.70 (0.61, 0.81)
	III	24.0	16.3	18.2	1.08 (0.88, 1.34)
	IV	0.7	25.9	24.2	0.93 (0.34, 2.56)
Total cardiovascular deaths	I	4.6	9.6	13.3	1.37 (0.76, 2.48)
	II	70.5	15.1	11.6	0.77 (0.67, 0.88)
	III	24.0	21.4	18.5	0.82 (0.68, 1.00)
	IV	0.7	22.2	18.2	0.90 (0.29, 2.78)
NYHA class at screening					
First heart failure hospitalization	I	0.3	7.1	21.4	2.07 (0.21, 20.95)
	II	64.7	13.7	9.9	0.70 (0.60, 0.82)
	III	33.4	18.9	18.0	0.92 (0.78, 1.09)
	IV	1.5	23.7	27.0	1.17 (0.58, 2.38)
Total cardiovascular deaths	I	0.3	0.0	14.3	--
	II	64.7	14.1	10.8	0.76 (0.66, 0.89)
	III	33.4	20.7	17.9	0.84 (0.71, 0.99)
	IV	1.5	25.4	25.4	1.06 (0.53, 2.15)

Source: Reviewer's analysis of applicant's dataset (*aendpt*).

Reviewer's comments:
It is not clear that the nominal variations in the results of the primary endpoint by NYHA class represent clinically meaningful differences in efficacy for several reasons:

1. *Given the large number of subgroups evaluated, there is a high likelihood of chance findings.*
2. *Only 24% of subjects were NYHA class III at randomization and <1% were NYHA class IV. With relatively small numbers, especially for NYHA class IV, the findings can be influenced by small changes in event numbers.*
3. *NYHA class is a relatively subjective assessment and subjects can move between classes over short periods of time as symptoms change. For the above analyses, simply using NYHA class at screening rather than at randomization gives a different point estimate and impression of the treatment effect.*
4. *No differences were observed for subgroups based on LVEF and BNP, other markers of disease severity.*
5. *The mechanistic pathways through which LCZ696 is hypothesized to provide clinical benefit should be relevant to NYHA classes II-IV so there is no obvious biologic rationale for differences in efficacy by NYHA class.*

Although NYHA class I subjects were not targeted for enrollment, a small number of subjects classified as NYHA class I at randomization entered the study through protocol violations or improvement in NYHA class during the run-in period. The results for this subgroup vary, at times favoring LCZ696 and other times not; however, it is difficult to draw conclusions about the effect of LCZ696 in asymptomatic NYHA class I subjects given the small numbers. The applicant is not seeking an indication for NYHA class I.

Results for the primary efficacy endpoint were consistent across quartiles of weight (Table 36). When evaluated by gender, there was more variability in the results for female subjects; however, women represented less than 25% of the total population so each quartile represents a small percentage of subjects and small differences in event numbers can influence the results.

Table 36: Primary efficacy endpoint by weight at randomization

Subgroup		**% of population**	**% with Endpoint**		**Hazard Ratio (95% CI)**
			Enalapril	**LCZ696**	
Weight quartiles	<67.5	25.0	25.4	21.3	0.83 (0.69, 0.99)
	67.5 to 78.9	24.8	27.6	23.2	0.80 (0.68, 0.95)
	79 to 91.6	25.2	26.5	22.0	0.82 (0.69, 0.97)
	>91.6	25.1	26.6	20.8	0.75 (0.63, 0.90)
Male/weight quartiles	<70	18.8	27.5	24.1	0.87 (0.71, 1.05)
	70 to 80.9	19.7	28.2	23.4	0.79 (0.65, 0.95)
	81 to 93.9	20.2	27.3	21.4	0.76 (0.62, 0.92)
	>93.9	19.5	27.7	22.6	0.80 (0.66, 0.97)
Female/ weight quartiles	<59.5	5.4	21.7	17.2	0.76 (0.50, 1.15)
	59.5 to 69.9	5.3	18.1	18.6	1.05 (0.68, 1.63)
	70 to 81.9	5.5	29.0	18.5	0.57 (0.38, 0.83)
	>81.9	5.5	21.7	17.6	0.77 (0.51, 1.17)

Source: Reviewer's analysis of applicant's dataset (*aendpt*).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant has proposed the following dosing recommendations:

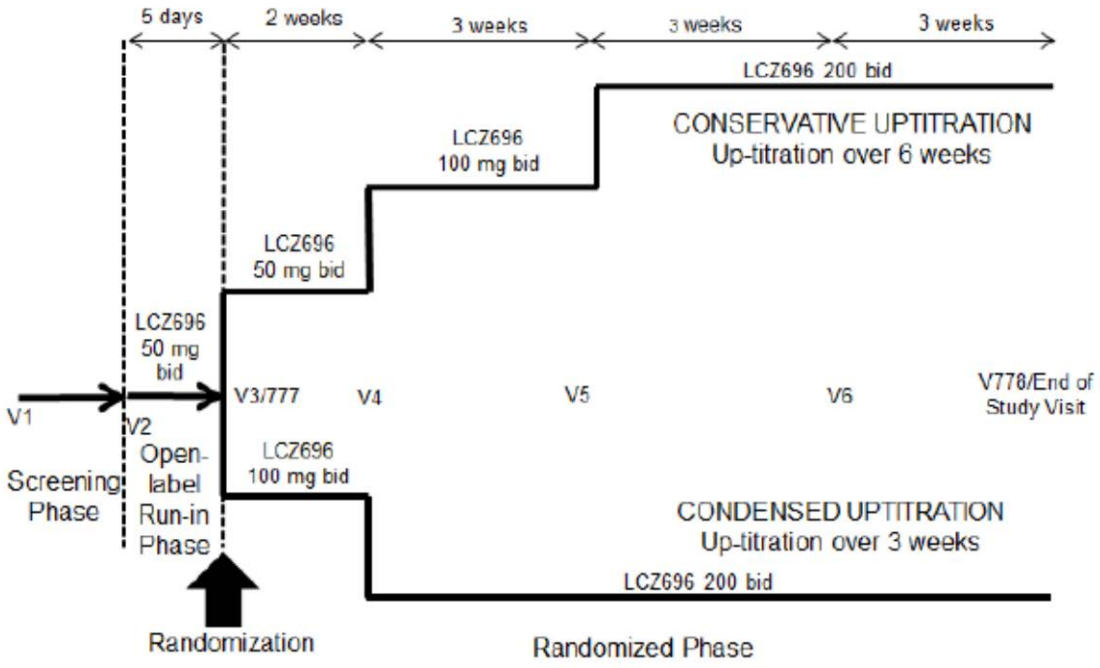
The applicant did not perform phase 2 dose-ranging studies for LCZ696 in patients with heart failure. Instead, the target dose of 200 mg bid was chosen to deliver valsartan exposure similar to the valsartan 160 mg bid dose approved for heart failure. In addition, the applicant stated that biomarker analyses (cGMP) indicated that this dose of LCZ696 provides approximately 90% neprilysin inhibition. While subjects in hypertension studies received LCZ696 400 mg once daily, the applicant elected to split the dose for subjects with heart failure to "ensure sustained NEP inhibition over 24 hours" and to mitigate the risk of hypotension.

As described in Section 5.3, all subjects in PARADIGM-HF were on an ACEi or ARB at screening before entering a single-blind run-in period. During the run-in period, subjects who tolerated enalapril 10 mg bid for at least two weeks were started on LCZ696 100 mg bid. Those who tolerated LCZ696 100 mg bid for at least two weeks were increased to LCZ696 200 mg bid. Subjects who tolerated LCZ696 200 mg bid for at least two weeks were eligible for randomization. Therefore, PARADIGM-HF does not provide information regarding the tolerability of LCZ696 or appropriate titration for patients who are ACEi/ARB naïve or on lower doses at baseline. Of note, a 50 mg tablet of LCZ696 was not available for upward dose-titration during the run-in period but was available for downward dose titration, as needed, during the randomized period.

The applicant proposes to recommend a starting dose of LCZ696 50 mg bid for patients who are ACEi/ARB naïve or on lower doses at baseline. To inform the titration regimen, the applicant conducted TITRATION (CLCZ696B2228), a 3-month, randomized, double-blind comparison of two different upward dose titration regimens in 497 subjects with HFrEF. All subjects in TITRATION received open-label LCZ696 50 mg bid during a run-in phase of approximately one week (see Figure 8). Subjects tolerating this dose were then randomized to a condensed titration regimen starting with 100 mg bid and titrating to 200 mg bid over 3 weeks (246 subjects) or a conservative up-titration regimen starting at 50 mg bid and titrating to 200 mg bid over 6 weeks. Randomization was stratified by ACEi/ARB use at screening as follows:

- High dose stratum: equivalent of >160 mg of valsartan or >10 mg enalapril daily.
- Low dose stratum: equivalent of ≤ 160 mg of valsartan or ≤10 mg enalapril daily, including subjects on no ACEi or ARB.

Figure 8: TITRATION study design



Source: Applicant Figure 9-1 in the CSR for study CLCZ696B2228

The incidence of key risks by stratum and titration regimen is shown in Table 37. Overall, there were no major differences in the titration regimens with the exception of hyperkalemia. The incidence of hyperkalemia was higher for the 3-week regimen compared to the 6-week regimen (19/246 [7.7%] vs. 12/251 [4.8%]). For subjects in the low dose stratum, the incidence of key risks was lower with the 6-week regimen compared with the 3-week regimen with the exception of angioedema. This was not observed for ACEi and ARB naïve subjects, but the small number of subjects limits interpretation of the data.

Reviewer's comment: The proposed titration scheme seems reasonable. A longer titration period with a starting dose of 50 mg bid may reduce the risk of hypotension, renal impairment and hyperkalemia in patients previously on a low dose of an ACEi or ARB.

Table 37: Incidence of safety topics of interest in the double-blind randomization phase[a]

Safety Topics	RAAS stratum at screening	LCZ696 200 mg bid	
		Condensed up-titration (3-week regimen) N=246	Conservative up-titration (6-week regimen) N =251
Hypotension[b]	**All**	**33/246 (13.4%)**	**31/251 (12.3%)**
	Low RAAS[d]	24/127 (18.9%)	18/124 (14.5%)
	-ACE/ARB Naive	3/17 (17.6%)	4/16 (25.0%)
	High RAAS[e]	9/119 (7.6%)	13/127 (10.2%)
Hyperkalemia[b]	**All**	**19/246 (7.7%)**	**12/251 (4.8%)**
	Low RAAS[d]	11/127 (8.7%)	6/124 (4.8%)
	-ACE/ARB Naive	1/17 (5.9%)	2/16 (12.5%)
	High RAAS[e]	8/119 (6.7%)	6/127 (4.7%)
Renal Impairment[c]	**All**	**19/246 (7.7%)**	**20/251 (8.0%)**
	Low RAAS[d]	14/127 (11.0%)	11/124 (8.9%)
	-ACE/ARB Naive	3/17 (17.6%)	3/16 (18.8%)
	High RAAS[e]	5/119 (4.2%)	9/127 (7.1%)
Angioedema	**All**	**0/246 (0.0%)**	**2/251 (0.8%)**
	Low RAAS[d]	0/127 (0.0%)	1/124 (0.8%)
	-ACE/ARB Naive	0/17 (0.0%)	0/16 (0.0%)
	High RAAS[e]	0/119 (0.0%)	1/127 (0.8%)

[a] The double-blind phase includes both up-titration and target treatment phases. The result in the up-titration phase was in general consistent with that in the double-blind phase. (see section 9.11).
[b] include relevant MedDRA preferred terms (see section 9.8)
[c] use MedDRA Acute Renal Failure Broad SMQ
[d] >160 mg of valsartan or >10 mg total daily dose of enalapril, or equivalent doses of other ACEis/ARBs
[e] ≤ 160 mg of valsartan or ≤10 mg total daily dose of enalapril, or equivalent doses of other ACEis/ARBs at screening, which included ACEi/ARB naïve patients
Review's Table, Data source: AIDENT & AEEV in TITRATION

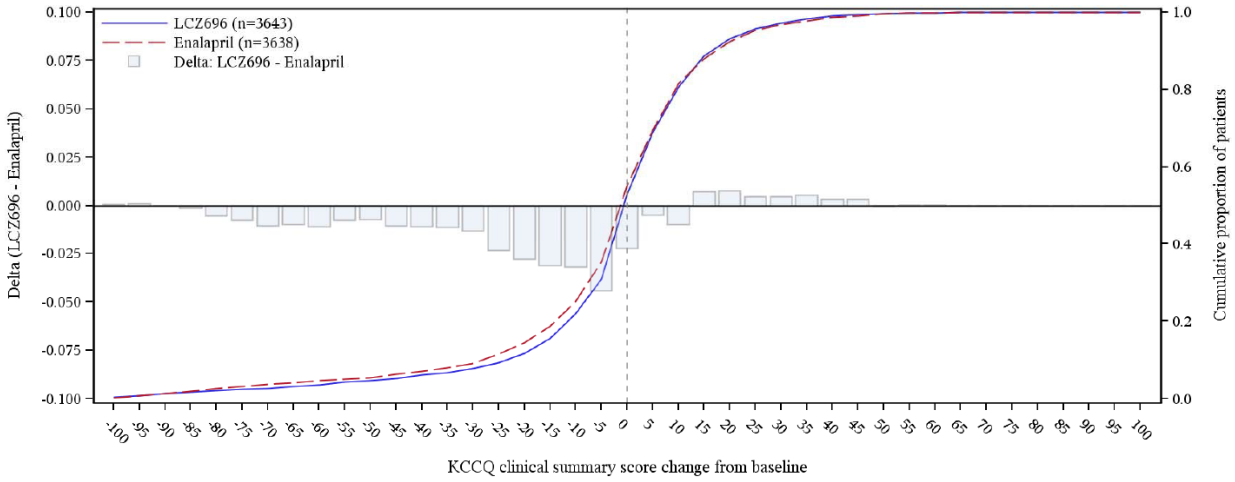
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The Kaplan-Meier curves for the primary composite endpoint of cardiovascular death or first hospitalization for heart failure and for the individual components suggest no loss of efficacy over time (see Section 6.1.4).

6.1.10 Additional Efficacy Issues/Analyses

Kansas City Cardiomyopathy Questionnaire
The applicant conducted several exploratory analyses of the KCCQ data. A plot of the cumulative distribution of the change in CSS from baseline to month 8 does not show evidence of a subpopulation with a more marked response (Figure 9).

Figure 9: Cumulative distribution of change from baseline in KCCQ at month 8



Source: Applicant, PARADIGM-HF CSR, Figure 14.2-2.4.post.02b.

Since, according to the applicant, a five point change in the CSS is believed to represent a small but clinically meaningful difference, the applicant conducted responder analyses based on the number of subjects with at least a five-point deterioration or improvement in the CSS from baseline to month 8. Fewer LCZ696 subjects deteriorated by ≥5 points on the CSS or its individual components compared with enalapril subjects (Table 38). There was no difference in the number of subjects with a ≥ 5 point improvement (Table 39).

Table 38: Subjects with a five point deterioration from baseline in KCCQ at month 8

	Enalapril n/N[2] (%)	LCZ696 n/N[2] (%)	Odds Ratio[3] (95% CI; 2-sided p-value)
Clinical summary score[1]	1283/3638 (35.3)	1124/3643 (30.9)	0.82 (0.74, 0.90; <0.001)
Physical limitation	1242/3589 (34.6)	1128/3588 (31.4)	0.87 (0.78, 0.96; 0.004)
Total symptom	1304/3635 (35.9)	1157/3640 (31.8)	0.83 (0.75, 0.92; <0.001)
Symptom frequency	1277/3632 (35.2)	1124/3637 (30.9)	0.82 (0.75, 0.91; <0.001)
Symptom burden	1358/3635 (37.4)	1244/3640 (34.2)	0.87 (0.79, 0.96; 0.005)

Source: Applicant, PARADIGM-HF CSR Table 11-8.
[1]Includes subjects with a KCCQ CSS score at both baseline and month 8 and subjects who died.
[2]Number of subjects with at least a five point deterioration (n)/number of patients with data for component (N).
[3]Based on logistic regression model with treatment and region as fixed factors. Odds ratio <1 favors LCZ696.

Table 39: Subjects with a five point improvement from baseline in KCCQ at month 8

	Enalapril n/N[2] (%)	LCZ696 n/N[2] (%)	Odds Ratio[3] (95% CI; 2-sided p-value)
Clinical summary score[1]	1113/3638 (30.6)	1132/3643 (31.1)	1.02 (0.93, 1.13; 0.64)
Physical limitation	1050/3589 (29.3)	1093/3588 (30.5)	1.06 (0.96, 1.17; 0.25)
Total symptom	1071/3635 (29.5)	1132/3640 (31.1)	1.08 (0.98, 1.2; 0.12)
Symptom frequency	1084/3632 (29.9)	1136/3637 (31.2)	1.07 (0.97, 1.18; 0.19)
Symptom burden	1131/3635 (31.1)	1153/3640 (31.7)	1.03 (0.93, 1.13; 0.59)

Source: Applicant, PARADIGM-HF CSR Table 14.2-3.23.
[1]Includes subjects with a KCCQ CSS score at both baseline and month 8 and subjects who died.
[2]Number of subjects with at least a five point improvement (n)/number of patients with data for component (N).
[3]Based on logistic regression model with treatment and region as fixed factors. Odds ratio >1 favors LCZ696.

As described in Section 5.3, the KCCQ was administered at the start of the double-blind treatment period (randomization visit), at the 4, 8, 12, 24, and 36 month visits, and at the end of the study. At each visit during which the KCCQ was to be administered, investigator's completed a page in the Case Report Form indicating whether the KCCQ questions had been fully or partially completed and, if not, checking the reason why. At randomization 89% of subjects in each group fully completed the KCCQ assessment (Table 40). By month eight, this number fell to 80.7% of enalapril and 81.9% of LCZ696 subjects. The most common reason for failure at both time points was the questionnaire was not available in the subject's language, a protocol-specified exemption. By month eight, 247 (5.9%) enalapril and 208 (5.0%) LCZ696 subjects had died. Of these, 30 enalapril and 25 LCZ696 did not have baseline KCCQ data and were therefore excluded from KCCQ analyses.

Table 40: Completion of KCCQ instrument at randomization and month eight visit (FAS)

	Enalapril (n=4212) n (%)	**LCZ696 (n=4187) n (%)**
Randomization		
Fully completed	3758 (89.2)	3733 (89.2)
Partially completed	68 (1.6)	64 (1.5)
Not completed	386 (9.2)	390 (9.3)
Questionnaire not available in language	323 (7.7)	334 (8.0)
Other	48 (1.1)	45 (1.1)
Institutional error	9 (0.2)	7 (0.2)
Patient refused (unrelated to health)	5 (0.1)	1 (0)
Patient missed scheduled assessment visit	1 (0)	0 (0)
Patient refused due to poor health	0 (0)	2 (0)
Study staff felt patient was too ill	0 (0)	1 (0)
Month eight		
Fully completed	3399 (80.7)	3428 (81.9)
Partially completed	53 (1.3)	55 (1.3)
Not completed – reason indicated	478 (11.3)	471 (10.0)
Questionnaire not available in language	293 (7.0)	302 (7.2)
Other	102 (2.4)	104 (2.5)
Patient missed scheduled assessment	33 (0.8)	34 (0.8)
Patient refused (unrelated to health)	21 (0.5)	18 (0.4)
Institutional error	19 (0.5)	11 (0.3)
Patient refused due to poor health	6 (0.1)	1 (0.0)
Study staff felt patient was too ill	4 (0.1)	1 (0.0)
Missing KCCQ data and completion information	282 (6.7)	233 (5.6)
Dead	247 (5.9)	208 (5.0)
Withdrew consent	2 (0)	3 (0.1)
Lost to follow-up	1 (0)	0 (0)
No data entered	32 (0.8)	22 (0.5)

Source: Reviewer's analysis of applicant's dataset (*aident, akcqsum*). Applicant's analyses (*Response to Information Request – Clinical* dated February 27, 2015; April 3, 2015).

To address missing data, the applicant conducted two sensitivity analyses. For the first, the CSS for visits following death was considered missing rather than 0, thereby excluding patients who died before month 8 from the analysis. This resulted in an attenuated treatment effect (Table 41).

For the second sensitivity analysis, a CSS of 0 was imputed following death as was done for the KCCQ secondary endpoint analysis but, instead of excluding other missing data, values were imputed using a multiple imputation approach applying varying penalty factors for data missing following a heart failure hospitalization. The result of this analysis was similar to the main secondary endpoint analysis.

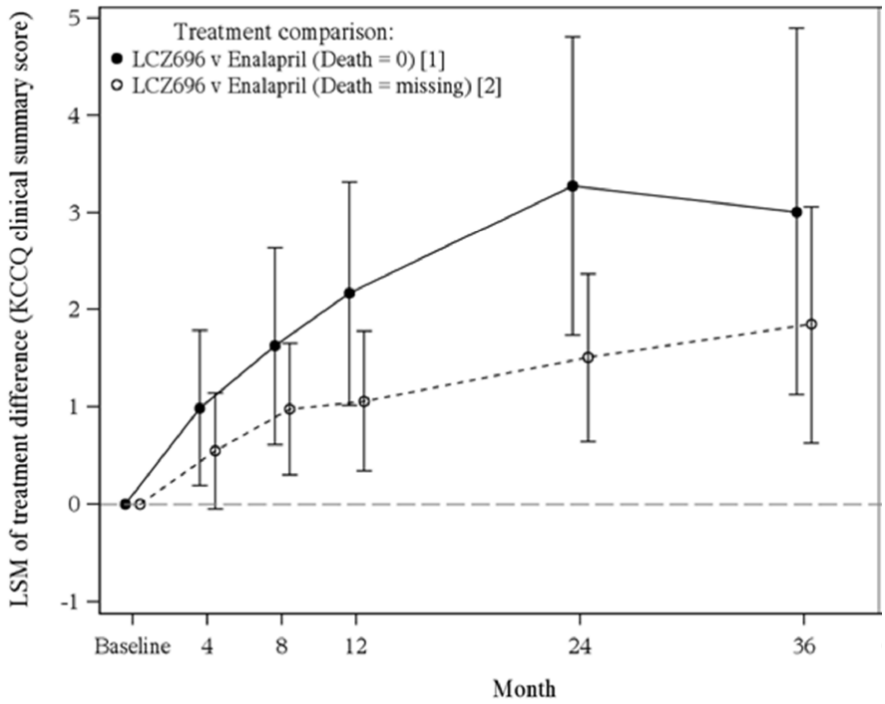
Table 41: Sensitivity analyses for KCCQ clinical summary score endpoint

	Enalapril		LCZ696		LSM of difference (95% CI; 2-sided p-value)
	n	LSM (SE)	n	LSM(SE)	
Death = missing	3421	-0.57 (0.24)	3460	0.41 (0.24)	0.98 (0.30, 1.66; 0.005)
Death = 0; other missing data imputed[1]	3638	-4.73 (0.36)	3643	-3.03 (0.36)	1.70 (0.70, 2.7; 0.004)

Source: Applicant, PARADIGM-HF CSR, Tables 14.2-3.21.1 and 14.2-2.4.1
[1]Results shown for worst penalty of 1 applied to data missing following heart failure hospitalization.

The LSM of the treatment difference favored LCZ696 throughout the duration of the study when a CSS of 0 was imputed following death, peaking around month 24 (Figure 10). Again, the treatment difference was attenuated when subjects who died were excluded from the analysis instead (death = missing).

Figure 10: Change in KCCQ clinical summary score from baseline with different assumptions for death (FAS)



Source: Applicant, PARADIGM-HF CSR Figure 11-5.

At baseline, the mean CSS was approximately 76 (Table 42). When a CSS of 0 was imputed following death, the CSS declined less from baseline to month 8 in the LCZ696 group compared with the enalapril group, although both groups declined by less than five points. When subjects who died before month 8 were excluded from the analysis, there was no change in the CSS through month 8.

Table 42: Mean KCCQ clinical summary score by month

	Death = 0				Death = missing			
	Enalapril		LCZ696		Enalapril		LCZ696	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Month 0	3826	75.3 (19.3)	3797	76.6 (19.3)	3826	75.3 (19.3)	3797	76.6 (19.3)
Month 4	3720	73.6 (23.6)	3699	75.5 (22.7)	3602	76.0 (19.8)	3605	77.4 (19.4)
Month 8	3701*	70.6 (27.4)	3691*	73.2 (26.2)	3452	75.7 (20.5)	3482	77.6 (19.7)

Source: Reviewer's analysis of applicant's dataset (*akcqsum*). Includes all data available at each time point.
* Includes 249 enalapril and 209 LCZ696 with CSS of 0 imputed.

Reviewer's comment: The difference in CSS between the treatment arms observed for the KCCQ secondary endpoint analysis appears to be driven primarily by the handling of missing data following death. More enalapril than LCZ696 subjects died before month 8 and were (b) (4)

(b) (4)

7 Review of Safety

Safety Summary

Overview of safety database

The clinical safety of LCZ696 in HFrEF was evaluated using the safety data from the phase 3 pivotal trial, PARADIGM-HF. As described in Section 5.3, subjects first entered sequential run-in periods in which they were exposed to enalapril 10 mg bid (median duration of 15 days) followed by LCZ696 100 mg bid, increasing to 200 mg bid (median duration of 29 days). Subjects who tolerated the study drug and met pre-specified safety criteria at the end of each run-in period could continue in the trial.

A total of 10,513 patients were exposed to enalapril and 9,419 patients were exposed to LCZ696 during the run-in periods. A total of 8,442 subjects who successfully completed the run-in periods were randomized to LCZ696 200 mg bid and enalapril 10 mg bid in the double-blind treatment period. The safety dataset contains a total of 8,432 subjects who received at least one dose of study drug in the double-blind period (n=4,229 and 4,203 in the enalapril and LCZ696 arms, respectively). Overall, the two treatment arms had a similar duration of drug exposure (median drug exposure: ~24 months) and similar patterns of dropouts and discontinuations.

Additional supportive safety data are provided by two phase 2 studies in HF patients who received the target dose of LCZ696 200 mg bid and studies in patients with hypertension (HTN) who received LCZ696 at doses up to 400 mg once daily. These studies provide information on safety in patients who are ACE inhibitor or ARB naïve (n=2187).

In sum, the safety database (size and duration of exposure at relevant doses) is sufficient to evaluate the safety of LCZ696 in patients with HFrEF.

Safety topics of interest

Based on the mechanism of action of LCZ696, class effects associated with RAAS inhibitors, and experience with omapatrilat, a combination neprilysin and ACEi, safety topics of interest included angioedema, hypotension, renal impairment and hyperkalemia. Moreover, cognitive impairment was also a safety topic of interest based on the theoretical risk that inhibition of neutral endopeptidase (NEP) could accentuate accumulation of beta amyloid in the brain and increase the risk of Alzheimer's disease. The main findings for these safety topics of interest are discussed below.

(1) Risk of angioedema

There were 54 confirmed angioedema events in PARADIGM-HF. The majority were not serious and none involved airway compromise or required airway support. Of these cases, 15 occurred during the enalapril run-in period (0.1% of subjects) and 10 occurred in the LCZ696 run-in period (0.1% of subjects). In the double-blind period, the incidence of angioedema was low overall, but somewhat higher in the LCZ696 arm than in the enalapril arm (n=19, 0.5% of subjects and n=10, 0.2% of subjects, respectively).

a. Increased risk of angioedema in blacks

Because of the small number of angioedema events, it is difficult to identify risk factors for angioedema. However, the incidence was higher in blacks in the LCZ696 arm (n = 5, 2.4% of black subjects) compared to the enalapril arm (n=1, 0.5% of black subjects) in the double-blind period. The incidence was highest in black subjects treated with LCZ696 in the United States (n = 3/54, 5.6%) compared to no cases (0/57) in the enalapril arm. Given that only 5% of PARADIGM-HF subjects were black, there is substantial uncertainty in these risk estimates. The findings are nonetheless concerning as a large proportion of HF patients in the United States are black and blacks are known to be more susceptible to angioedema induced by ACEis and neprilysin inhibitors. Hence, we believe that a postmarking observational study is needed to better characterize the risk of serious angioedema in black patients treated with LCZ696 in the United States.

b. Transition from ACE inhibitor to LCZ696 and vice versa

Because the risk of angioedema may be increased by concomitant administration of ACE and NEP inhibitors (see discussion in Section 7.2.6 describing the experience with omapatrilat, a combined ACE/NEP inhibitor), the applicant employed a short washout period (~36 hours) between (1) the enalapril run-in period and LCZ696 run-in period and (2) the LCZ696 run-in period and double-blind treatment period. Evaluation of the time course of angioedema events did not suggest a clustering of cases during these transition periods, suggesting that the strategy was effective. However, three confirmed cases of angioedema occurred in subjects given an ACEi within < 36 hours of discontinuing LCZ696 or vice versa. The applicant proposes to address this safety issue via prescriber labeling including a contraindication which states" (b) (4) The applicant has also proposed a (b) (4). We believe a contraindication is reasonable but it should address the transition both from an ACEi to LCZ696 and from LCZ696 to an ACEi. (b) (4)

(b) (4)

(2) Risk of hypotension

Hypotension-related AEs were reported more frequently in the LCZ696 arm compared to the enalapril arm (24.4% vs. 18.6%; event rate: 13.2 vs. 9.5 per 100 patient-years; HR 1.4, 95% CI 1.3, 1.5). However, the incidence of hypotension-related SAEs was not higher in the LCZ696 arm compared to the enalapril arm (2.8% vs. 3.5%). There was also no imbalance between the two arms with regard to the incidence of events of greater clinical severity such as syncope, pre-syncope, and loss of consciousness (Table 64). Vital sign data were generally consistent with the AE findings.

About half of the hypotension-related events in the LCZ696 arm did not require any intervention and the rest were largely manageable by adjusting the dose of LCZ696 and/or adjusting/interrupting concomitant medications (e.g., diuretics). Very few events (<0.1%) lead to study drug discontinuation in the double-blind period. The hypotension results were consistent for all subgroups evaluated with a HR >1.2, indicating an increased risk in the LCZ696 arm.

(3) Risk of renal impairment

The incidence of renal impairment-related AEs was similar between the LCZ696 arm and the enalapril arm during the double-blind period in PARADIGM-HF (16.2% vs. 17.6%; event rate: 7.9 vs. 8.8 per 100 patient-years, HR 0.9, 95% CI 0.8,1.0). The incidence of renal impairment-related SAEs was also similar in the two treatment arms.

(4) Risk of hyperkalemia

The incidence of hyperkalemia-related AEs was slightly lower in the LCZ696 arm compared to the enalapril arm during the double-blind period in PARADIGM-HF (11.9% vs. 14.3%; event rate: 5.7 vs. 7.1 per 100 patient-years; HR 0.8, 95% CI 0.7, 0.9). Hyperkalemia-related SAEs were also reported less frequently in the LCZ696 arm (0.4%) compared to the enalapril arm (1.0%).

(5) Theoretical risk of amyloid deposition in the brain resulting in cognitive impairment/Alzheimer's disease

NEP is a plasma membrane glycoprotein of the neutral zinc metallo-endopeptidase family and is believed to be a major beta amyloid-degrading enzyme in the brain. In theory, inhibition of NEP could accentuate accumulation of beta amyloid and increase the risk of Alzheimer's disease (AD). In monkeys, treatment with LCZ696 was associated with increases in beta amyloid (β-Amyloid 1-38, 1-40 & 1-41) in the CSF, but not in the brain tissue. Administration of LCZ696 400 mg qd for 2 weeks in healthy subjects was associated with a 42% increase in CSF β-Amyloid 1-38 relative to baseline and a 50% increase in plasma β-Amyloid 1-40. However, the clinical significance of these findings is not known.

In PARADIGM-HF, there was no detected safety signal with regard to the risk of cognitive impairment/Alzheimer's disease; the incidence of cognitive impairment-related AEs was low (~2 %) and similar between the two treatment arms (Table 77). While it would be ideal to further characterize this risk, given the favorable mortality findings, we do not believe that it would be feasible to do so via a post-marketing trial in patients with HFrEF. We note that the applicant is planning to (1) (b) (4) and (2) conduct a stand-alone trial ((b) (4)) in a patient population similar to (b) (4) , which will include additional neurocognitive testing. Both may provide further insight into the theoretical risk of amyloid-β deposition in the brain. At present, it is unclear whether cognitive impairment/Alzheimer's disease is a potential risk of LCZ696. However, this safety concern is mitigated by the projected lifespan of patients with HFrEF and the relatively early mortality benefit of LCZ696 observed in PARADIGM-HF.

(6) Other safety issues of interest

a. Considerations related to the interpretation of safety findings

While the risk of known toxicities was similar between the two treatment arms in the double-blind period in PARADIGM-HF, one should interpret the results with caution given the design of PARADIGM-HF. PADRADIGM-HF included sequential run-in periods in which subjects were exposed to enalapril followed by LCZ696. Approximately 20% of subjects entering the run-in period did not tolerate one of these drugs and were excluded from the study. The most common reasons for study drug discontinuation in the run-in period were adverse events such as hyperkalemia, hypotension and renal impairment. These adverse reactions were seen early following initiation of therapy and a sizeable portion of subjects were excluded from the study in the run-in period because of these adverse reactions (Table 50). Subjects with worse renal function (eGFR < 60 mL/min) and NYHA class III and IV subjects were more likely to fail the run-in period (Table 51). The run-in design thus resulted in a highly selected patient population entering into the double-blind period, which diminishes the generalizability of the safety results. As a result, the trial results may underestimate the incidence of key toxicities.

Similarly, for angioedema, 23 out of 25 subjects with a confirmed angioedema event in the run-in period were excluded from the study prior to the double-blind treatment period. The angioedema events in the run-in period also had an earlier time course compared to events occurring in the double-blind period (Table 59). Furthermore, patients with history of angioedema were excluded from the study. Thus, the incidence of angioedema in the indicated population may be higher in the post-market setting.

Of note, patients with HFrEF naïve to ACEi or ARB were not studied in PARADIGM-HF. Available evidence does not suggest that the safety profile of LCZ696 would be significantly different between ACEi/ARB naïve patients and ACEi/ARB experienced patients; though very small numbers of ACEi/ARB naïve patients were studied in the indicated population.

b. Proposed titration strategy

The results of the phase 2 dose regimen study (TITRATION) suggests that patients who were previously on low dose of ACEi and ARBs might benefit from a slow up-titration regimen (a 6-week regimen) rather than a fast up-titration regimen (a 3-week regimen) to increase tolerability and reduce the risk of adverse events such as hypotension, hyperkalemia and renal impairment. We agree with the proposed titration strategy from a safety perspective.

Overall, LCZ696 has an acceptable safety profile in patients with HFrEF. We believe that the key toxicities of LCZ696 can be managed through proper labeling. There are no safety issues that would preclude the approval of LCZ696.

7.1 Methods

The pivotal phase 3 trial, PARADIGM-HF, and two supportive phase 2 studies, PARAMOUNT and TITRATION, serve as the primary sources of safety data for the application. The applicant also provided supportive safety data from six completed studies in patients with hypertension (HTN). These short-term, controlled studies (treatment duration ranged from 8-14 weeks) tested doses up to 400 mg once daily and included patients who were ACEi or ARB naïve (n =2187/4637, 47%). See Section 7.1.1 for an overview of these studies.

Safety analyses of PARADIGM-HF

PARADIGM-HF provides the greatest patient exposure in the target patient population; hence safety analyses were primarily based on the data from this trial. The safety review focused on characterizing the risk of angioedema and the known adverse effects of RAAS inhibitors including hypotension, renal impairment and hyperkalemia.

Safety analyses used the safety set in PARADIGM-HF - all patients who took at least one dose of study drugs during the treatment period. Since angioedema or angioedema-like events were adjudicated in PARADIGM-HF, safety analyses focused on these adjudicated cases. For other safety topics of interest, searches were performed using either a standardized MedDRA query (SMQ), or groupings of relevant MedDRA preferred terms (PTs) (see Section 9.8). In general, exposure-adjusted event rates (per 100 patient-years), in addition to incidence rates, were calculated for safety topics of interest.

In addition to focusing on the aforementioned safety topics of interest, analyses also focused on:

- Cognitive impairment: NEP is believed to be a major beta amyloid-degrading enzyme in the brain; in theory, inhibition of NEP could accentuate accumulation of beta amyloid in the brain and increase the risk of Alzheimer's disease
- Gastric lesions: Local irritant effects of LCZ696 resulting in gastric lesions were reported in preclinical studies

AEs/SAEs related to cognitive impairment and gastric lesions in PARADIGM-HF were evaluated using the MedDRA Dementia SMQ and groupings of MedDRA PTs that might be indicative of gastric lesion (see Section 9.8).

Other routine safety assessments including, assessments for hepatotoxicity and cancer promotion were also performed. The review also assessed for other potential risks by evaluating AEs using all levels of MedDRA terms and standard MedDRA queries (SMQs).

Safety analyses using data from other studies
Safety data from other supportive studies were primary used to evaluate additional confirmed angioedema events in subjects treated with LCZ696 and to assess whether the safety profile of LCZ696 in ACEi/ARB naïve patients was consistent with that seen in PARADIGM-HF.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 43 provides an overview of the three HF studies supporting the safety of LCZ696. See Section 5.3 for a detailed discussion of the design of PARADIGM-HF (B2314) and Section 6.1.8 for the design of the TITRATION study (B2228). A brief description of the PARAMOUNT study (B2214) is provided below.

Table 43: Summary of LCZ696 Phase 2 and Phase 3 controlled studies

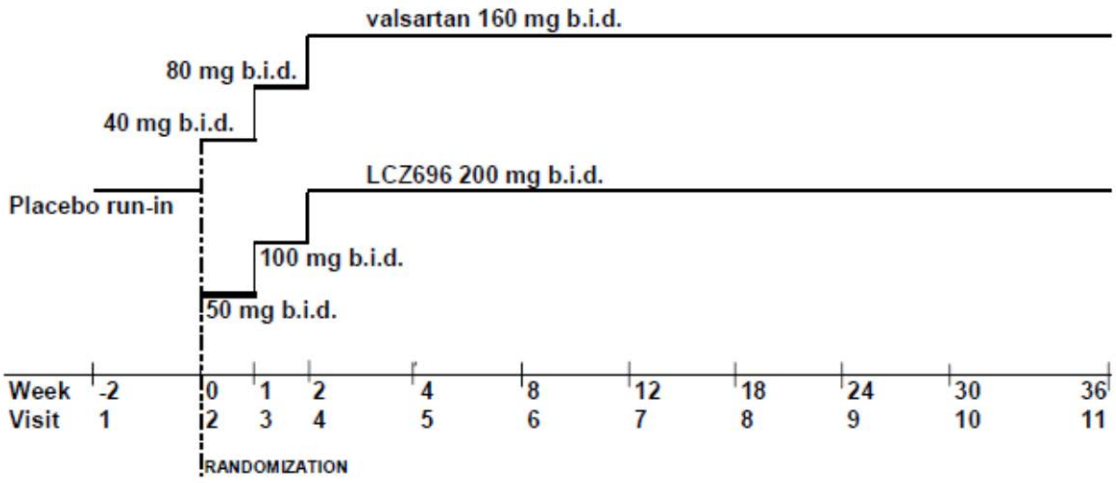
Study	Description	Primary endpoint	Treatment dose/day	Treatment duration
Phase 3, pivotal controlled study				
B2314 Run-in period: N=10521; Double-blind period: (N=8442*)	Efficacy and safety of LCZ696 vs enalapril in patients with **HFrEF**	Composite 1° endpoint (CV death or heart failure hospitalization)	LCZ696 200 mg bid (n=4209) Enalapril 10 mg bid (n=4233)	Median f/u time post randomization: 27 mo; Maximum f/u time post randomization: 51 mo
Phase 2, supportive studies				
B2214 (N=301*)	Efficacy, safety and tolerability of LCZ696 vs. valsartan in patients with **HFpEF**	Change of NT-proBNP from baseline after 12 weeks	LCZ696 200 mg bid (n=149) Valsartan 160 mg bid (n=152)	9 mo fixed
B2228 (N=498*)	Safety and tolerability of LCZ696 at 2 titration regimens in patients with **HFrEF**	Assess safety and tolerability	LCZ696 50 mg bid, then randomized and uptitrated to either: -200 mg bid over 6 wks (n=251); (conservative uptitration) -200 mg bid over 3 wks(n=247) (condensed uptitration)	3 mo fixed

Source: Applicant, Table 1-1 in the applicant's Summary of Clinical Safety (SCS)

PARAMOUNT (CLCZ696B2214):

PARAMOUNT was a 9-month, randomized, double-blind, multi-center, parallel group, active-controlled study comparing the efficacy, safety and tolerability of LCZ696 200 mg bid to valsartan 160 mg bid in HF patients with preserved EF (HFpEF, EF≥45%). All enrolled patients entered a one to two week, single-blind, placebo run-in period; eligible subjects were then randomized into a 9-month double-blind treatment period. ACE inhibitors or ARBs were discontinued 24-hours prior to the randomization visit. During the double-blind phase, subjects were titrated to the target study drug dose over a period of 2 to 4 weeks, as deemed appropriate by the investigator. Figure 11 shows the design of PARAMOUNT.

Figure 11: Study Design of PARAMOUNT



Source: Applicant, Figure 9-1 in the CSR for CLCZ696B2214

Table 44 provides an overview of the six pooled controlled studies in HTN patients. In addition to these studies, the applicant provided safety data from six ongoing HTN trials. These studies were not pooled because of their open-label design, lack of a comparator arm or because they were still ongoing at the data cut-off date, 01-July-2014.

Table 44: Overview of pooled controlled Hypertension studies

Study	Description	Treatment dose (mg/day); n
CLCZ696A2201 phase 2 (N=1328)	Dose ranging study in essential HTN (9 wks)	• LCZ 100, 200, 200 → 400 (forced up-titration) (n=497) • VAL 80, 160, 160 → 320 (forced up-titration) • AHU 200 • Placebo Randomized withdrawal period • LCZ 100, 200, 400 • VAL 80, 160, 320 • AHU 200 • Placebo
CLCZ696A2219 phase 2 (N=389)	Dose ranging study in essential HTN (8 wks)	• LCZ 100, 200, 200 → 400 (forced up-titration) (n=297) • Placebo Withdrawal period • Placebo (single-blind)
CLCZ696A2223 phase 2 (N=907)	Dose ranging study in mild-mod. systolic HTN (8 wks)	• LCZ 200 → 400 (forced up-titration) (n=142) • AHU/VAL 50/160 → 50/320, 50/160 → 100/320, 100/160 → 200/320, 100/160 → 200/320 → 400/320 (forced up-titration) • VAL 160 → 320 (forced up-titration) • Placebo
LCZ696A1306 phase 3 (N=1161)	Efficacy/safety study in Japanese subjects with essential HTN (8 wks)	• LCZ 200, 200 → 400 (forced up-titration) (n=772) • OLM 20
LCZ696A2316 phase 3 (N=588)	Efficacy/safety study in elderly subjects with essential HTN (14 wks)	• LCZ 100 → 200 (forced up-titration) (n=296) → 400 (optional up-titration) • OLM 10 → 20 (forced up-titration) → 40 (optional up-titration)
LCZ696A2319 phase 3 (N=266)	Efficacy/safety study in essential HTN (8 wks)	• LCZ 200 + AML 5 (n=130) • AML 5

AHU= sacubitril; AML= amlodipine; HTN= hypertension; LCZ= LCZ696; OLM= olmesartan; Val= valsartan; wks= weeks;
Source: Applicant Table 1-2 in SCS

7.1.2 Categorization of Adverse Events

The applicant categorized AEs/SAEs by systemic organ class (SOC) and preferred term (PT) using MedDRA version 17.0. An SAE was defined as an event that resulted in death; was life-threatening; was a congenital anomaly/birth defect; required or prolonged hospitalization; or was a medically important event. All deaths were adjudicated in PARADIGM-HF. SAEs were reported up to one-month after the patient stopped study participation. Any SAEs experienced after this 30 day period were to be reported to Novartis only if the event was thought to be

related to the study drug. The applicant also conducted additional searches for selected safety topics of interest using a SMQ, a Novartis MedDRA Query (NMQ), or pre-defined criteria using laboratory abnormalities (see Section 9.9).

Reviewer's Comments: In general, the applicant's approach to assessing AEs of interest by evaluating related MedDRA PTs and using SMQ/NMQ seems reasonable. However, some groupings may be too broad and have low specificity for the safety topic of interest, e.g., gastric lesions. In addition, the applicant should have recorded the outcome of the AEs/SAEs in the CRF (e.g., resolved with sequelae, not resolved, or death) as an alternative severity indicator for the event.

In this review, safety topics of interest were assessed by grouping related PTs for a given medical condition or using available MedDRA SMQs (see Section 9.8), an approach similar to the applicant's. In addition, to assess for new safety signals, AEs were evaluated using MedDRA high level group terms (HLGT) or high level terms (HLT).

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Data were not pooled across the HF studies. The applicant's single pivotal phase 3 study, PARADIGM-HF, provides much greater patient exposure (much larger sample size and longer treatment duration) than the other two phase 2 HF studies that were included in the application. Thus, pooling would not contribute significantly to the assessment of overall safety.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.1.1 Run-in period in PARADIGM-HF

In the enalapril run-in period, the median duration of study drug exposure, accounting for drug interruption was 15 days (interquartile range: 14 to 21 days). In contrast, the median duration of exposure in the LCZ696 run-in period was 29 days (interquartile range 26 to 35 days). By design, the exposure duration in the LCZ696 run-in period was longer than that in the enalapril run-in period.

7.2.1.2 Double-blind period in PARADIGM-HF

The median duration of study drug exposure, accounting for drug interruptions, was ~ 24 months in both arms during the double-blind treatment period. Table 45 provides information on study drug exposure by treatment groups and by different subsets (e.g., NYHA class). Overall, exposure was slightly higher in the LCZ696 arm compared to the enalapril arm across most investigated subgroups.

Table 45: Study Drug Exposure in PARADIGM-HF during the double-blind period

Population	Exposure (days)	Enalapril	LCZ696
Safety set	n	4229	4203
	Mean	720	743.1
	SD	356.7	346.2
	Median	703.5	735.0
	IQR[a]	491-1009.5	512-1017
	Subject-Years	8334.30	8547.28
Age			
≥75	Median	682	720.5
<75	Median	708	742
Race			
Caucasian	Median	720	759
Black	Median	609.5	618
NYHA			
I	Median	667.5	711
II	Median	729	751
III	Median	643.5	706
IV	Median	798	707
LVEF			
≤35%	Median	680	708
>35%	Median	1084	1097
Prior use of ACEi			
Yes	Median	710	738
No	Median	684	731
Prior use of ARB			
Yes	Median	692	732.5
No	Median	707	737
Region			
North America	Median	795.5	793
US	Median	811	829
Latin America	Median	657	698
Western Europe	Median	728	743
Central Europe	Median	694	752
Asia/Pacific and Other	Median	712.5	732

Reviewer's Table, Data Source: AIDENT & ADAR.
[a] IQR: interquartile range

In PARADIGM-HF, subjects could be down titrated from the targeted dose at the investigator's discretion based on safety and tolerability (0 mg, 50 mg, or 100 mg for LCZ696 and 0 mg 2.5 mg or 5 mg for enalapril). See Section 5.3 for additional information on instructions given to investigators regarding dose titration.

Approximately 60% of subjects in both arms maintained study drug at the target dose throughout the double-blind period. A similar percentage of subjects in the LCZ696 and enalapril arms had at least once dose reduction during the trial (41.8% vs. 42.5%, respectively). In both arms, approximately 33% of subjects who had a dose reduction had a dose reduction because of an AE. The most common AEs leading to dose reduction in the double-blind period were hypotension, renal impairment and hyperkalemia (Table 46). A higher percentage of subjects had dose reduction due to hypotension in the LCZ696 arm compared to the enalapril arm (9.8% vs. 7.0%, respectively).

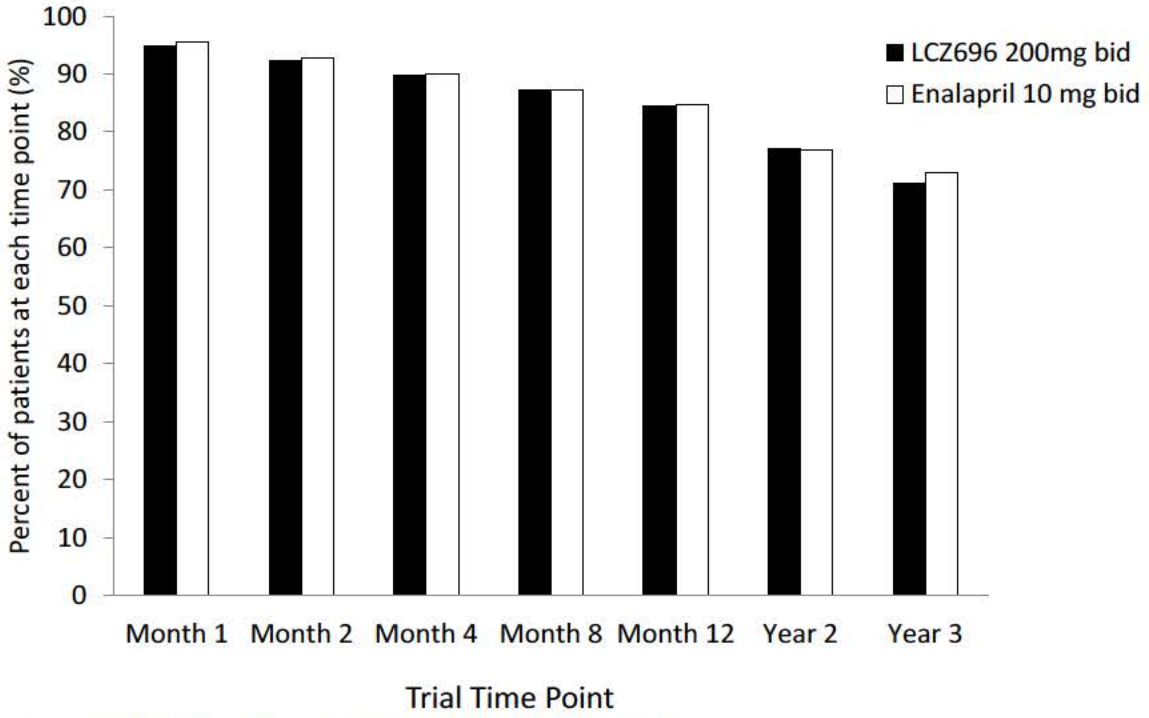
Table 46 Reasons for study drug dose reduction in the double-blind period in PARADIGM

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

Source: Applicant, Table 2-8 in SCS

Figure 12 shows the percentage of patients on the target dose of LCZ69 (200 mg bid) or enalapril (10 mg bid) at different trial time points. As previously noted, the majority of patients were on the targeted dose in both arms throughout the double-blind period.

Figure 12 Percentage of patients on the targeted dose during the double-blind period in PARADIGM-HF[a]



Reviewer's Figure Data Source: Table 12-2 in PARADIGM-HF CSR
[a] Percentage was calculated based on number of subjects who were on treatment at each time point in the respective treatment groups

The overall mean daily dose during the double-blind treatment period[1] per patient was 374.9 mg (interquartile range: 396.7-400 mg) in the LCZ696 arm and 18.9 mg (interquartile: 19.9-20 mg) in the enalapril arm. At the last available record, the percentage of subjects on the target dose was similar in the two treatment arms (69.6% for LCZ696 vs. 67.5% for enalapril).

7.2.2 Explorations for Dose Response

See Section 6.1.8.

1 The double-blind treatment period is defined as the time from the date of the first dose to the end of treatment (date of last study drug intake or the death of the patient, whichever was earlier). Temporary treatment interruptions were included in the calculation (i.e., a dose level of zero was assigned for these days).

7.2.3 Special Animal and/or In Vitro Testing

Non-clinical testing was in general adequate to investigate potential adverse reactions. See Section 4.3 Preclinical Pharmacology/Toxicology.

7.2.4 Routine Clinical Testing

See Section 5.3 and Section 9.10 for detailed information on the visit schedule during the double-blind treatment period in PARADIGM-HF and the testing that was performed at these visits. Briefly, subjects were to return to the site for study visits every 2 to 8 weeks during the first 4 months of the double-blind period and every four months thereafter. In addition, subjects could be seen anytime throughout the study at the discretion of the investigator to follow-up laboratory abnormalities or adverse events. Data on vital signs and concomitant medications were collected at each visit. Laboratory chemistries such as potassium, BUN and serum creatinine were collected every other week in the first month and every 4 to 8 months thereafter. Serum chemistries were measured every other month in the first four months and yearly thereafter. Other laboratory assessments (hematology and urine parameters) and 12-lead ECGs were performed yearly.

Reviewer's Comment: Safety assessments were adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

See Section 4.4 Clinical Pharmacology.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The applicant identified a number of safety topics of interest based on the recognized class effects of ARBs including hypotension, hyperkalemia, renal impairment, and embryo-fetal and infantile toxicity.

Angioedema was also a safety topic of interest based on the experience with omapatrilat (a combined ACE/NEP inhibitor). In brief:

- In the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial, a multicenter, double-blind, 24-week trial in 25,302 patients with untreated or uncontrolled hypertension, the incidence and severity of angioedema was worse with omapatrilat than enalapril (274 [2.2%] adjudicated angioedema events on omapatrilat and 86 [0.7%] on enalapril with a risk ratio of 3.2 [95% CI 2.5 to 4.1]) (Lawrence and Stockbridge, 2002). Of the omapatrilat cases, 88 occurred on the first day of exposure compared with three in the enalapril group. The risk was 3-fold higher in black subjects than Caucasians.

- In the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial, a multicenter, randomized, double-blind trial in 5,770 patients with NYHA class II-IV heart failure, an LVEF ≤ 30%, and a recent heart failure hospitalization, the incidence of angioedema was low but was also greater in the omapatrilat than in the enalapril arm (24 [0.8%] vs. 14 [0.5%], greater).

Reviewer's Comments: The identification of AEs of interest was appropriate and aligned with reported AEs for similar drugs.

7.3 Major Safety Results

7.3.1 Deaths

Cardiovascular death and all-cause mortality were efficacy endpoints in PARADIGM-HF. See Section 6.1.4 for further discussion of treatment effects on cardiovascular death and all-cause mortality. The discussion that follows focuses on non-cardiovascular causes of death during the double-blind treatment period and deaths during the run-in periods of PARADIGM-HF.

7.3.1.1 Run-in period

There were 55 subjects (0.5%) who died during the enalapril run-in period and 63 subjects (0.7%) who died during the LCZ696 run-in period. Table 47 shows the adjudicated primary causes of death during the run-in period. Overall, the frequency and causes of death were similar in the two run-in periods.

Table 47: Adjudicated primary cause of death during the run-in period in PARADIGM-HF

	Enalapril run-in N = 10,513	LCZ696 run-in N = 9,419
Number of subjects who died	55 (0.5%)	63 (0.7%)
Cardiovascular Death	50 (0.5%)	54 (0.6%)
Sudden death	29 (0.3%)	26 (0.3%)
Pump failure	9 (0.1%)	15 (0.2%)
Presumed CV death	4 (0.0%)	5 (0.1%)
Infection	2 (0.0%)	4 (0.0%)
Fatal stroke	3 (0.0%)	4 (0.0%)
Fatal myocardial infarction	3 (0.0%)	2 (0.0%)
Presumed sudden death	2 (0.0%)	1 (0.0%)
Primary arrhythmic death	0	1 (0.0%)
Non-Cardiovascular Death	3 (0.0%)	8 (0.1%)
Malignancy	0	1 (0.0%)
Accidental	0	1 (0.0%)
Other Non-CV death	0	2 (0.0%)[a]
Suicide	1 (0.0%)	0
Unknown	2 (0.0%)	1 (0.0%)

Reviewer's Table, Data Source: ADJ & AIDENT
[a] One subject died due to post operational complication and one due to pulmonary hemorrhage

7.3.1.2 Double-blind period

As noted in the discussion of efficacy, there were 835 (19.7%) deaths in the enalapril arm compared to 713 (17.0%) deaths in the LCZ696 arm in the double-blind period in PARADIGM-HF. The majority of deaths in both treatment groups were cardiovascular deaths.

The incidence of non-cardiovascular deaths was similar in the two treatment arms (2.9% vs. 2.6% in the LCZ696 and enalapril arms, respectively). As shown in the table below (Table 48), there were a slightly greater number of accidental deaths and deaths due to gastrointestinal

causes in the LCZ696 arm. Given this slight imbalance, the narratives for these deaths were reviewed.

Table 48 Adjudicated primary cause of death during the double-blind period in PARADIGM-HF

	Enalapril N = 4229	LCZ696 200 N = 4203
Number of subjects who died	835 (19.7%)	713 (17.0%)
Cardiovascular death	692 (16.4%)	559 (13.3%)
Sudden death	309 (7.3%)	250 (5.9%)
Pump failure	185 (4.4%)	147 (3.5%)
Presumed CV death	95 (2.2%)	67 (1.6%)
Fatal stroke	34 (0.8%)	30 (0.7%)
-Ischemic	22 (0.5%)	20 (0.5%)
-Ischemic with hemorrhagic conversion	2 (0.0%)	2 (0.0%)
-Primary intracranial hemorrhage	9 (0.2%)	5 (0.1%)
-Unknown	1 (0.0%)	3 (0.1%)
Fatal myocardial infarction	33 (0.8%)	25 (0.6%)
Presumed sudden death	23 (0.5%)	26 (0.6%)
CV procedural	4 (0.1%)	3 (0.1%)
Pulmonary embolism	3 (0.1%)	4 (0.1%)
Other Cardiovascular death	6 (0.1%)	7 (0.2%)
-Fatal Arrhythmia	2	4 (0.1%)
-Peripheral arterial disease	3 (0.1%)	2(0.0%)
-Tamponade	1 (0.0%)	0
-Abdominal aorta dissection	0	1(0.0%)
Non-cardiovascular death	110 (2.6%)	120 (2.9%)
Malignancy	41 (1.0%)	41 (1.0%)
Infection	34 (0.8%)	36 (0.9%)
GI	10 (0.2%)	16 (0.4%)
Pulmonary	13 (0.3%)	7 (0.2%)
Accidental	6 (0.1%)	13 (0.3%)
Suicide	1 (0.0%)	4 (0.1%)
Renal	1 (0.0%)	1 (0.0%)
Other Non-CV death	4 (0.1%)	2 (0.0%)
Post-procedure complication	3(0.1%)	1(0.0%)
Diabetic ketoacidosis	1	0
Unknown	33 (0.8%)	34 (0.8%)

Reviewer's Table, Data Source: ADJ & AIDENT

Accidental deaths
All 13 accidental deaths in the LCZ696 arm were on-treatment deaths, while 4 of the 6 accidental deaths in the enalapril arm occurred on-treatment. Of 13 on-treatment accidental deaths in the LCZ696 arm, 6 were due to road traffic accident and 4 were due to fall-related deaths (Table 49). Of note, one accidental death in the LCZ696 arm occurred when the patient experienced syncope while driving and had motor vehicle accident (crashed into a tree). The actual cause of syncope was not known but it could be hypotension or arrhythmia-related.

Reviewer's Comment: Compared to the enalapril arm, the LCZ696 arm also had a higher incidence of fall AEs (see Section 7.3.5.2.1) and road traffic accidents. Although these AEs were not frequent and majority of them were not serious, the possibility that some of these AEs were secondary to hypotension cannot be excluded.

Table 49: Causes of accidental and GI deaths during the double-blind period in PARADIGM-HF

	Enalapril	LCZ696
Accidental Deaths	6	13
On treatment deaths	4	13
-Fall-related deaths	2	4
-Road traffic accident	1	6
-subdural hematoma (unknown accident cause)	0	1
-hypovolemic shock /vascular injury (fell on knife)	0	1
-head injury (sudden fell of a tree)	0	1
-drowning	1	0

Reviewer's Table, Source: the applicant's response to FDA information request submitted on 2/11/2015

GI deaths
Review of the narratives for the GI deaths did not raise any safety concerns. The causes of these deaths varied (e.g., pancreatitis, GI hemorrhage, intestine perforation, and intestinal obstruction) and several occurred after subjects were off treatment for several months.

7.3.2 Nonfatal Serious Adverse Events

The incidence of SAEs in the double-blind period was similar in the two treatment groups (46.1% for LCZ696 vs. 50.7% for enalapril). Most SAEs were cardiac in nature. SAEs for the safety topics of interest are discussed in Section 7.3.5; no other safety signals were seen.

7.3.3 Dropouts and/or Discontinuations

7.3.3.1 Run-in period

As shown in Table 50, AEs such as hypotension, renal dysfunction and hyperkalemia were the most common AEs leading to study drug discontinuation during both run-in periods.

Table 50: Adverse events leading to study drug discontinuation during the run-in period*

	Enalapril run-in N = 10,513	LCZ 696 N = 9,419
Number of patients discontinued due to AE	643 (6.1%)	532 (5.6%)
Hypotension[a]	154 (1.5%)	171 (1.8%)
Renal impairment[b]	201 (1.9%)	154 (1.6%)
Hyperkalemia[a]	181(1.7%)	108 (1.1%)
Cough	48 (0.5%)	12 (0.1%)
Cardiac failure[b]	21 (0.2%)	27 (0.2%)
Angioedema[c]	10 (0.1%)	8 (0.1%)

Reviewer's Table. Data Source: AAEV & AIDENT
* This table presented data collected on the "adverse event" CRF page and the values were different compared to those in Table 15. Data presented in Table 15 were collected from the "end of run-in" CRF page.
[a] Including all-relevant PTs (see section 9.8)
[b] MedDRA SMQ broad
[c] Adjudicated angioedema case

Table 51 compares the baseline characteristics of subjects who failed the run-in periods with those who were randomized in the double-blind treatment period. Compared to subjects who were randomized, subjects who failed the run-in periods had, on average, lower eGFRs and higher serum creatinine at baseline. Close to 50% of subjects who failed the run-in period (49% and 45% in enalapril and LCZ696 run-in, respectively) had an eGFR <60 mL/min/1.73m^2 compared to 35% of subjects who were randomized. About 20% of subjects who failed the run-in period had an eGFR <45 mL/min/1.73 m^2. In addition, compared to the randomized set, a slightly higher proportion of subjects with NYHA class III and IV, failed the run-in period.

Table 51: Baseline Characteristics among subjects failed run-in period

Variables at screening	Randomized set N = 8,442	Enalapril run-in failure N= 1102	LCZ 696 run-in failure N = 982
Age (years)-mean (IQR[a])	63.8 (57-72)	65.1 (58-74)	64.3 (56-73)
LVEF (%)- mean (IQR[a])	29.5 (25-34)	28.4 (24-34)	28.6 (25-34)
eGFR (ml/min/1.73m^2)- mean (IQR[a])	68.1 (54-80)	63.2 (47-76)	64.9 (49-77)
SBP (mmHg)-mean (IQR[a])	121.4 (110-130)	125.3 (110-135)	124.6 (110-135)
Potassium (mmol/L) – mean (IQR[a])	4.5 (4.2-4.8)	4.5 (4.2-4.9)	4.5 (4.2-4.8)
eGFR < 60 ml/min	2976 (35.3%)	534 (48.5%)	440 (44.8%)
eGFR <45 ml/min	848 (10.1%)	232 (21.1%)	182 (18.5%)
Female	1847 (21.9%)	274 (24.9%)	225 (22.9%)
Race			
Caucasian	5579 (66.1%)	689 (62.5%)	630 (64.2%)
Black	428 (5.1%)	66 (6.0%)	65 (6.6%)
Asian	1510 (17.9%)	206 (18.7%)	175 (17.8%)
Others	753 (8.9%)	141 (12.8%)	112 (11.4%)
NYHA class			
I	396 (4.7%)	8 (0.7%)	3 (0.3%)
II	5937 (70.3%)	655 (59.4%)	609 (62.0%)
III	2035 (24.1%)	416 (37.7%)	344 (35.0%)
IV	60 (0.7%)	19 (1.7%)	23 (2.0%)
Prior HF hospitalization-Yes	5299 (62.8%)	677 (61.4%)	622 (63.3%)
Prior coronary heart disease –Yes	4607 (54.6%)	612 (55.5%)	540 (55.0%)
Prior stroke – Yes	729 (8.6%)	101 (9.2%)	103 (10.5%)
Prior MI - Yes	3649 (43.2%)	491 (44.6%)	451 (45.9%)
Prior use of ACEi – No	1882 (22.3%)	290 (26.3%)	212 (21.6%)
Prior use of ARB - No	6535 (77.4%)	815 (74.0%)	767 (78.1%)

Reviewer's Table, Data Source: AIDENT and ALRS
[a] Inter-quartile R

7.3.3.2 Double-blind period

The most common reason for permanent treatment discontinuation during the double-blind period was an AE (Table 17). Cardiac-related conditions were the most common AEs leading to study drug discontinuation in both arms. Table 52 shows the incidence of study discontinuations due to AEs of interest. The incidence of study discontinuations due to hypotension, renal impairment and hyperkalemia was low (<1% for each AE) in the LCZ696 arm during the double-blind period.

Table 52: Adverse events that lead to study drug discontinuation during double-blind period

	Enalapril run-in N= 4229	LCZ 696 N= 4203
Study drug discontinuations due to an AE	516 (12.2)	450 (10.7)
Cardiac failure[a]	112 (2.6%)	101 (2.4%)
Cardiac arrhythmias[a]	122 (2.9%)	95 (2.3%)
Hypotension[b]	29 (0.7%)	36 (0.9%)
Renal impairment[a]	56 (1.3%)	29 (0.7%)
Hyperkalemia[b]	15 (0.4%)	11 (0.3%)
Cough	30 (0.7%)	8 (0.2%)
Angioedema[c]	4 (0.1%)	7(0.2%)

[a] MedDRA SMQ broad
[b] Including all-relevant PTs (see section 9.8)
[c] Adjudicated angioedema cases
Reviewer's Table. Data Source: AAEV & AIDENT

7.3.4 Significant Adverse Events

The applicant identified several safety topics of interest based on known class effects of RAAS inhibitors and pre-clinical findings (see Section 7.2.6). See Section 7.3.5 for further discussion of these safety topics.

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Angioedema

Angioedema was an adverse event of interest in PARADIGM-HF. Investigators were instructed to pay special attention to symptoms that resembled angioedema or angioedema-like events. If such an event occurred, the investigator was to complete the "Adjudication Questionnaire for an Angioedema-like Event form". Events could also be identified by the study monitor or Novartis Clinical Team. In addition, investigators were asked whether there was a suspicion of angioedema in all cases of premature discontinuation of study medication. All angioedema reports were forwarded to an angioedema adjudication committee (AAC) and were adjudicated in a blinded manner by a three-member panel of external experts. The AAC determined if an event was a confirmed angioedema case and graded the severity of the case as following:

I. No treatment administered or antihistamines only
II. Treated with catecholamines or steroids
III. Hospitalized but no mechanical airway protection
    a. No airway compromise
    b. With airway compromise
IV. Mechanical airway protection or death from airway compromise

The AAC did not determine the cause of the event or the likely role of the study drug in the event.

7.3.5.1.1 Adjudicated Cases of Angioedema in PARADIGM-HF

Table 53 provides an overview of angioedema and angioedema-like events in PARADIGM-HF. There were a total of 147 investigator reported events in 144 subjects. Of these, 25 events occurred during the enalapril run-in period, 29 occurred during the LCZ696 run-in period, and 93 occurred during the double-blind treatment period (45 in the enalapril arm and 48 in the LCZ696 arm). Of the 147 events, 48 events were suspected by the investigator to be related to the study drug and 54 events were adjudicated as confirmed angioedema cases.

Of the 54 confirmed cases of angioedema, 15 cases (0.1%) occurred during the enalapril run-in period, 10 cases (0.1%) occurred during the LCZ696 run-in period, and 29 cases occurred during the double-blind treatment period (10 (0.2%) in the enalapril arm and 19 (0.5%) in the LCZ696 arm). Hence, overall, the incidence of angioedema was low; however, it was also somewhat higher in the LCZ696 arm relative to the enalapril arm in the double-blind period.

Table 53: Overview of angioedema/angioedema-like event in PARADIGM-HF

Study Period (median drug exposure)	Run-in period (15 days/29 days)		Double-blind period (24 months)	
	Enalapril N=10,513	LCZ696 N=9,419	Enalapril N=4,229	LCZ696 N=4,203
Investigator reported events (N = 147)	25 (0.2%)	29 (0.3%)	45 (1.1%)	48 (1.1%)
- related to the study drug (N=48)	15 (0.1%)	13 (0.1%)	8 (0.2%)	12 (0.3%)
AAC confirmed cases (N = 54)	15 (0.1%)	10 (0.1%)	10 (0.2%)	19 (0.5%)

AAC: angioedema adjudication committee
Reviewer's table, Data source: AAEV & AEDEMA

The severity of and time course of these events during the run-in and double-blind treatment periods are described below.

Run-in Period

Table 54 shows adjudicated angioedema events during the run-in period. There were 15 confirmed events (0.14%) in the enalapril run-in period and 10 confirmed events (0.11%) in the LCZ696 run-in period. The majority of cases did not require treatment or were treated with antihistamines (severity grade I or II). Only one case, which was reported in a Caucasian subject in the enalapril run-in period, required hospitalization. There were no cases of severe angioedema involving airway compromise or death during the run-in period. The incidence of angioedema was higher in black subjects (0.41% vs. 0.36% in the LCZ696 and enalapril arms, respectively), compared to non-black subjects (0.09% vs. 0.13% in the LCZ696 and enalapril arms, respectively).

Table 54: Adjudicated Angioedema during the run-in phase in PARADIGM-HF

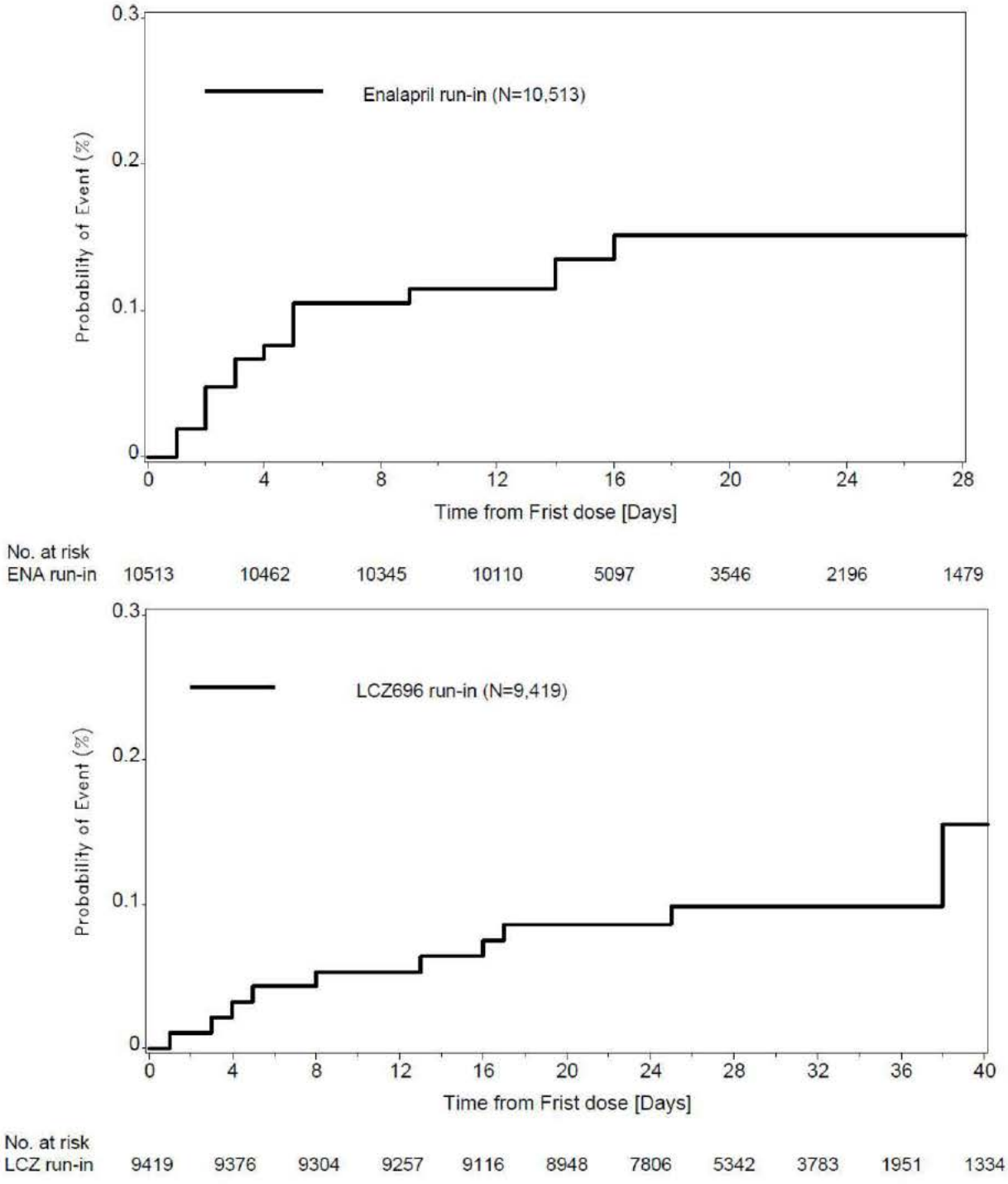
Race		Enalapril run-in N = 10,513 n (%)	LCZ696 run-in N = 9,419 n (%)
All-race	Adjudicated angioedema	15 (0.14)	10 (0.11)
	Severity		
	I. No treatment administered or antihistamines only	8	8
	II. Treated with catecholamines or steroids	6	2
	III. Hospitalized but no mechanical airway protection[a]	1	0
	Median time (days) to the event (IQR)	4 (2-9)	10.5 (4-17)
Black	Total number of subjects	559	493
	Adjudicated angioedema	2 (0.36)	2 (0.41)
	Severity		
	I. No treatment administered or antihistamines only	1	2
	II. Treated with catecholamines or steroids	1	0
	III. Hospitalized but no mechanical airway protection	0	0
Non-Black	Total number of subjects	9954	8926
	Adjudicated angioedema	13 (0.13)	8 (0.09)
	Severity		
	I. No treatment administered or antihistamines only	7	6
	II. Treated with catecholamines or steroids	5	2
	III. Hospitalized but no mechanical airway protection[a]	1	0

[a] No hospitalized case with airway comprise
Reviewer's Table, Data Source: AIDENT, AEDEMA & ADTTER

Figure 13 shows the Kaplan-Meier plot of the time to first adjudicated angioedema event in each run-in period. The median time to the event was 4 days and 10.5 days in the enalapril and LCZ696 run-in periods, respectively. Most cases during the run-in period occurred within 10 days after the first dose of study drug [n = 12 (80%) in the enalapril run-in period vs. n = 5 (50%) in the LCZ696 run-in period]. Five cases (33%) in the enalapril run-in period vs. 1 case in the LCZ696 run-in period occurred within 1 day. The time course of the cases in black subjects was consistent with that seen in non-blacks. The two cases in black subjects in the enalapril run-in period occurred on days 2 and 4, while the two cases in black subjects in the LCZ696 run-in period occurred on days 8 and 25.

Angioedema led to study drug discontinuation in all 15 cases in the enalapril run-in period, and 8 of 10 cases in the LCZ696 run-in period. Two of the angioedema cases that occurred in the LCZ696 run-in period were randomized and treated in the double-blind period (one was treated with enalapril and the other was treated with LCZ696). No recurrence of angioedema was reported in these two subjects in the double-blind period.

Figure 13: Kaplan-Meier Plot of time to first adjudicated angioedema event in the enalapril run-in and LCZ696 run-in periods



Reviewer's figure. Data Source: ADTTER & AIDENT

Double-blind treatment

There were 19 (0.45%) and 10 (0.24%) confirmed angioedema events during the double-blind period in the LCZ696 and enalapril arms, respectively (RR= 1.9, 95% CI: 0.8-4.5). None of these events involved airway compromise or death. Most events were non-serious and did not require treatment or were treated with antihistamines (severity grade I or II) (Table 55). Three cases (0.07%) in the LCZ696 arm and 1 case (0.02%) in the enalapril arm resulted in hospitalization (severity grade III). The narratives for the 3 cases in the LCZ696 arm are provided at the end of this section.

Table 55 Adjudicated angioedema events during the double-blind phase in PARADIGM-HF

Race		Enalapril N = 4229 n (%)	LCZ696 N = 4203 n (%)
All-race	Adjudicated angioedema	10 (0.24)	19 (0.45)
	Severity		
	I. No treatment administered or antihistamines only	5	10
	II. Treated with catecholamines or steroids	4	6
	III. Hospitalized but no mechanical airway protection[a]	1	3
	Median time (days) to the event (IQR)	256.5 (44-384)	87 (52-464)
Black	Total number of subjects	214	213
	Adjudicated angioedema	1 (0.47)	5 (2.35)
	Severity		
	I. No treatment administered or antihistamines only	1	2
	II. Treated with catecholamines or steroids	0	2
	III. Hospitalized but no mechanical airway protection[a]	0	1
	Median time (days) to the event (IQR)	490 (-)	53 (8-87)
Non-Black	Total number of subjects	4015	3990
	Adjudicated angioedema	9 (0.22)	14 (0.35)
	Severity		
	I. No treatment administered or antihistamines only	4	8
	II. Treated with catecholamines or steroids	4	4
	III. Hospitalized but no mechanical airway protection[a]	1	2
	Median time (days) to the event (IQR)	183 (44-370)	128.5 (58-512)

[a]No hospitalized cases had airway compromised
Reviewer's Table. Source Data: AIDENT, AEDEMA, ADTTE.

Adjudicated angioedema events were more common in subjects who were black (2.3% vs. 0.5% in the LCZ696 and enalapril arms), compared to subjects who were not black (0.4% vs. 0.2%). Table 56 shows angioedema events by other subgroups of interest. The incidence of angioedema was slightly higher in the LCZ696 arm compared to the enalapril arm among younger (< 65 years) subjects, females, current smokers and subjects who did not have prior use of an ARB at screening; though these differences are due to small numbers of events. The incidence was also higher in the LCZ696 arm compared to the enalapril arm in North America and Central Europe. The incidence of cases among black subjects in the US was 5.6% (n = 3/54) in the LCZ696 arm vs. 0/57 in the enalapril arm. The severity of the angioedema events in black subjects is summarized in Table 57.

Table 56: Adjudicated angioedema events by subgroup during the double-blind period in PARADIGM-HF

	Enalapril N = 4,229 n (%)[a]	LCZ696 N = 4,203 n (%)[a]
Age		
<65 years	6/2174 (0.3%)	12 /2120(0.6%)
≥ 65 years	4/2055 (0.2%)	7/2083 (0.3%)
Black		
Yes	1/214 (0.5%)	5/213 (2.3%)
No	9 (0.2%)	14 (0.4%)
Black – US only	0/57	3/54 (5.6%)
Gender		
Male	8/3270 (0.2%)	12/3316 (0.4%)
Female	2/959 (0.2%)	7/887 (0.8%)
Previous use of ARBs[b]		
Yes	2/968 (0.2%)	1/936 (0.1%)
No	8/3261 (0.2%)	18/3267 (0.6%)
Current Smoker		
Yes	0/607 (0.0%)	3/604 (0.5%)
No	10/3622 (0.3%)	16/3599 (0.4%)
Region		
North America	1/292 (0.3%)	3/310 (1.0%)[c]
-US	1/209 (0.5%)	3/225 (1.3%)
Latin America	0/732 (0.0%)	1/726 (0.1%)
Western Europe	6/1025 (0.6%)	5/1027 (0.5%)
Central Europe	1/1438 (0.1%)	7/1397 (0.5%)
Asia/Pacific and Other	2/742 (0.3%)	5/743 (0.4%)

Reviewer's Table. Data source: AIDENT & AEDEMA,
[a] The denominator is the number of subjects in corresponding subgroup within the treatment
[b] Data collected at screening. By design, subjects who were not previously on ARBs were on ACEis.
[C] All three cases were black in US

Table 57: Incidence and severity of angioedema event in blacks in the double-blind period in PARADIGM-HF

	Enalapril N = 4,229	LCZ696 N = 4,203
Confirmed cases of angioedema	10 (0.2%)	19 (0.5%)
- Blacks	1/214 (0.5%)	5/213 (2.4%)
- Blacks, US only	**0/57**	**3/54 (5.6%)**[a]
Severity grade for cases in Blacks		
I No treatment administered or antihistamines only	1	**1**/2
II Treated with catecholamines or steroids	0	**1**/2
III Hospitalized but no mechanical airway protection (No airway compromise)	0	**1**/1
IV Mechanical airway protection or death from airway compromise	0	0

Reviewer's Table. Data source: AEDEMA & AIDENT

Table 58 provides information on actions taken with respect to study drug administration in these cases. In the double-blind period, 4 out of the 10 confirmed cases in the enalapril arm and 7 out of the 19 cases permanently discontinued the study drug due to the angioedema event. Similarly, 4 cases in the enalapril arm and 7 cases in the LCZ696 arm did not have any action taken for the study drug during the time of the event. Two cases in the enalapril arm and 5 cases in the LCZ696 arm stopped the study drug temporally due to the event and resumed the study drug later without recurrence of angioedema.

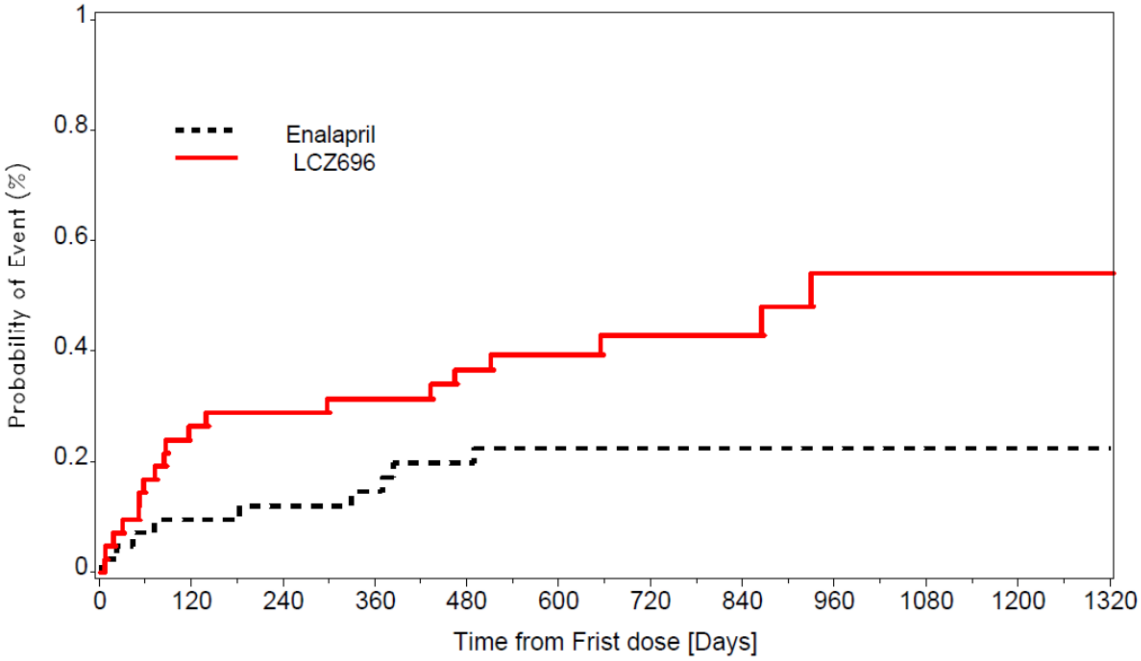
Table 58: Study drug discontinuations due to angioedema and rechallenge cases in PARADIGM-HF

Study Period	Run-in period		Double-blind period	
	Enalapril N=10,513	LCZ696 N = 9,419	Enalapril N = 4,229	LCZ696 N = 4,203
AAC confirmed cases (n)	15	10	10	19
-Permanent study drug discontinuation	15	8	4	7
No action taken for the study drug	0	2	4	7
Temporary interruption with negative rechallenge	--	--	2	5

Reviewer's Table. Data source: AEDEMA & AAEV & Narratives for angioedema event

The time course for the adjudicated angioedema events in the double-blind period is shown in Figure 14. The Kaplan-Meier curves show an early separation (between Day 30 to 90 following randomization) between the two treatment arms.

Figure 14: Kaplan-Meier plot of time to first adjudicated angioedema during the double-blind period in PARADIGM-HF[a]



No. at risk												
Enalapril	4229	4202	4177	4151	4119	4058	3863	3297	2463	1793	1062	332
LCZ696	4203	4180	4152	4123	4100	4055	3887	3358	2529	1783	1067	334

Reviewer's Figure, Data Source: ADTTE & AIDENT
[a] There was one case in enalapril run-in occurred on day 1343 during the double-blind period

Table 59 provides information on time course of the angioedema events in both run-in and double-blind periods. In the double-blind period, the median time to the event was shorter in the LCZ696 arm compared to the enalapril arm (87 vs. 256 days). Two events in the LCZ696 arm (days 7 & 8, both in black subjects) vs. 1 event in the enalapril arm (day 3) occurred within 10 days after the first dose of the double-blind treatment. In the LCZ696 arm, the median time to the event in the 5 cases that occurred in black subjects was 53 days compared to 128.5 days in the 14 cases that occurred in subjects who were not black. Overall, most angioedema cases occurred within 180 days after randomization and it does not appear that the events were clustered around the transition from the LCZ696 run-in period to the double-blind treatment period in both treatment groups.

Table 59: Time to confirmed angioedema cases in PARADIGM-HF

	Run-in period		Double-blind period	
	Enalapril N=10,513	LCZ696 N=9,419	Enalapril N=4,229	LCZ696 N=4,203
Angioedema cases (n)	15	10	10	19
Median time (days) to the event (IQR[a])	4 (2-9)	10.5 (4-17)	256 (44-384)	87 (52-464)
Cases within 10 days (n)	12	5	1	2
Cases within 1 day (n)	5	1	0	0

Reviewer's Table, Data Source: ADTTER from PARADIGM-HF
[a] IQR: Interquartile range

Narratives for severe angioedema events in subjects treated with LCZ696

Case 1: This case occurred in a 55-year-old Caucasian male in Slovakia who was on trandolapril 2 mg daily at screening and was randomized to LCZ696. On Day 926, he was hospitalized for coronary artery disease and, on Day 929, underwent a percutaneous coronary intervention with iodinated contrast. Following the procedure he developed hypotension, dyspnea, itching, and edema of the upper extremities and was diagnosed with anaphylactic shock. He was treated with epinephrine, norepinephrine, and the anti-histamine bisulepin. Concomitant medications included clopidogrel, heparin, spironolactone, morphine, mannitol, and hydroxyethyl starch solution. The event was considered resolved on Day 931. The patient completed the study and received the last dose of LCZ696 on Day 1322. The adjudication committee considered the event of anaphylactic shock to be angioedema with severity Grade IIIa.

Case 2: This case occurred in a 55-year-old Caucasian female in Bulgaria who was on ramipril 5 mg daily at screening and was randomized to LCZ696. On Day 464, she experienced shortness of breath and facial swelling and was hospitalized with a diagnosis of angioedema. Treatment with LCZ696 was temporarily interrupted and she was treated with epinephrine, methylprednisolone, famotidine, and the anti-histamine chloropyramine. Concomitant medications included nadroparin, fraxiparin, and chlorphazoline. On the day before the event, the patient had used an insecticide spray, which the investigator believed was the cause of the angioedema. The event was considered resolved on Day 466 and LCZ696 was restarted on

Day 467 without recurrence of angioedema. The patient completed the study and received the last dose of LCZ696 on Day 1093. The adjudication committee considered the event to be angioedema with severity Grade IIIa.

Case 3: This case occurred in a 63-year-old black male in the United States who was on lisinopril 40 mg daily at screening and was randomized to LCZ696. On Day 6, he was hospitalized with bradycardia, chest pain, shortness of breath, and lower extremity edema and was diagnosed with worsening heart failure. Treatment with LCZ696 was permanently discontinued and the patient was started on enalapril the same day. The following day he was transitioned to lisinopril. On Day 8, two days after the last dose of LCZ696, the patient developed tongue swelling, shortness of breath, difficulty swallowing, and difficulty speaking and was diagnosed with angioedema. Lisinopril was discontinued and he was treated with epinephrine, methylprednisolone, famotidine, and diphenhydramine. Concomitant medications included isosorbide dinitrate, and hydralazine. He had eaten shrimp on the day of the event so a shellfish allergy was considered to be a possible etiology although he had no prior history of shellfish allergy. The event was considered resolved on Day 10. He completed the study off of study drug. The adjudication committee considered the event to be angioedema with severity Grade III.

Reviewer's Comments: It is reassuring that the first two subjects had other potential causes of angioedema and were able to continue LCZ696 without recurrence of angioedema. The third case suggests a risk of angioedema with overlapping ACEi and LCZ696, a situation the applicant attempted to mitigate by requiring a 36-hour washout period when transitioning between agents, which did not occur for Case 3.

Considering the two safety issues with regard to angioedema: (1) higher incidence among blacks treated with LCZ696 and (2) concomitant and proximate use of ACEi and LCZ696, additional narratives related to these issues were summarized below:

<u>Narratives for angioedema events in black subjects treated with LCZ696:</u>

Case 1: This case occurred in a 56-year-old black female in United States who was on lisinopril 10mg at screening and was randomized to LCZ696. On Day 433, she developed moderate facial, neck and tongue swelling and was diagnosed with angioedema. She was treated with prednisone and hydroxyzine. The investigator attributed the event to an unknown medication for sleep the patient had taken. LCZ696 was continued and the event was considered resolved on Day 434. The patient completed the study and received the last dose of LCZ696 on Day 1120. The adjudication committee considered the event to be angioedema of severity Grade II.

Case 2: This case occurred in a 68-year-old black female in South Africa who was on perindopril 4mg daily at screening and was randomized to LCZ696. On Day 8, she developed swelling of lower part of the right side of her face. No treatment was reported, LCZ696 was continued, and the event was considered resolved the same day. The patient completed the study and received the last dose of LCZ696 on Day 748. The adjudication committee considered the event to be angioedema of severity Grade I.

Case 3: This case occurred in a 61-year-old black female in South Africa who was on candesartan 16 mg daily at screening and was randomized to LCZ696. On Day 83, the patient

developed edema in the left zygomatic area and left periorbital region of the face and was diagnosed with angioedema. She was treated with prednisone and the anti-histamine chlorphenamine and LCZ696 was continued. The event resolved on Day 88. The patient completed the study and received the last dose of LCZ696 on Day 670. The adjudication committee considered the event to be angioedema of severity Grade II.

Case 4: This case occurred in a 43-year-old black female in United Status who was on Lisinopril 40 mg daily at screening and was randomized to LCZ696. On Day 87, she developed swelling of the face (periorbital area, head, neck, and lips), dyspnea, and dysphagia with oropharyngeal edema. Treatment with LCZ696 was permanently discontinued. No other treatment was reported. The event was considered resolved on Day 88. The adjudication committee considered the event to be angioedema of severity Grade I.

Narratives for angioedema events in subjects with concomitant/proximate use of ACEi and LCZ696:

Case 1: This case occurred in a 95-year-old Caucasian female in Germany who was on enalapril 10 mg daily at screening and was randomized to LCZ696. The patient finished the enalapril run-in and started LCZ696 the same day without a 36-hour wash-out period (protocol deviation). On Day 16 of LCZ696 100mg twice daily, she developed swelling of the lips and right side of her face and was diagnosed with angioedema. LCZ696 was permanently discontinued and she was treated with prednisolone. The event was considered resolved on Day 20. The patient was considered a run-in failure and was not randomized. The adjudication committee considered the event to be angioedema of severity Grade II.

Case 2: This case occurred in a 63-year-old Caucasian male in Bulgaria who was on ramipril/hydrochlorothiazide 5/25mg daily at screening and was randomized to LCZ696. On Day 506, the subject started ramipril/hydrochlorothiazide 5/25 mg in addition to LCZ696. Over the next several days, he noted a systolic blood pressure below 100 mmHg. On Day 512, he developed edema of upper lip and right cheek and was diagnosed with angioedema. He was treated with methylprednisolone. On Day 513, the patient again took both LCZ696 and ramipril/hydrochlorothiazide and experienced lip, cheek, and periorbital edema. He was again diagnosed with angioedema and both LCZ696 and ramipril/hydrochlorothiazide were permanently discontinued. He was treated with dexamethasone and the anti-histamine levocetirizine. The event was considered resolved on Day 515. The adjudication committee considered the event to be angioedema of severity Grade II.

7.3.5.1.2 Angioedema defined by MedDRA SMQ in PARADIGM-HF

Angioedema-related AEs/SAEs were also evaluated using the MedDRA Angioedema SMQ (Table 60). There was no difference between the two treatment arms with regard to the incidence of these events using broad and narrow SMQs.

Table 60: Incidence of Angioedema SMQ/PTs during the double-blind period in PARADIGM-HF

	Enalapril 10 mg bid		LCZ696 200 mg bid	
	AE	SAE	AE	SAE
Angioedema SMQ broad[2]	312 (7.4%)	30 (0.7%)	300 (7.1%)	18 (0.4%)
Angioedema SMQ narrow	37 (0.9%)	6 (0.1%)	40 (1.0%)	3 (0.1%)
Angioedema	10 (0.2%)	4 (0.1%)	11 (0.3%)	3 (0.1%)
Urticaria	10 (0.2%)	1(0.02%)	9 (0.2%)	0
Swelling face	6 (0.1%)	0	11 (0.3%)	0
Face edema	5 (0.1%)	0	3 (0.1%)	0
Lip edema	1 (0.02%)	1(0.02%)	2 (0.05%)	0
Lip swelling	0	0	3 (0.1%)	0
Periorbital edema	3 (0.1%)	0	0	0
Eye swelling	1 (0.02%)	0	1 (0.02%)	0
Eyelid edema	0	0	2 (0.05%)	0
Conjunctival edema	0	0	1 (0.02%)	0
Corneal edema	1 (0.02%)	0	0	0
Laryngeal edema	1 (0.02%)	1(0.02%)	0	0

Reviewer's Table, Data source: AAEV & AIDENT

A number of angioedema-related AE terms in the narrow SMQ, such as urticaria, corneal edema and conjunctival edema were not included in the applicant's list of terms for angioedema-like events. There were 9 subjects in the LCZ696 arm and 9 in the enalapril arm with these AEs and no other event/term that would have triggered adjudication. Thus, these cases were never sent for adjudication. However, further review of the narratives for these cases did not raise any concerns. Only one subject in the LCZ696 arm permanently discontinued from the study drug due to the event (urticaria).

2 PTs under Angioedema SMQ broad include: angioedema, breast swelling, choking sensation, conjunctival edema, corneal edema, drug hypersensitivity, endotracheal intubation, eye swelling eyelid edema, face edema, generalized edema, hypersensitivity, laryngeal edema, lip edema, lip swelling, local swelling, localized edema, nasal obstruction, obstructive airways disorder, edema, edema peripheral, periorbital edema, scrotal edema, scrotal swelling, swelling face, throat tightness, urticarial, wheezing

7.3.5.1.3 Adjudicated angioedema cases in other studies

There were 4 confirmed angioedema cases treated with LCZ696 in the other studies that were included in the safety database (3 cases in the two HF studies and 1 case in the completed HTN studies) (Table 61). There were no cases in black subjects (n = 74) or ACEi/ARB naïve subjects (n = 1,206) in these studies.

Table 61: Confirmed angioedema events in other HF and HTN studies

Study (Treatment period)	PARAMOUNT (9 months)	TITRATION (3 months)	All completed HTN studies (8-14 weeks)
Treated with LCZ696	**149**	**498**	**2880**
-Blacks	4	23	47
-ACEi/ARB naïve	10	33	1163
Confirmed angioedema cases	**1 (0.7%)**	**2 (0.4%)**	**1 (0.03%)**
-LCZ696 dose received	100 mg	50 mg	200 mg
-Time to event (days)	5[a]	4/6	237

Reviewer's Table, Data source: AIDENT from two HF studies, ADSL from ISS and narratives from SCS
[a] 5 days after up titration to 100 mg and 12 days after the first dose of LCZ696

Narratives for confirmed angioedema cases in other studies:

Angioedema events in PARAMOUNT: There was one angioedema event (1/149, 0.7%) in the LCZ696 arm and none in the valsartan arm (0/152) during the double-blind period in PARAMOUNT. The case of angioedema was reported in a 76 year-old Caucasian female who was on an ACEi prior to screening. The angioedema event occurred 12 days after the first dose of LCZ696 and 5 days after up titration of LCZ696 to 100 mg bid. The patient experienced periorbital edema, urticaria and peripheral edema and discontinued study medication as a result of the event. The event resolved without treatment (severity grade I).

Angioedema events in TITRATION: There were two angioedema events (2/498, 0.4%) in TITRATION, one during the LCZ696 run-in period and one during the double-blind period. The first case occurred in a 63-year-old Caucasian male who experienced swelling of the lips 4 days after starting LCZ696 50 mg bid during the run-in period. The patient was treated with the anti-histamine clemastine and methylprednisolone for the event (severity grade II) and LCZ696 was permanently discontinued. The patient was on an ARB prior to the study. The second case occurred in a 60-year-old Caucasian male who experienced edema of the periorbital area as well as redness and pruritus of the face 6 days after starting LCZ696 50 mg bid during the double-blind period. LCZ696 was permanently discontinued. The event resolved without treatment (severity grade I).The patient was on an ACE inhibitor prior to the study.

Among the completed HTN trials, there was only 1 adjudicated angioedema event among 2880 patients exposed to LCZ696. The case occurred in a 34-year-old Asian female who experienced dyspnea, tongue edema, and difficulty swallowing on day 237, while on LCZ696 200 mg qd. LCZ696 was permanently discontinued. The event resolved without treatment (severity class I). The patient was on an ARB prior to the study.

Reviewer's Comments: The low incidence of angioedema as well as non-serious nature of these events in other HF trials and HTN studies are reassuring. Safety data from the HTN trials also do not suggest an increased risk of angioedema among patients who are ACEi/ARB naïve.

7.3.5.2 Hypotension

7.3.5.2.1 Hypotension in PARADIGM-HF

Hypotension was a safety topic of interest based on the recognized class effect of RAAS agents. The Investigators were instructed to monitor blood pressure closely. If subjects developed symptomatic hypotension, investigators were instructed to correct any treatable causes first (e.g., hypovolemia), then to down-titrate or stop antihypertensive or non-life saving, and finally to down-titrate or temporarily discontinue study drug if hypotension persists. The investigators were instructed to follow the guidelines as much as possible with regard to re-challenging dose or restarting study drug (see Section 5.3). The protocol defined that any patient who experienced SBP < 95 mmHg during the run-in period should be withdrawn from the study.

The risk of hypotension during the run-in and double-blind periods is summarized below.

Run-in period

Hypotension was one of the most common AEs leading to run-in failure in PARADIGM-HF (see Table 50). Table 62 shows hypotension-related AEs/SAEs during the enalapril run-in and the LCZ696 run-in periods. The incidence of hypotension related AEs was 3.2% in the enalapril run-in period and 5.1% in the LCZ696 run-in period. The incidence of hypotension-related SAEs was low and similar in the two run-in periods. The exposure-adjusted event rate for hypotension-related AEs was 59.3 vs.61.1 per 100 patient-years in the enalapril and LCZ696 run-in periods, respectively.

Table 62: Hypotension-related AEs during the run-in period in PARADIGM-HF

Safety Topic/MedDRA PT	AE		SAE	
	Enalapril Run-in N =10,513 n (%)	LCZ696 Run-in N=9,419 n (%)	Enalapril Run-in N =10,513 n (%)	LCZ696 Run-in N=9,419 n (%)
Hypotension-related event[a]	**337 (3.2%)**	**485 (5.1%)**	**21 (0.1%)**	**25 (0.3%)**
Hypotension	214 (2.0%)	291 (3.1%)	10 (0.1%)	9 (0.1%)
Dizziness	98 (0.9%)	163 (1.7%)	4 (0.0%)	2 (0.0%)
Syncope	13 (0.1%)	29 (0.2%)	3 (0.0%)	10 (0.1%)
Orthostatic hypotension	7 (0.1%)	24 (0.3%)	1 (0.0%)	3 (0.0%)
Dizziness postural	9 (0.1%)	9 (0.1%)	0 (0.0%)	0 (0.0%)
Presyncope	7 (0.1%)	5 (0.1%)	1 (0.0%)	1 (0.0%)
Loss of consciousness	3 (0.0%)	5 (0.1%)	2 (0.0%)	1 (0.0%)
BP decreased	1 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
Depressed level of consciousness	0 (0.0%)	1 (0.0%)	0 (0.0%)	1 (0.0%)
BP fluctuation	1 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
Dizziness exertional	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Reviewer's Table. Data Source: AIDENT, AEEV & ADARTLB.
a Relevant MedDRA PTs were listed in Section 9.8. One subject can have more than one hypotension-related event.

Most of the hypotension-related AEs in both arms did not require any intervention (Table 63). Of those that did, study drug discontinuation was the most common action taken during the run-in periods. About 1.8% of subjects in the LCZ696 run-in period were permanently discontinued from the study drug due to hypotension-related AEs compared to 1.5% in the enalapril run-in period.

Table 63: Actions taken for hypotension-related events during the run-in period in PARADIGM-HF

	Enalapril N =10,513 n (%)	LCZ696 N=9,419 n (%)
Hypotension-related AE[a]	**337 (3.2%)**	**485 (5.1%)**
- No action taken	150 (1.4%)	258 (2.7%)
- Study dose adjusted/temporary interruption	11 (0.1%)	38 (0.4%)
- Study drug permanently discontinued	154 (1.5%)	171 (1.8%)
- Concomitant medication taken[b]	29 (0.3%)	41 (0.4%)
- Non-drug therapy given	6 (0.1%)	5 (0.1%)
- Hospitalization/prolonged hospitalization	11 (0.1%)	16 (0.2%)

Reviewer's Table, Data source: AAEV & AIDENT &
[a] Subjects could have more than one hypotension-related AE thus the number for actions taken for each event did not sum up as number of subjects with hypotension-related AEs
[b] Concomitant medication taken includes any drug therapy or discontinuation/interruption/adjustment of concomitant medications

Double-blind period

Hypotension-related AEs were reported more frequently in the LCZ696 arm compared to the enalapril arm (24.4% vs. 18.6%; event rate: 13.2 vs. 9.5 per 100 patient-years, HR 1.4, 95% CI 1.3, 1.5). Table 64 provides an overview of hypotension-related AEs/SAEs during the double-blind period. The higher incidence of hypotension-related events in the LCZ696 arm compared to the enalapril arm was mainly driven by the following preferred terms (PTs): hypotension, dizziness, and orthostatic hypotension. For potential hypotension-related events of greatest concern, such as syncope, pre-syncope, and loss of consciousness, the incidence was similar between groups. The incidence of potential hypotension-related SAEs was not higher in the LCZ696 arm compared to the enalapril arm (2.8% vs. 3.5%).

Table 64 Hypotension-related AEs during the double-blind period in PARADIGM-HF

	AE		SAE	
Safety Topic/MedDRA PT	Enalapril N =4,229 n (%)	LCZ696 N=4,203 n (%)	Enalapril N =4,229 n (%)	LCZ696 N=4,203 n (%)
Hypotension-related event	**786 (18.6%)**	**1027 (24.4%)**	**147 (3.5%)**	**117 (2.8%)**
Hypotension	506 (12.0%)	740 (17.6%)	68 (1.6%)	59(1.4%)
Dizziness	206 (4.9%)	266 (6.3%)	5 (0.1%)	10 (0.2%)
Syncope	114 (2.7%)	94 (2.2%)	68 (1.6%)	43 (1.0%)
Orthostatic hypotension	34 (0.8%)	64 (1.5%)	3 (0.1%)	5 (0.1%)
Dizziness postural	12 (0.3%)	24 (0.6%)	0 (0.0%)	0 (0.0%)
Presyncope	21 (0.5%)	15 (0.4%)	7 (0.2%)	5 (0.1%)
Loss of consciousness	10 (0.2%)	5 (0.1%)	4 (0.1%)	2 (0.0%)
BP inadequately controlled	5 (0.1%)	1 (0.0%)	1 (0.0%)	0 (0.0%)
BP decreased	3 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
Procedural hypotension	0 (0.0%)	3 (0.1%)	0 (0.0%)	0 (0.0%)
BP systolic decreased	2 (0.0%)	1 (0.0%)	1 (0.0%)	0 (0.0%)
Depressed level of consciousness	3 (0.1%)	0 (0.0%)	2 (0.0%)	0 (0.0%)
BP fluctuation	1 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
BP orthostatic abnormal	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
Diastolic dysfunction	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dizziness exertional	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Reviewer's Table. Data Source: AIDENT & AEEV

About half of the hypotension-related AEs in both arms did not require any intervention (Table 65). Dose adjustment or temporally interruption of therapy was the second most common action taken for hypotension-related AEs (7.7% vs. 11.3% in the enalapril and LCZ696 arms respectively).

Table 65: Actions taken for hypotension-related events during the double-blind period in PARADIGM-HF

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

Reviewer's Table, Data source: AAEV & AIDENT
[a] Subjects could have more than one hypotension-related AE thus the number for actions taken for each event did not sum up as number of subjects with hypotension AEs
[b] Concomitant medication taken includes any drug therapy or discontinuation/interruption/adjustment of concomitant medications

Table 66 provides additional information on dose adjustments and temporary interruptions for hypotension-related events. Among subjects who experienced dose adjustment or temporary interruptions due to hypotension, about 60% were titrated down to enalapril 5 mg or LCZ696 100 mg, while 15% were titrated down to enalapril 2.5 mg or LCZ69 50 mg. About 22% of subjects who had a dose adjustment or temporary interruption of therapy due to hypotension in the LCZ696 arm had their dose titrated up to the targeted dose at the end of double-blind treatment (15% in the enalapril arm).

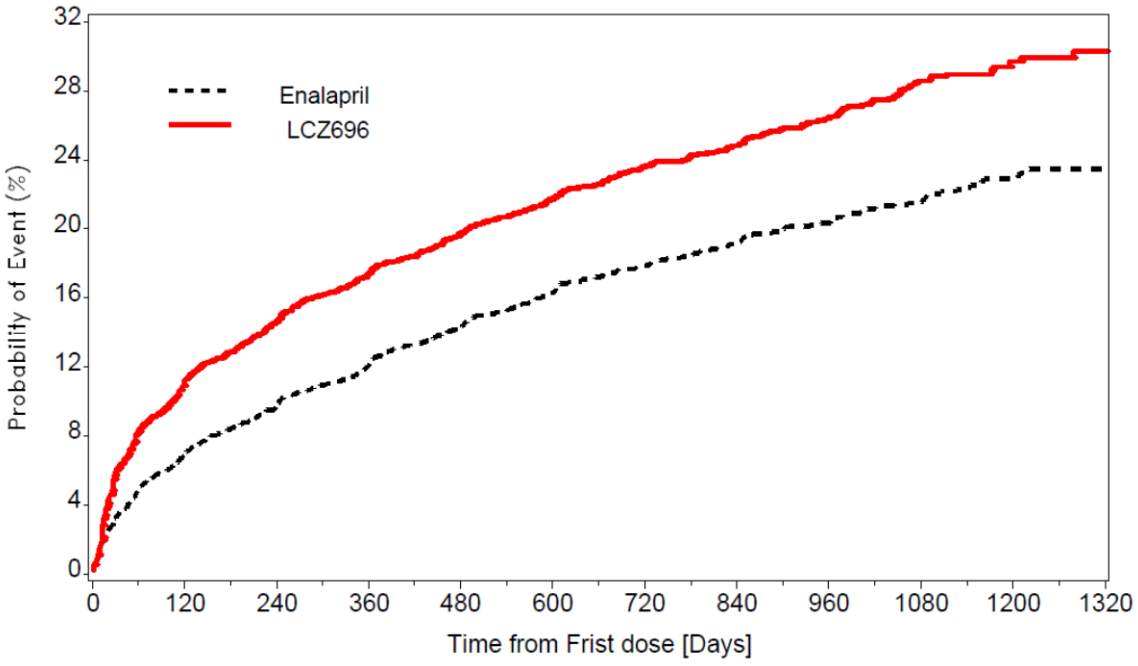
Table 66: Study Dose adjustment or temporary study interruption due to Hypotension in PARADIGM-HF[a]

	Number of patients had dose adjustment due to hypotension	
	Enalapril N =300	LCZ696 N =415
Dose adjusted level [b]		
-Level 1[c]	50 (13.5%)	77 (14.5%)
-Level 2[d]	212 (57.3%)	328 (61.2%)
-No treatment	108 (29.2%)	126 (23.7%)
Median Days of exposure (IQR)[b]		
-Level 1 [c]	132.5 (49-344)	278 (86-455)
-Level 2 [d]	212 (61.5-470.5)	188 (64.5-498)
-No treatment	23 (7-115)	15 (5-95)
Dose at the end of study[e]		
-Level 1[c]	35 (11.7%)	48 (11.6%)
-Level 2[d]	109 (36.3%)	156 (37.6%)
-Level 3 (targeted dose)	45 (15.0%)	89 (21.5%)
-No treatment	111 (37.0%)	122 (29.4%)

Reviewer's Table, Data source: ADARTLB & AIDENT
[a] Data were collected from the "Dose Administration Record" CRF page (page 63). The number of hypotension event is slightly different between this table and Table 64

Figure 15 shows the K-M estimate of the time to first hypotension-related AE. The K-M curves show an early separation of the curves for LCZ696 and enalapril; the magnitude of the difference appears to remain relatively stable over the subsequent course of the double-blind treatment period. More than half of the hypotension events (~52%) in the LCZ696 arm occurred within 6 months after the first dose of study drug.

Figure 15: Kaplan-Meier plot of time to the first hypotension-related AE during the double-blind period in PARADIGM-HF



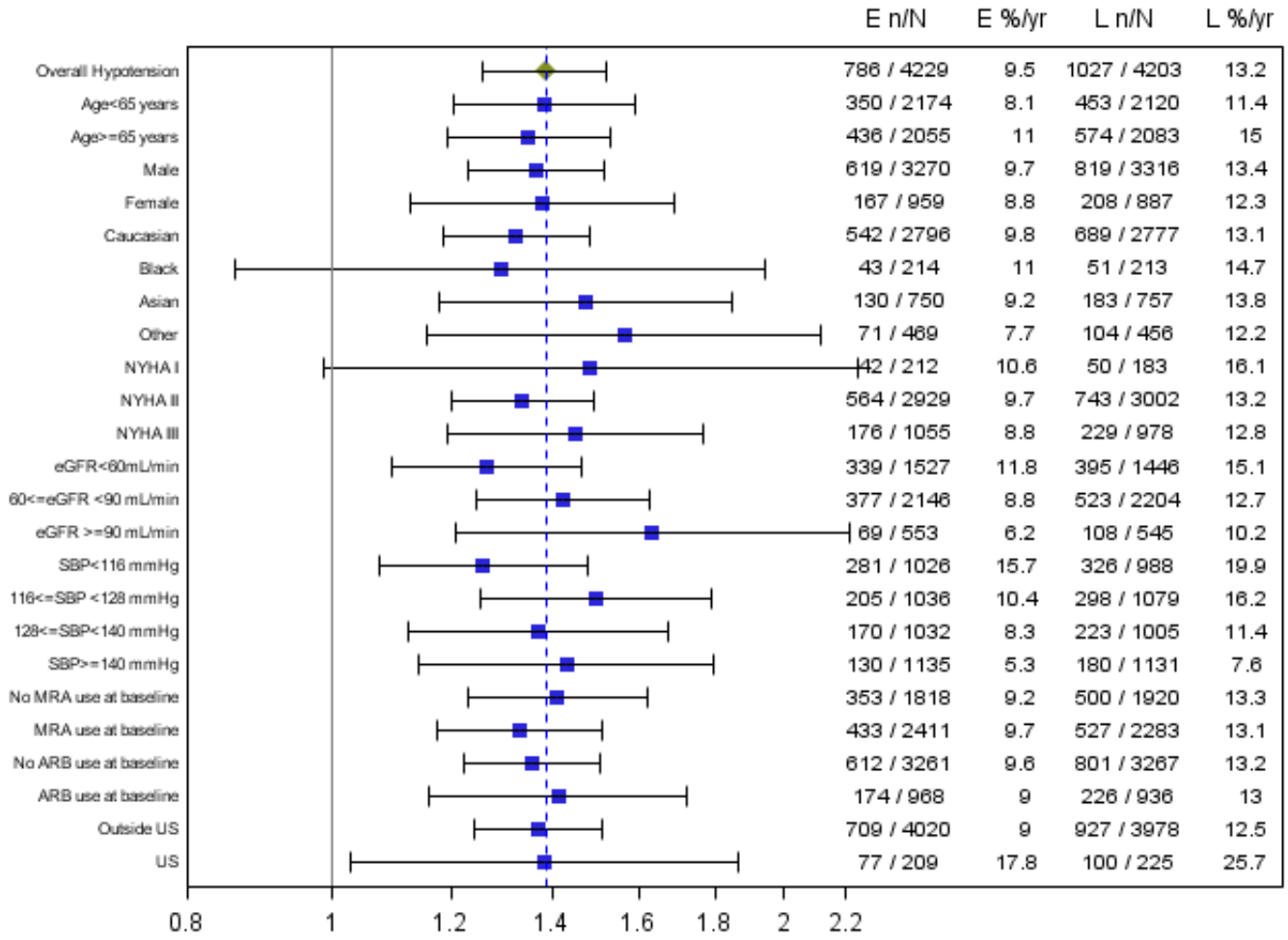
No. at risk

Enalapril	4229	4067	3974	3909	3831	3727	3438	2846	2057	1463	864	464
LCZ696	4203	3935	3815	3744	3648	3547	3227	2690	1971	1350	774	403

Reviewer' Figure, Data source: ADTTE from ISS

Subgroup analyses for hypotension-related AEs were performed based on age, gender, race, NYHA class, eGFR at screening (< 60, 60-<90, ≥90 mL/min/1.73m^2), SBP at screening (quartile), use of mineralocorticoid receptor antagonist (MRA) therapy at baseline, prior use of ARB (at screening) and region (Figure 16). In both arms, hypotension events were more frequently reported in patients with the following characteristics: age≥ 65 years, lower baseline eGFR and lower baseline SBP; however, the risk ratio (LCZ696/enalapril) in these groups was consistent with that seen in the overall population. Overall, the hypotension results were consistent across subgroups with a HR >1.2 for all categories indicating an increased risk in the LCZ696 arm.

Figure 16 Hypotension by subgroup during the double-blind period in PARADIGM-HF



Reviewer's Figure, Data source: ARISKT. Hazard ratio on the x-axis is in log scale
Results for NYHA IV: HF 0.9 (0.2-4.4), corresponding to 3/33 events (ER: 4.6 %/yr) vs. 3/27 events (ER: 4.8 %/yr) in the LCZ696 and enalapril arms, respectively

Of note, falls (MedDRA PT) were reported more frequently in the LCZ696 arm compared to the enalapril arm (80/4203, 2% vs 54/4229, 1.3%) during the double-blind period in PARADIGM-HF.

Among subjects who had a fall AE, 48 (60%) of them in the LCZ696 arm compared to 20 (37%) in the enalapril arm also reported a hypotension-related AEs during the double-blind period in PARADIGM-HF. Whether hypotension contributed to these falls or any fall-related injuries cannot be ruled out.

Vital sign data were consistent with the AE results (see Section 7.4.3).

7.3.5.2.2 Hypotension in other studies

Hypotension-related AEs in PARAMOUNT

In PARAMOUNT, there was no major difference in the incidence of hypotension-related events in the LCZ696 200 mg bid and valsartan 160 mg bid treatment arms [30/149 (20.1%) vs. 28/152 (18.4%), respectively].

Hypotension-related AEs in TITRATION

See Section 6.1.8 for discussion of the findings in TITRATION.

Hypotension-related AEs in the pooled HTN studies

The incidence of hypotension-related AEs was 1.5% (31/2004 subjects) in the LCZ696 monotherapy group and 2.5% (8/323 subjects) in the placebo group (Table 67).

Table 67: Hypotension-related AEs in the pooled HTN studies with selected monotherapy groups

	LCZ696 monotherapy N =2004	Placebo N=323	Olmesartan monotherapy N=681	Valsartan monotherapy N=636
N of patients who had an event	31 (1.5%)	8 (2.5%)	9 (1.3%)	5 (0.8%)
Dizziness	25 (1.2%)	7 (2.2%)	5 (0.7%)	5 (0.8%)
Hypotension	3 (0.1%)	0 (0.0%)	2 (0.3%)	0 (0.0%)
Dizziness postural	1 (0.0%)	0 (0.0%)	2 (0.3%)	0 (0.0%)
Orthostatic hypotension	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Presyncope	1 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Syncope	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Reviewer's Table, data source: ADSL & ADAE in ISS

Reviewer's comment: In the HF population, the risk of hypotension with LCZ696 in the 2 phase 2 studies is consistent with the overall findings in PARADIGM-HF. There is limited utility to looking at the risk of hypotension in the HTN studies since enrolled subjects had hypertension and the goal of therapy is to lower BP in these patients.

7.3.5.3 Renal Impairment

7.3.5.3.1 Renal Impairment in PARADIGM-HF

Renal impairment was a safety topic of interest based on the recognized class effect of RAAS agents. The Investigators were instructed to monitor serum creatinine closely and respond to an elevated serum creatinine by first correcting any reversible causes of renal dysfunction such as volume depletion or stopping medications known to affect creatinine. If study drug was stopped, serum creatinine was monitored weekly until levels returned to acceptable values. The investigators were instructed to make every effort to restart the study drug, according to the clinical condition. The protocol defined that any patient who had eGFR < 30 mL/min/1.73 m^2 or >25% decline between screening and end of each run-in period should be considered as a run-in failure and withdrawn from the study.

The risk of renal impairment during the run-in and double-blind periods is summarized below.

Run-in period

Renal impairment was one of the most common AEs leading to run-in failure in PARADIGM-HF (see Table 50). Table 68 shows renal impairment AEs/SAEs that were reported during the enalapril and LCZ696 run-in periods. The incidence of renal impairment AEs was 2.2% in the enalapril run-in period and 2.3% in the LCZ696 run-in period. The incidence of renal impairment SAEs was very low and similar in both run-in periods. The exposure-adjusted event rate of renal impairment AEs was 50.6 vs. 35.4 per 100 patient-years in the enalapril and LCZ696 run-in periods, respectively.

Study drug discontinuation was the most common action taken for renal impairment-related AEs during the run-in period (Table 69). About 1.6% of subjects in the LCZ696 run-in period were permanently discontinued from the study due to renal impairment-related AEs compared to 2.0% in the enalapril run-in period.

Table 68: Renal Impairment during the run-in period in PARADIGM-HF

Safety Topic/MedDRA PT	AE		SAE	
	Enalapril Run-in N =10,513 n (%)	LCZ696 Run-in N=9,419 n (%)	Enalapril Run-in N =10,513 n (%)	LCZ696 Run-in N=9,419 n (%)
Renal Impairment-related event[a]	**290 (2.8%)**	**285 (3.0%)**	**9 (0.1%)**	**13 (0.1%)**
Renal impairment	229 (2.2%)	212 (2.3%)	2 (0.0%)	5 (0.0%)
Renal failure	23 (0.2%)	32 (0.4%)	1 (0.0%)	2 (0.0%)
Renal failure acute	7 (0.1%)	9 (0.1%)	5 (0.0%)	5 (0.0%)
Glomerular filtration rate decreased	13 (0.1%)	13 (0.1%)	0 (0.0%)	0 (0.0%)
Blood creatinine increased	5 (0.0%)	11 (0.1%)	0 (0.0%)	1 (0.0%)
Blood urea increased	5 (0.0%)	3 (0.0%)	0 (0.0%)	0 (0.0%)

Reviewer's Table, Data source: AAEV & AIDENT
[a] Using MedDRA renal failure broad SMQ. Table only lists preferred terms with ≥ a total of 5 AEs in the study. Table lists AEs/SAEs reported on the AE page of CRF during the run-in period. It did not include patients who failed the run-in period due to renal impairment (e.g. patient did not meet the safety criterion of eGFR >30 mL/min/1.73m^2, thus these events were not necessary recorded on the AE page of CRF)

Table 69: Actions taken for renal impairment AEs during the run-in period in PARADIGM-HF

	Enalapril N =10,513 n (%)	LCZ696 N=9,419 n (%)
Renal Impairment AE[a]	290 (2.8%)	285 (3.0%)
- No action taken	79 (1.2%)	107 (1.1%)
- Study dose adjusted/temporary interruption	3 (0.0%)	12 (0.1%)
- Study drug permanently discontinued	201 (1.9%)	154 (1.6%)
- Concomitant medication taken[b]	13 (0.1%)	15 (0.1%)
- Non-drug therapy given	6 (0.1%)	5 (0.0%)
- Hospitalization/prolonged hospitalization	8 (0.1%)	10 (0.1%)

Reviewer's Table, Data source: AAEV & AIDENT
[a] Subjects could have more than one renal impairment AE thus the number for actions taken for each event did not sum up as number of subjects with renal impairment AEs
[b] Concomitant medication taken includes any drug therapy or discontinuation/interruption/adjustment of concomitant medicatio

Double-blind period

The incidence of renal impairment-related AEs was similar between the LCZ696 arm and the enalapril arm during the double-blind period in PARADIGM-HF (16.2% vs. 17.6%; event rate: 7.9 vs. 8.8 per 100 patient-years, HR 0.9, 95% CI 0.8, 1.0). Renal impairment SAEs were also similar between the two treatment arms (Table 70).

Table 70: Renal Impairment during the double-blind period in PARADIGM-HF

	AE		SAE	
Safety Topic/MedDRA PT	Enalapril N =4,229 n (%)	LCZ696 N=4,203 n (%)	Enalapril N =4,229 n (%)	LCZ696 N=4,203 n (%)
Renal Impairment-related event[a]	**746 (17.6%)**	**682 (16.2%)**	**188 (4.4%)**	**161 (3.8%)**
Renal impairment	487 (11.5%)	426 (10.1%)	57 (1.3%)	46 (1.1%)
Renal failure	144 (3.4%)	111 (2.6%)	54 (1.3%)	42 (1.0%)
Renal failure acute	93 (2.2%)	95 (2.3%)	79 (1.9%)	74 (1.8%)
Glomerular filtration rate	48 (1.1%)	58 (1.4%)	1 (0.0%)	2 (0.0%)
Blood creatinine increased	34 (0.8%)	33 (0.8%)	2 (0.0%)	4 (0.1%)
Blood urea increased	23 (0.5%)	22 (0.5%)	0 (0.0%)	0 (0.0%)
Azotaemia	6 (0.1%)	8 (0.2%)	0 (0.0%)	1 (0.0%)
Acute prerenal failure	6 (0.1%)	4 (0.1%)	0 (0.0%)	0 (0.0%)
Prerenal failure	6 (0.1%)	4 (0.1%)	0 (0.0%)	0 (0.0%)

Reviewer's Table, Data source: AAEV & AIDENT
[a] Using MedDRA renal failure broad SMQ. Table only lists preferred terms with ≥ a total of 10 AEs in the study

In both arms, most of the renal impairment AEs did not require any intervention (Table 71). Less than 1% of subjects in the LCZ696 arm permanently discontinued study drug because of a renal impairment-related AE. Overall, there was no major difference between the two arms regarding the type of interventions for theses AEs.

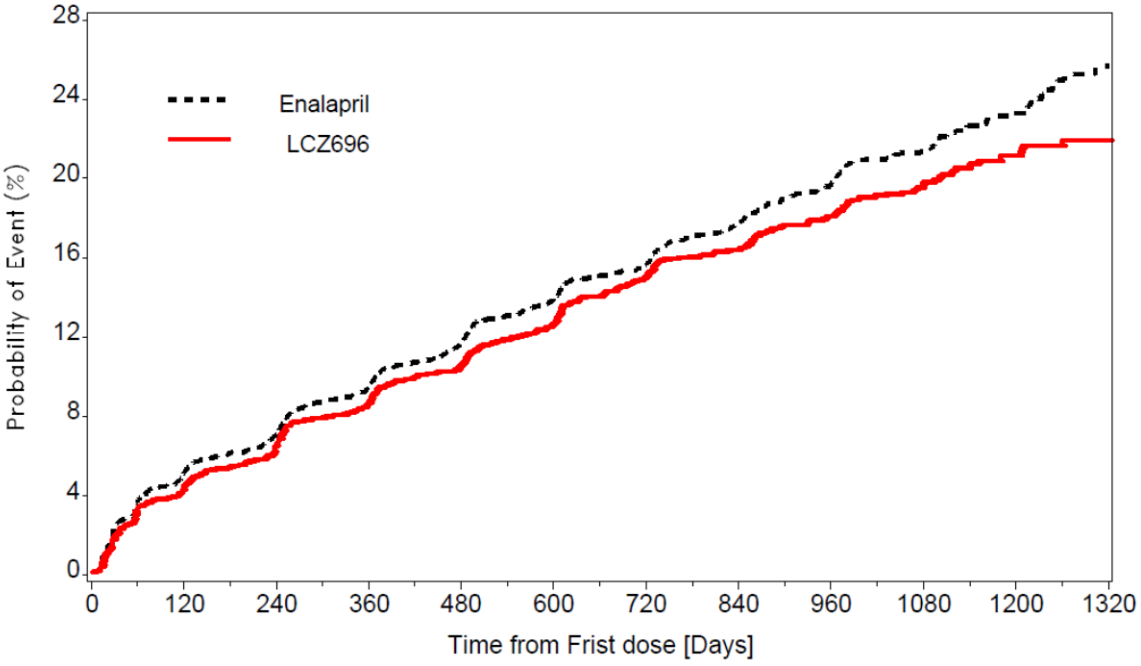
Table 71: Actions taken for renal impairment AEs during the double-blind period in PARADIGM-HF

	Enalapril N =4,229 n (%)	LCZ696 N=4,203 n (%)
Renal Impairment AE[a]	746 (17.6%)	682 (16.2%)
- No action taken	441 (10.4%)	413 (9.8%)
- Study dose adjusted/temporary interruption	236 (5.6%)	211(5.0%)
- Study drug permanently discontinued	56 (1.3%)	29 (0.7%)
- Concomitant medication taken[b]	130 (17.6%)	98 (2.3%)
- Non-drug therapy given	61 (1.4%)	46 (1.1%)
- Hospitalization/prolonged hospitalization	132 (3.1%)	115 (2.7%)

Reviewer's Table, Data source: AAEV & AIDENT
[a] Subjects could have more than one renal impairment AE thus the number for actions taken for each event did not sum up as number of subjects with renal impairment AEs
[b] Concomitant medication taken includes any drug therapy or discontinuation/interruption/adjustment of concomitant medications

Figure 17 shows that the renal impairment AEs were evenly distributed over time and the difference in incidence remained small at all time points. Laboratory parameters for renal function (eGFR and serum creatinine) were consistent with the AE findings (see Section 7.4.2.1).

Figure 17: Kaplan-Meier Plot of time to first renal impairment AE during the double-blind in PARADIGM-HF

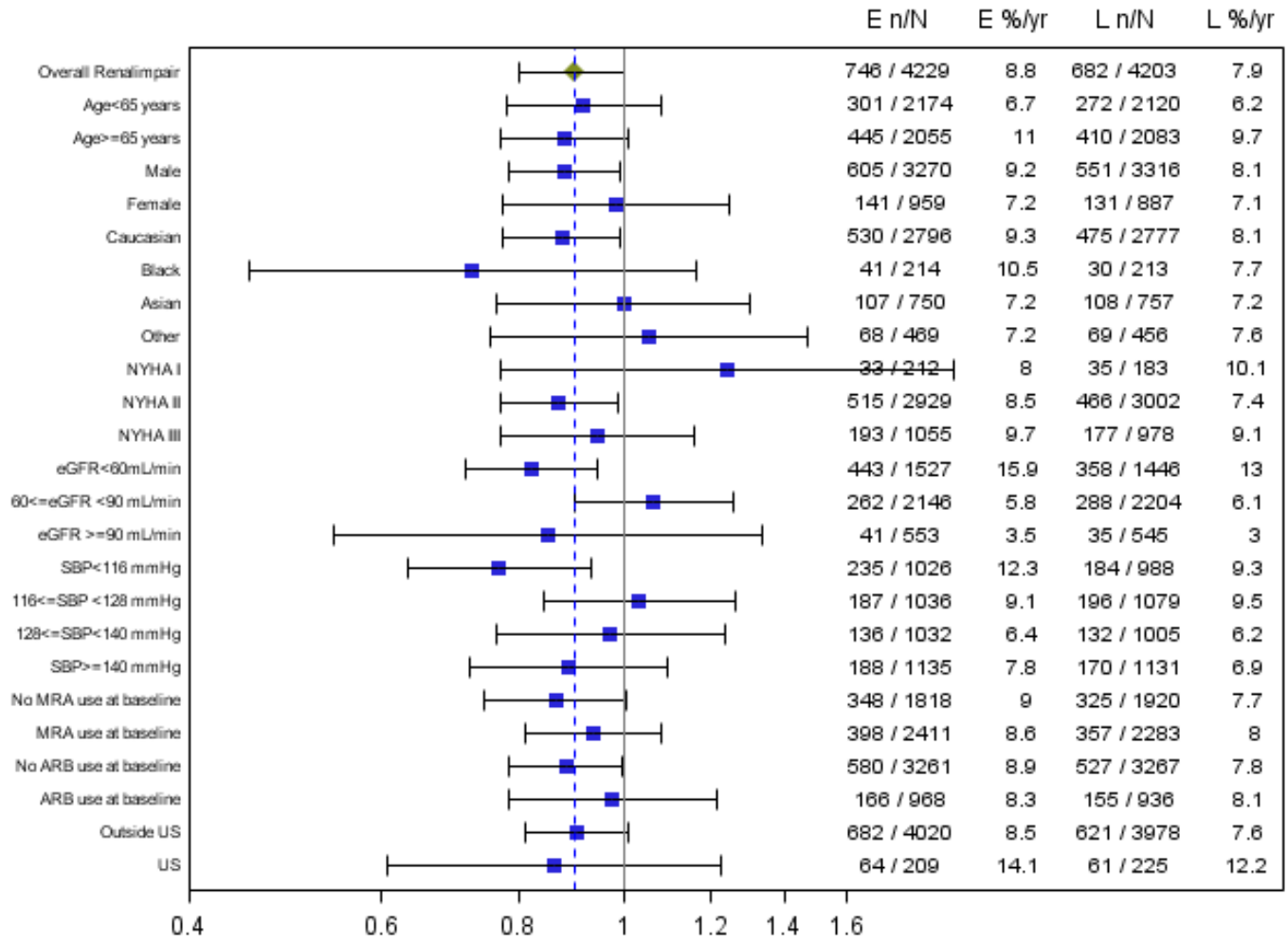


No. at risk												
Enalapril	4229	4101	4026	3974	3914	3824	3539	2936	2132	1521	888	489
LCZ696	4203	4100	4023	3982	3934	3862	3596	3025	2205	1526	888	483

Reviewer's Figure, Data source: ADTTE from ISS

Subgroup analyses for renal impairment events were performed by age, gender, race, NYHA class, eGFR at screening (< 60, 60-<90, ≥90 mL/min/1.73m^2), SBP at screening (quartile), use of MRA therapy at baseline, prior use of ARB (at screening) and region. Overall, the results were consistent across the majority of the subgroups with the point estimate favoring LCZ696. The risk was slightly higher (HR: 1.2) in the LCZ696 arm compared to the enalapril arm among subjects with NYHA class I and IV, though both subgroups included small numbers of subjects and thus the confidence intervals around these point estimates were very wide. In both treatment groups, the rate of renal impairment was particularly high in patients with low eGFR at baseline (eGFR <60 mL/min/1.73m^2) and in the US; however the risk ratio (LCZ696/enalapril) remained similar across these subgroups.

Figure 18: Renal Impairment by subgroup during the double-blind period in PARADIGM-HF



Reviewer's figure, Data source: ARISKT, Hazard ration on the x-axis is in log scale
Results for NYHA IV: HF 1.2 (0.3-5.5), corresponding to 4/33 events (ER: 6.1%/yr) vs. 3/27 events (ER: 4.9 %/yr) in the LCZ696 and enalapril arms, respectively

7.3.5.3.2 Renal Impairment in other studies

Renal impairment in PARAMOUNT

In PARAMOUNT, the incidence of renal impairment events was slightly lower in the LCZ696 arm compared to the valsartan arm [5/149 (3.4%) vs. 8/152 (5.3%), respectively].

Renal impairment in TITRATION
See Section 6.1.8 for discussion of the findings in TITRATION.

Renal impairment in the pooled HTN studies
The incidence of renal impairment AEs was low and similar between the LCZ696 monotherapy group (0.5%, 10/2004 subjects) and the placebo group (0.3%, 1/323 subject) in these studies. Blood urea increased was the most commonly reported preferred term in the LCZ696 monotherapy group (4/2004). The incidence of renal impairment was similar in ACEi/ARB naïve subjects and subjects with prior ACEi/ARB experience in the LCZ696 monotherapy group (6/1012, 0.6% vs 4/992, 0.4%, respectively) in these trials.

7.3.5.4 Hyperkalemia

7.3.5.4.1 Hyperkalemia in PARADIGM-HF

Hyperkalemia was a safety topic of interest based on the class effect of RAAS inhibitors. Investigators were instructed to manage subjects with elevated potassium value (>5.3-< 6.0 mmol/L) following the protocol specified actions including reinforcing low potassium diet, down-titration of concomitant therapy known to cause hyperkalemia, and down-titration or temporary discontinuation of study drug according to investigator's medical judgment. The protocol defined that any patient who experienced a potassium level ≥ 5.5 mmol/L during the run-in period should be withdrawn from the study. In the double-blind period, study drug should be immediately discontinued if subjects had serum potassium ≥ 6.0 mmol/L.

The risk of hyperkalemia during the run-in and double-blind periods is summarized below.

Run-in period

Hyperkalemia was one of the most common AEs leading to run-in failure in PARADIGM-HF (see Table 50). Table 72 shows the reported hyperkalemia AEs/SAEs during the enalapril and LCZ696 run-in periods. The incidence of hyperkalemia was 2.8% in both enalapril and LCZ696 run-in periods. The incidence of hyperkalemia SAEs was very low and similar in both run-in periods. The exposure-adjusted event rate of hyperkalemia AEs was 50.8 vs. 32.3 per 100 patient-years in the enalapril and LCZ696 run-in periods, respectively.

Table 72: Hyperkalemia AEs during the run-in period in PARADIGM-HF

	AE		SAE	
	Enalapril Run-in N =10,513 n (%)	LCZ696 Run-in N=9,409 n (%)	Enalapril Run-in N =10,513 n (%)	LCZ696 Run-in N=9,409 n (%)
Hyperkalemia-related event	**290 (2.8%)**	**260 (2.8%)**	**5 (0.0%)**	**6 (0.1%)**
Hyperkalemia	279 (2.7%)	259 (2.7%)	5 (0.0%)	6 (0.2%)
Blood potassium increased	10 (0.1%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
Blood potassium abnormal	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Reviewer's Table, Data source: AAEV & AIDENT
a Event rate per 100 patient-year

Permanent discontinuation of study drug was the most common action taken for hyperkalemia-related AEs in both run-in periods (Table 73). Approximately 1.1 % of subjects in the LCZ696 run-in period were permanently discontinued from the study due to hyperkalemia-related AEs compared to 1.7% in the enalapril run-in period.

Table 73: Actions taken for hyperkalemia AEs during the run-in period in PARADIGM-HF

	Enalapril N =10,513 n (%)	LCZ696 N=9,409 n (%)
Hyperkalemia-related AE[a]	290 (2.8%)	260 (2.8%)
No action taken	70 (0.6%)	94 (1.0%)
Study dose adjusted/temporary interruption	6 (0.1%)	16 (0.2%)
Study drug permanently discontinued	181(1.7%)	108 (1.1%)
Concomitant medication taken	32 (0.3%)	37 (0.4%)
Non-drug therapy given	8 (0.1%)	23 (0.2%)
Hospitalization/prolonged hospitalization	5 (0.0%)	3 (0.0%)

Reviewer's Table, Data source: AAEV & AIDENT
[a] Subjects could have more than one hyperkalemia-related AE thus the number for actions taken for each event did not sum up as number of subjects with hyperkalemia AEs
[b] Concomitant medication taken includes any drug therapy or discontinuation/interruption/adjustment of concomitant medications

Double-blind period

The incidence of hyperkalemia-related AEs was slightly lower in the LCZ696 arm compared to the enalapril arm during the double-blind period in PARADIGM-HF (11.9% vs. 14.3%; event rate: 5.7 vs. 7.1 per 100 patient-year, HR 0.8, 95% CI 0.7, 0.9). Hyperkalemia SAEs were also reported less frequently in the LCZ696 arm compared to the enalapril arm (Table 74).

Table 74: Hyperkalemia AEs during the double-blind period in PARADIGM-HF

	AE		SAE	
	Enalapril N =4,229 n (%)	LCZ696 N=4,203 n (%)	Enalapril N =4,229 n (%)	LCZ696 N=4,203 n (%)
Hyperkalemia-related event	**605 (14.3%)**	**500(11.9%)**	**42 (1.0%)**	**17 (0.4%)**
Hyperkalemia	592 (14.0%)	488(11.6%)	42 (1.0%)	17 (0.4%)
Blood potassium increased	18 (0.4%)	14 (0.3%)	0 (0.0%)	0 (0.0%)
Blood potassium abnormal	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Reviewer's Table, Data source: AAEV & AIDEN

In both arms, most of the hyperkalemia AEs (~60%) did not require any intervention (Table 75). Less than 0.5% of subjects in both arms were permanently discontinued from the study drug due to hyperkalemia-related AEs. Overall, there was no major difference between the two arms with regard to the types of interventions for these AEs.

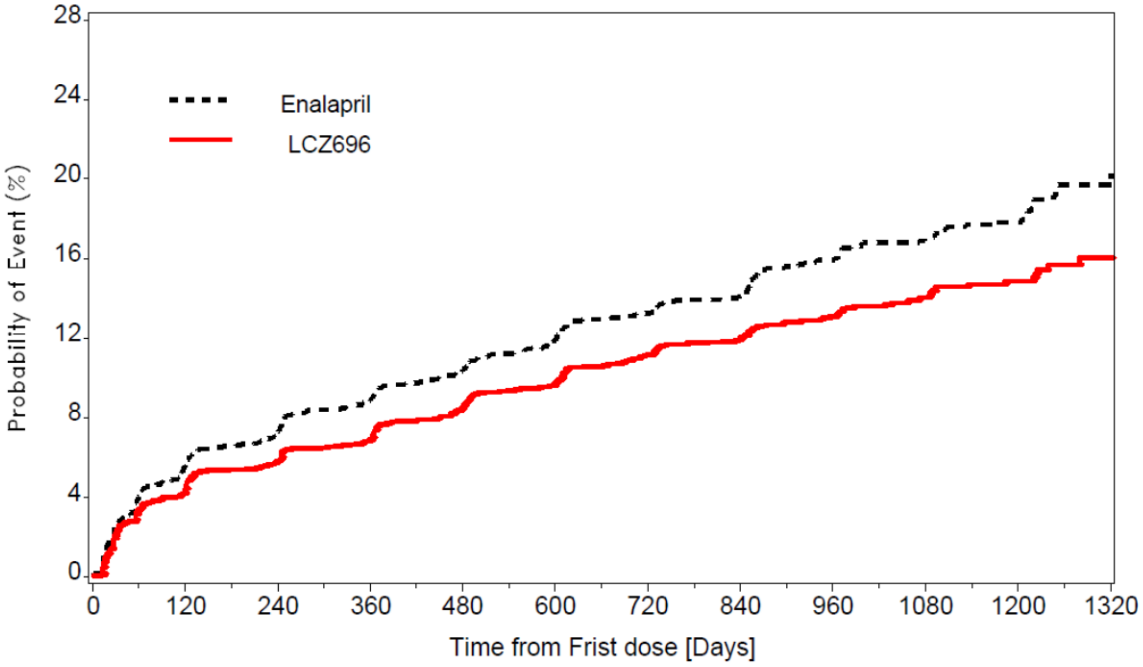
Table 75: Actions taken for hyperkalemia AEs during the double-blind period in PARADIGM-HF

	Enalapril N =605 n (%)	LCZ696 N=500 n (%)
Hyperkalemia-related AE[a]	605 (14.3%)	500(11.9%)
No action taken	357 (8.4%)	304 (7.2%)
Study dose adjusted/temporary interruption	178 (4.2%)	151 (3.6%)
Study drug permanently discontinued	15 (0.4%)	11 (0.3%)
Concomitant medication taken[b]	124 (2.9%)	88 (2.1%)
Non-drug therapy given	79 (1.9%)	67 (1.6%)
Hospitalization/prolonged hospitalization	31 (0.7%)	13 (0.3%)

Reviewer's Table, Data source: AAEV & AIDENT
[a] Subjects could have more than one hyperkalemia-related AE thus the number for actions taken for each event did not sum up as number of subjects with hyperkalemia AEs
[b] Concomitant medication taken includes any drug therapy or discontinuation/interruption/adjustment of concomitant medications

Figure 19 shows early separation of the two curves at about 60 days after randomization, with continued separation over time in favor of the LCZ696 arm. Laboratory findings for potassium levels were consistent with the AE findings (see Section 7.4.2.2).

Figure 19: Kaplan-Meier Plot of time to first hyperkalemia AE during the double-blind in PARADIGM-HF

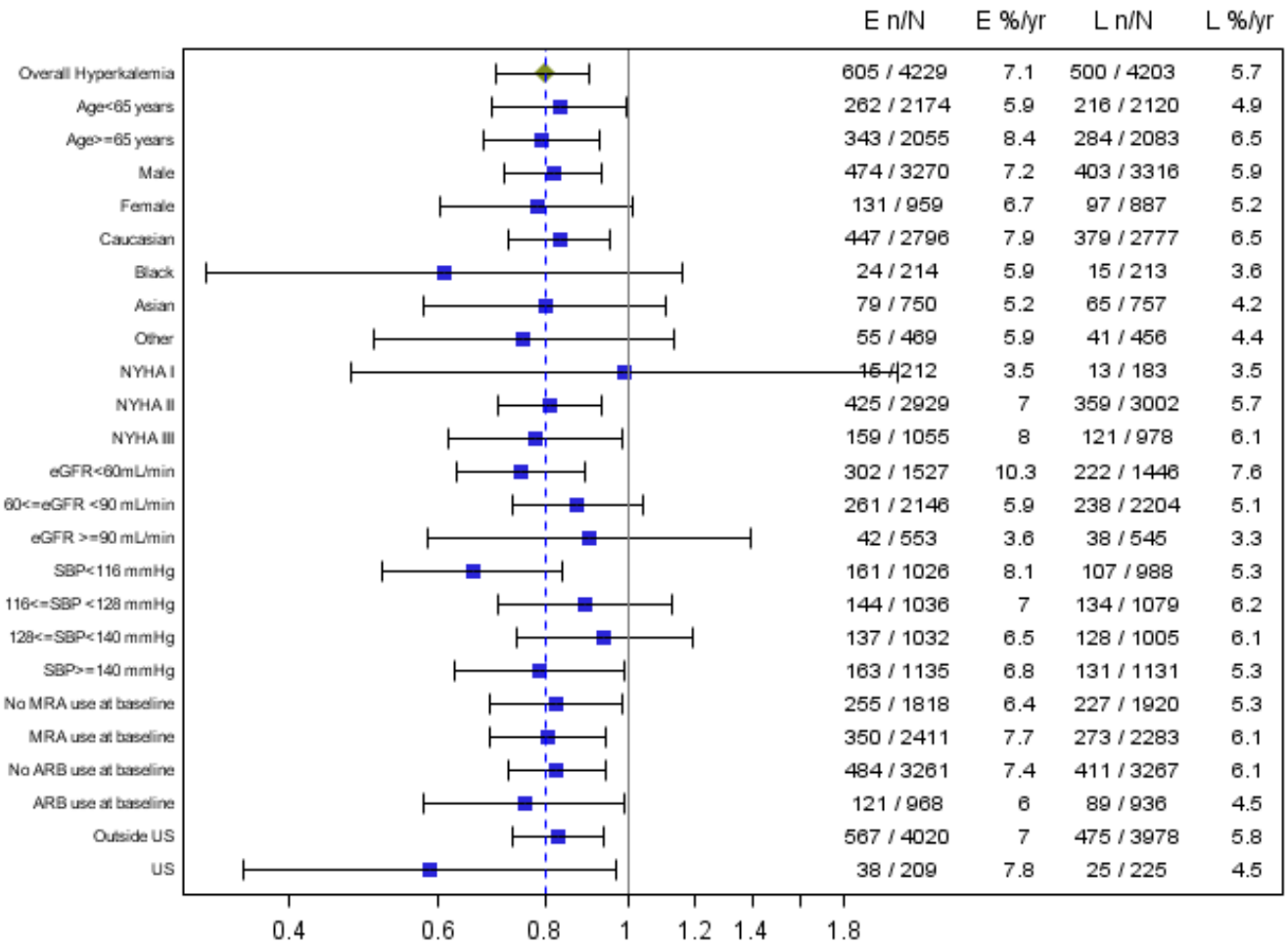


No. at risk												
Enalapril	4229	4093	4006	3957	3892	3803	3543	2956	2161	1540	899	494
LCZ696	4203	4090	4018	3971	3928	3853	3639	3072	2273	1573	935	505

Reviewer's Figure, Data source: ADTTER from ISS

Subgroup analyses for hyperkalemia-related AEs were performed by age, gender, race, NYHA class, eGFR at screening (< 60, 60-<90, ≥90 mL/min/1.73m^2), SBP at screening (quartile), use of MRA therapy at baseline, prior use of ARB (at screening) and region. Overall, the results were consistent across these subgroups with a point estimate of ≤ 1 in favor of the LCZ696 arm (Figure 20).

Figure 20: Hyperkalemia AEs by subgroup during the double-blind period in PARADIGM-HF



Reviewer's figure, Data source: ARISKT, Hazard ration on the x-axis is in log scale
Results for NYHA IV: HF 0.7 (0.2-2.3), corresponding to 5/33 events (ER: 8.1%/yr) vs. 6/27 events (ER: 11.4 %/yr) in the LCZ696 and enalapril arms, respectively.

7.3.5.4.2 Hyperkalemia in other studies

Hyperkalemia in PARAMOUNT

The incidence of hyperkalemia-related AEs was higher in the LCZ696 arm compared to the valsartan arm [12/149 (8.1%) vs. 9/152 (5.9%), respectively]. Relative to the valsartan arm, there was also a slightly higher percentage of subjects with a post-baseline serum potassium > 5.5 mmol/mL in the LCZ696 arm (16.2% vs. 11.2%); however, post-baseline serum potassium levels ≥ 6 mmol/mL were reported infrequently and at a similar incidence in the two treatment arms (3.4% vs. 4.2% in the LCZ690 and valsartan arms, respectively).

Reviewer's Comments: Hyperkalemia-related AEs were reported more frequently in the LCZ696 arm compared to the valsartan arm in this phase 2 study in HFpEF patients. These findings are somewhat different from what was seen in PARADIGM-HF possibly because of the differences in active control arm, study duration and patient population.

Hyperkalemia in TITRATION

See Section 6.1.8 for discussion of the findings in TITRATION.

Hyperkalemia in the pooled HTN studies

The incidence of hyperkalemia-related AEs in the pooled HTN studies was 0.6% (12/2004 subjects) in the LCZ696 monotherapy group and 0 in the placebo group (Table 76). In the LCZ696 monotherapy group, the incidence of hyperkalemia-related AEs was not greater in ACEi/ARB naïve subjects compared to subjects with prior ACEi/ARB experience (2/1012, 0.2% vs 10/992, 1.0%).

Table 76: Hyperkalemia-related AEs in the pooled HTN studies

	LCZ696 monotherapy N =2004	Placebo N=323	Olmesartan monotherapy N=681	Valsartan monotherapy N=636
N of patients who had an event	12 (0.6%)	0 (0.0%)	3 (0.4%)	2 (0.3%)
Hyperkalemia	6 (0.3%)	0 (0.0%)	3 (0.4%)	2 (0.3%)
Blood potassium increased	6 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Reviewer's Table, data source: ADSL & ADAE in ISS

7.3.5.5 Cognitive impairment

NEP is believed to be a major beta amyloid-degrading enzyme in the brain. Cognitive impairment is a safety topic of interest due to the theoretical potential that inhibition of NEP could accentuate accumulation of beta amyloid in the brain and increase the risk of Alzheimer's disease.

7.3.5.5.1 Cognitive impairment in PARADIGM-HF

The incidence of potential dementia-related AEs (as defined using the broad SMQ) was similar in the two treatment arms during the double-blind period in PARADIGM-HF (2% each, event rate: 0.9 per 100 patient-years, HR 1.0, CI 0.8, 1.4) (Table 77). A similar result was observed when the narrow SMQ was used to identify potential dementia-related adverse events.

Table 77: Potential dementia-related AEs during the double-blind period in PARADIGM-HF

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

Reviewer's Table, Data source: AAEV &AIDENT
The incidence of Dementia narrow SMQ (highlighted in grey) was 15 (0.4%) and 12 (0.3%) in the enalapril and LCZ696 arms, respectively.

A slightly higher percentage of dementia-related events was suspected by investigators to be related to the study drug in the LCZ696 arm compared to the enalapril arm [42(1.0%) vs. 32 (0.8%), respectively]. The incidence of dementia-related events leading to study drug discontinuation was similar in both arms [23(0.5%) vs. 19(0.4%) in the LCZ696 and enalapril arms, respectively].

7.3.5.5.2 Cognitive impairment in other studies

The incidence of dementia (broad SMQ) was very low in other HF and HTN studies (ranged from 0 to <0.8%). Since these studies were short term (majority were ≤ 3 months), they have limited utility for assessing the risk of cognitive impairment with LCZ696.

7.3.5.6 Gastric lesions

Local irritant effects resulting in gastric lesions were reported in preclinical studies of LCZ696. Gastric lesion-related AEs were evaluated using the gastritis HLT in combination with the MedDRA gastrointestinal perforation, ulcer, hemorrhage, or obstruction SMQ and additional MedDRA PTs including dyspepsia, abdominal pain upper and abdominal pain, gastroesophageal reflux disease, esophagitis and nausea.

Run-in period

The incidence of gastric lesion-related AEs was low in the run-in period [127/10513, (1.2%) in the enalapril run-in period and 131/9414 (1.4%) in the LCZ696 run-in period) (Table 78). There were 12 events leading to study discontinuation (6 nausea, 2 dyspepsia, 2 abdominal pain, 1 abdominal pain upper and 1 gastric hemorrhage) in the enalapril arm and 8 events (3 dyspepsia, 2 abdominal pain upper, 1 colitis ulcerative, 1 gastritis/nausea and 1 abdominal pain) in the LCZ696 arm.

Table 78: Gastric lesion-related AEs during the run-in treatment period in PARADIGM-HF

	AE		SAE	
	Enalapril Run-in N =10,513 n (%)	LCZ696 Run-in N=9,419 n (%)	Enalapril Run-in N =10,513 n (%)	LCZ696 Run-in N=9,419 n (%)
Gastric lesion-related event[a]	**127 (1.2%)**	**131 (1.4%)**	**5 (0.1%)**	**8 (0.1%)**
Nausea	21 (0.2%)	32 (0.3%)	1 (0.0%)	0 (0.0%)
Dyspepsia	21 (0.2%)	26 (0.3%)	0 (0.0%)	0 (0.0%)
Abdominal pain upper	20 (0.2%)	17 (0.2%)	0 (0.0%)	2 (0.0%)
Abdominal pain	12 (0.1%)	13 (0.1%)	0 (0.0%)	0 (0.0%)
Gastritis	11 (0.1%)	15 (0.2%)	2 (0.0%)	3 (0.0%)
Gastrointestinal hemorrhage SMQ	5 (0.0%)	11 (0.1%)	0 (0.0%)	1 (0.0%)
Gastrointestinal ulceration SMQ	3 (0.0%)	7 (0.1%)	0 (0.0%)	2 (0.0%)
Gastrointestinal perforation, ulcer, hemorrhage, obstruction non-specific SMQ	11(0.1%)	8 (0.1%)	1 (0.0%)	0 (0.0%)
Gastrointestinal perforation SMQ	1 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
Gastrointestinal obstruction SMQ	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[a] Gastric lesions-related events were defined by combining three separate group of terms: Gastritis and related PTs, Diarrhea and related PTs and GI perforation and related SMQs (see appendix for all PTs)
This table lists the relevant SMQs and most frequently reported PTs in the run-in treatment period.
Reviewer's Table, Data source: AAEV & AIDENT

Double-blind period

The incidence of gastric lesion-related AEs was similar in the two treatment arms in the double-blind period in PARADIGM-HF (11.8% vs. 11.3% in the enalapril and LCZ696 arms, respectively) (Table 79).

Table 79: Gastric lesions-related AEs during the double-blind period in PARADIGM-HF

	AE		SAE	
	Enalapril N =4,229 n (%)	LCZ696 N=4,203 n (%)	Enalapril N =4,229 n (%)	LCZ696 N=4,203 n (%)
Gastric lesion-related event[a]	**497(11.8%)**	**474 (11.3%)**	**145 (3.4%)**	**120 (2.9%)**
Nausea	100 (2.4%)	88 (2.1%)	6 (0.1%)	6 (0.1%)
Abdominal pain	83 (2.0%)	67 (1.6%)	23 (0.5^)	15 (0.4%)
Gastritis	70 (1.7%)	62 (1.5%)	10 (0.2%)	7 (0.2%)
Abdominal pain upper	61 (1.4%)	59 (1.4%)	7 (0.2%)	6 (0.1%)
Gastroesophageal reflux disease	40 (0.9%)	24 (0.6%)	6 (0.1%)	4 (0.1%)
Gastrointestinal hemorrhage SMQ	90 (0.9%)	97 (0.9%)	53 (0.5%)	49 (0.5%)
Gastrointestinal ulceration SMQ	62 (0.6%)	49 (0.5%)	28 (0.3%)	18 (0.2%)
Gastrointestinal perforation, ulcer, hemorrhage, obstruction non-specific SMQ	27 (0.3%)	29 (0.3%)	2(0.0%)	4 (0.0%)
Gastrointestinal perforation SMQ	19 (0.2%)	23 (0.2%)	15 (0.1%)	17 (0.2%)
Gastrointestinal obstruction SMQ	20 (0.2%)	15 (0.1%)	14 (0.1%)	11 (0.1%)

[a] Gastric lesions-related events were defined by combining two separate group of terms: Gastritis and related PTs and GI perforation and related SMQs (see appendix for all PTs)
This table lists the relevant SMQs and most frequently reported PTs.
Reviewer's Table, Data source: AAEV & AIDENT

Information on the types of gastrointestinal (GI) hemorrhages is provided in Table 80.

Table 80: Gastrointestinal hemorrhage SMQ by PTs in the double-blind period in PARADIGM-HF

SMQ/Preferred Terms	AE		SAE	
	Enalapril N =4,229 n (%)	LCZ696 N=4,203 n (%)	Enalapril N =4,229 n (%)	LCZ696 N=4,203 n (%)
Gastrointestinal hemorrhage SMQ	**90 (0.9%)**	**97 (0.9%)**	**53 (0.5%)**	**49 (0.5%)**
Gastrointestinal hemorrhage	23 (0.2%)	23 (0.2%)	22 (0.2%)	22 (0.2%)
Upper gastrointestinal hemorrhage	10 (0.1%)	10 (0.1%)	6 (0.1%)	9 (0.1%)
Rectal hemorrhage	9 (0.1%)	26 (0.2%)	3 (0.0%)	8 (0.1%)
Melaena	18 (0.2%)	10 (0.1%)	5 (0.1%)	3 (0.2%)
Hemorrhoidal hemorrhage	3 (0.1%)	10 (0.1%)	1 (0.0%)	2 (0.1%)
Hematemesis	10 (0.1%)	5 (0.0%)	3 (0.1%)	2 (0.1%)
Hematochezia	5 (0.0%)	6 (0.1%)	1 (0.0%)	1 (0.0%)
Gastric hemorrhage	6 (0.1%)	1 (0.0%)	3 (0.1%)	1 (0.0%)

This table only lists PTs with more than 5 subjects in either group for gastrointestinal hemorrhage SMQ.
Reviewer's Table, Data source: AAEV & AIDENT

The incidence of GI hemorrhage during the double-blind period was similar in the two arms; though lower GI hemorrhage (i.e., rectal hemorrhage and hemorrhoidal hemorrhage) was reported somewhat more frequently in the LCZ696 arm (n=38, 0.9%) compared to the enalapril arm (n=14, 0.3%) (Table 81). At screening, there was no obvious imbalance between the treatment arms with regard to a history of hemorrhoids or lower GI hemorrhage. Of the subjects with lower GI hemorrhage events, few reported a history of hemorrhoids or of GI hemorrhage prior to screening (3/14 in the enalapril arm and 8/38 in the LCZ696 arm).

Table 81 Distal GI hemorrhage in PARADIGM-HF

SMQ/Preferred Terms	At screening		Double-Blind	
	Enalapril N =4,229 n (%)	LCZ696 N=4,203 n (%)	Enalapril N =4,229 n (%)	LCZ696 N=4,203 n (%)
Distal GI Hemorrhage	**8(0.2%)**	**13 (0.3%)**	**14 (0.3%)**	**38 (0.9%)**
Rectal hemorrhage	6 (0.1%)	9 (0.2%)	9 (0.1%)	26 (0.2%)
Hemorrhoidal hemorrhage	1 (0.0%)	2 (0.0%)	3 (0.1%)	10 (0.1%)
Anal hemorrhage	1 (0.0%)	2 (0.0%)	2 (0.1%)	2 (0.1%)
Hemorrhoids	**47 (1.1%)**	**56 (1.3%)**	**18 (0.4%)**	**35 (0.8%)**

Reviewer's Table. Data source: AIDENT, ACND & AAEV

Few gastric lesion-related AEs were suspected to be related to the study drug by investigators in both arms [16/4229 (0.4%) vs. 23/4203 (0.5%) in the enalapril and LCZ696 arms, respectively]. There were similar numbers of gastric lesions-related AEs leading to study drug discontinuation between both arms [13/4229 (0.3%) vs. 12/4203 (0.3%) in the enalapril and LCZ696 arms, respectively].

The incidence of gastric lesion-related AEs was low and similar between the LCZ696 arm and the comparators in other HF and HTN studies. There is no safety signal from other studies suggesting an increased risk of gastric lesion associated with LCZ696.

Reviewer's Comments: There was a slight imbalance between the two treatment arms in lower GI bleeding. However, lower GI hemorrhage was not reported in the pre-clinical studies. In addition, rectal hemorrhage and hemorrhoidal hemorrhage are not listed in the valsartan USPI or the enalapril USPI. Considering that these events were infrequent and the lack of a clear mechanistic basis for these events, a causal relationship seems unlikely.

7.3.5.7 Hepatotoxicity

LCZ696 has limited liver metabolism which suggests a low risk of hepatotoxicity. There was also no safety signal for hepatotoxic potential for LCZ696, sacubitril or valsartan in the non-clinical toxicity studies.

In PARADIGM-HF, pre-defined liver-related events were reviewed by an external liver safety expert in a blinded manner:

- AST/ALT > 3x ULN and TBL > 2x ULN at the same day
- AST/ALT > 5x ULN
- SAE with the following PTs: acute hepatic failure, hepatic failure, drug-induced liver injury, hepatotoxicity, jaundice, hepatic steatosis, hepatitis, hepatic function abnormal and liver function test abnormal.

The external liver expert determined a categorical clinical assessment of causality for these pre-defined events (Table 82).

Table 82: Definition of the clinical assessment of liver function tests

Label (Score)	Likelihood	Description
Definite (1)	>95%	The evidence for the drug causing the injury is beyond a reasonable doubt.
Highly likely (2)	75-95%	The evidence for the drug causing the injury is clear and convincing but not definite.
Probable (3)	50%-74%	The preponderance of the evidence supports the link between the drug and the injury
Possible (4)	25-49%	The evidence for the drug causing the injury is equivocal but present.
Unlikely (%)	<25%	There is evidence that an etiological factor other than a drug caused the injury

Source: Table 9-8 in PARADIGM-HF CSR

7.3.5.7.1 Liver enzyme abnormalities in PARADIGM-HF

In general, the incidence of the pre-defined liver-related events was low and similar between the two treatment arms (Table 83). Combined liver abnormalities (ALT/AST >3xULN and TBL > 2xULN at the same visit) were reported in only 1 subject in the LCZ696 arm and in 4 subjects in the enalapril arm. All of these cases had ALP ≤2xULN, thus raising concern for a potential Hy's law case (based on chemistry findings). These cases were reviewed by the external liver expert; all were considered unlikely to be related to study drug. The narrative for the single case in the LCZ696 arm is described at the end of this section.

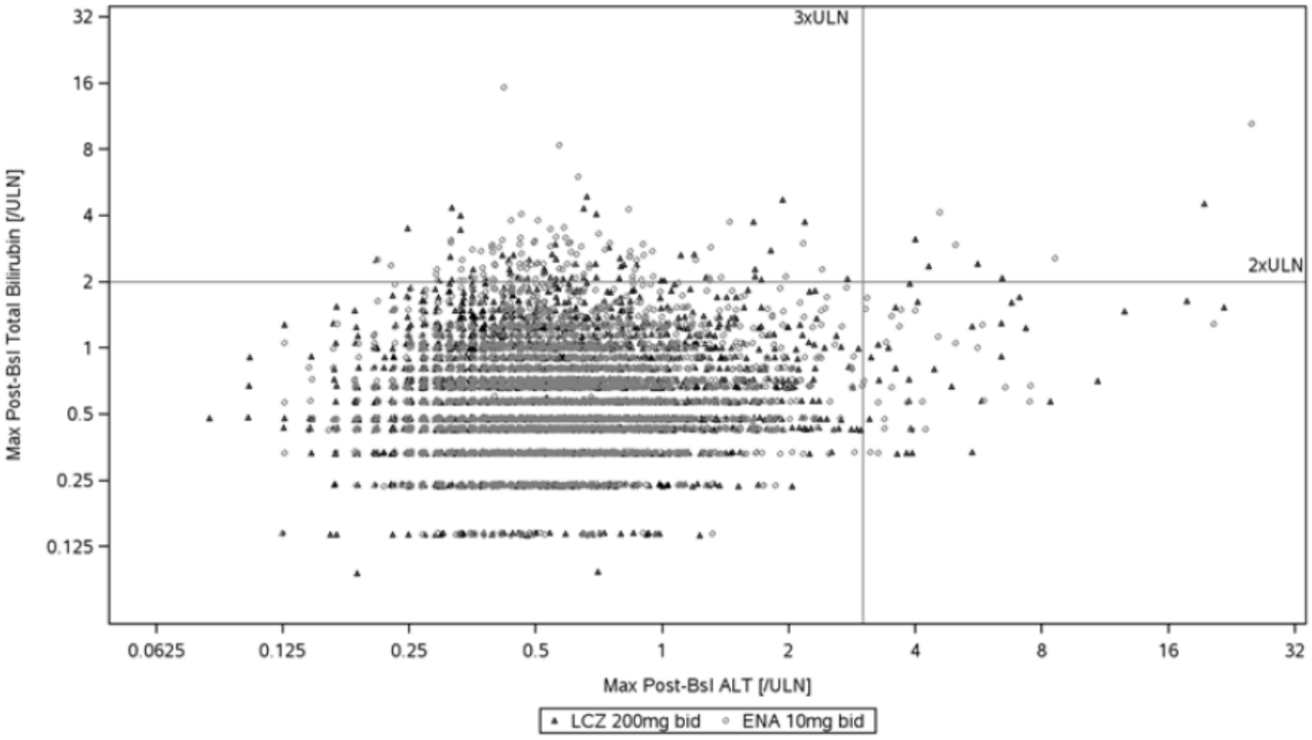
Table 83: Number of subjects with notable abnormal liver enzymes in the double-blind period in PARADIGM-HF

Liver enzymes classification	Enalapril N = 4,229	LCZ696 N=4,203
ALT or AST > 3xULN	42 (1.0%)	53 (1.3%)
ALT or AST > 5xULN[a]	13 (0.3%)	21 (0.5%)
ALT or AST > 10xULN	5 (0.1%)	6 (0.2%)
TBL >1.5xULN	219 (5.4%)	165 (4.1%)
TBL > 2xULN	103 (2.5%)	61 (1.5%)
TBL >3xULN	19 (0.5%)	13 (0.3%)
ALT or AST > 3xULN & TBL>2xULN[a]	4 (0.1%)	1 (0.02%)
ALT or AST >3xULN & TBL>2xULN & ALP≤ 2xULN	4 (0.1%)	1 (0.02%)

Reviewer's Table, Source: Table 12-22 in the PARADIGM-HF CSR
[a] pre-defined liver abnormalities that were reviewed by an external liver safety expert

Figure 21 shows the peak serum ALT on the x-axis and the peak TBL on the y-axis as multiples of the ULN on the log scale. The number of subjects with peak ALT versus peak TBL in the upper right hand quadrant of the plot was small and similar in the two treatment arms.

Figure 21: eDISH plots of peak ALT versus peak total bilirubin (TBL)



Source: Figure 2-4 in the SCS

Narratives for 1 potential Hy's law case based on liver chemistries in the LCZ696 arm

This case occurred in a 49-year-old Asian male who had a history of chronic heart failure (2-5 years, NYHA class II, LVEF 15%) attributed to ischemic cardiomyopathy. The patient had an eGFR of 49 mL/min/1.73m^2 and ALT of 23 IU/L and AST level of 30 IU/L at baseline.

On Day 394, while on LCZ696 200 mg, the patient was hospitalized and diagnosed with renal impairment (eGFR 34 mL/min/1.73m^2) and cardiomegaly. The patient was treated with dobutamine, furosemide, spironolactone, torsemide, carvedilol, and nicorandil. LCZ696 was permanently discontinued due to renal impairment and the patient was discharged from the hospital 3 days after the last dose of LCZ696.

Seventeen days after the last dose of LCZ696, the patient was noted to have elevated liver enzymes with an AST of 830 IU/L and ALT of 720 IU/. The next day, an echo showed severe left ventricular dysfunction with moderate to severe tricuspid regurgitation. The patient was diagnosed with right ventricular dysfunction with abnormal hepatic function. AST and ALT

levels declined over the course of a week and the patient was discharged from the hospital 2 weeks after the event. The hepatic event was assessed unlikely related to LCZ696 by an external expert.

Reviewer's Comment: The elevated liver abnormalities in this case were likely secondary to the patient's underlying cardiac disease and not LCZ696.

7.3.5.7.2 Liver related AEs/SAEs in PARADIGM-HF

The incidence of liver-related AEs (MedDRA drug-related hepatic disorder –comprehensive search SMQ) was 188/4229 (4.4%) in the enalapril arm and 143/4203 (3.4%) in the LCZ696 arm during the double-blind period in PARADIGM-HF (Table 84). Liver-related SAEs were reported slightly less frequently in the LCZ696 arm compared to the enalapril arm (0.9% vs.1.2%, corresponding to 36 and 50 subjects).

Table 84: Incidence of liver-related AEs during the double-blind period in PARADIGM-HF

SMQ/PT	Enalapril N=4,229	LCZ696 N=4,203
Liver-related AEs (Drug-related hepatic disorder-comprehensive SMQ)	188 (4.4%)	143 (3.4%)
Hepatic steatosis	21 (0.5%)	18 (0.4%)
Ascites	22 (0.5%)	15 (0.4%)
International normalised ratio increased	21 (0.5%)	11 (0.3%)
Hepatic function abnormal	14 (0.3%)	9 (0.2%)
Hyperbilirubinaemia	13 (0.3%)	9 (0.2%)
Hepatic enzyme increased	11 (0.3%)	8 (0.2%)
Alanine aminotransferase increased	6 (0.1%)	13 (0.3%)
Hepatic cirrhosis	13 (0.3%)	4 (0.1%)
Hepatic congestion	10 (0.2%)	5 (0.1%)
Aspartate aminotransferase increased	2 (0.0%)	13 (0.3%)

Reviewer's Table, Data source: AIDENT & AEEV
This table only includes preferred terms with ≥ 10 events in either group

There were 53 liver-related SAEs (i.e., meeting the pre-specified preferred terms) that were assessed by the external liver expert; 28 were in the LCZ696 arm and 25 were in the enalapril arm. All 28 cases in the LCZ696 arm were considered unlikely related to the study drug by the external liver expert review and three cases in the enalapril arm were considered possibly related to the study drug.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In addition to the safety topics of interest (see Section 7.4.5), I also performed routine safety assessments for cancer promotion, hypersensitivity reactions and QT prolongation. Potential safety signals were also evaluated by searching AE data using all MedDRA hierarchical terms and SMQs. Table 85 shows the results of these assessments. The incidence of AEs related to malignancies, hypersensitivity and QT prolongation was similar in the two treatment arms.

Table 85: Additional safety assessments of AEs in the double-blind period in PARADIGM-HF

	Enalapril N = 4,229	LCZ696 N = 4,203
Safety assessment topics[a]		
-Malignancies (SMQ)	163 (3.9%)	138 (3.3%)
-Hypersensitivity reactions[b]	1379 (32.6%)	1335 (31.8%)
-Torsade de pointes/QT prolongations (SMQ)	587 (13.9%)	488 (11.9%)
Notable imbalanced AEs[c]		
Hypokalemia[d]	112 (2.6%)	143 (3.4%)
Gynecomastia	50 (1.2%)	24 (0.6%)
Fall	54 (1.3%)	80 (1.9%)
Peripheral vasoconstriction, necrosis and vascular insufficiency (HLT)[e]	93 (2.2%)	64 (1.5%)
-Peripheral arterial occlusive disease	18 (0.4%)	36 (0.9%)
-Peripheral ischemia	15 (0.4%)	23 (0.5%)
-intermittent claudication	14 (0.3%)	23 (0.5%)

[a] using MedDRA SMQ broad term
[b] Hypersensitivity reactions include three SMQs: anaphylactic reaction, hypersensitivity and severe cutaneous adverse reaction
[c] This table only lists imbalanced AEs that are unlikely to be chance findings or deserve further discussions
d MedDRA PTs: hypokalemia and blood potassium decreased
[e] Only PTs with more than 10 events in each arm was included.

The incidence of hypokalemia AEs was slightly higher in the LCZ696 arm compared to the enalapril arm (3.4% vs. 2.6%). This finding is anticipated due to the diuretic effects of LCZ696

and is consistent with the laboratory findings showing that a higher percent of subjects in the LCZ696 arm compared to the enalapril arm had potassium levels <3.5 mmol/L (Table 87).

The incidence of gynecomastia AEs was low but doubled in the LCZ696 arm compared to the enalapril arm in PARADIGM-HF (1.2% vs.0.6%). The majority of these AEs were mild. There were no SAEs and no event led to study drug discontinuation. Gynecomastia is a rare condition and known risk of spironolactone, a concomitant medication commonly used in HFrEF patients. In PARADIGM-HF, there was no imbalance between the two treatment arms in spironolactone use at randomization (50.3% vs. 52.2% in the LCZ696 and enalapril arms, respectively). The majority of subjects with gynecomastia in each treatment group were on spironolactone [n=42/50 (84.0%) vs. n=22/24 (91.7%) in the LCZ696 and enalapril arms respectively]. The number of gynecomastia events reported in subjects not using spironolactone or any other MRA in PARADIGM-HF was very low.

In addition, the incidence of gynecomastia was very low in other heart failure studies and in the pooled HTN studies. Two additional gynecomastia events were reported in subjects treated with LCZ696 in these studies (1/149 in HFpEF patients and 1/2004 in HTN patients). No findings were seen in pre-clinical studies that might suggest an increased risk for the development of gynecomastia with LCZ696.

Reviewer's Comments: Considering the totality of evidence, the observed numerical imbalance in gynecomastia in PARADIGM-HF is most likely a chance finding.

There was slightly higher incidence of AEs including falls and events related to peripheral vascular insufficiency. The incidence of these events was low and the majority of the events were mild. However, the possibility that these events could be secondary to hypotension cannot be excluded.

Common AEs that led to study drug discontinuation during the run-in and double-blind periods are discussed in Section 7.3.3 (see Table 50 and Table 52)

7.4.2 Laboratory Findings

Analyses of the laboratory data did not raise any major safety concerns. Laboratory parameters of interest are discussed further below.

7.4.2.1 Renal parameters

In PARADIGM-HF, approximately 9% of subjects had a >25% decline in eGFR from baseline in the LCZ696 run-in period, compared to 5.5% in the enalapril run-in period. Very few subjects had an eGFR decline >50% from baseline in either run-in period. In the double-blind period, the percentage of subjects who met predefined eGFR decline thresholds was similar in the two treatment arms (Table 86). The percentage of subjects who met predefined serum creatinine increases was also similar in the two treatment arms.

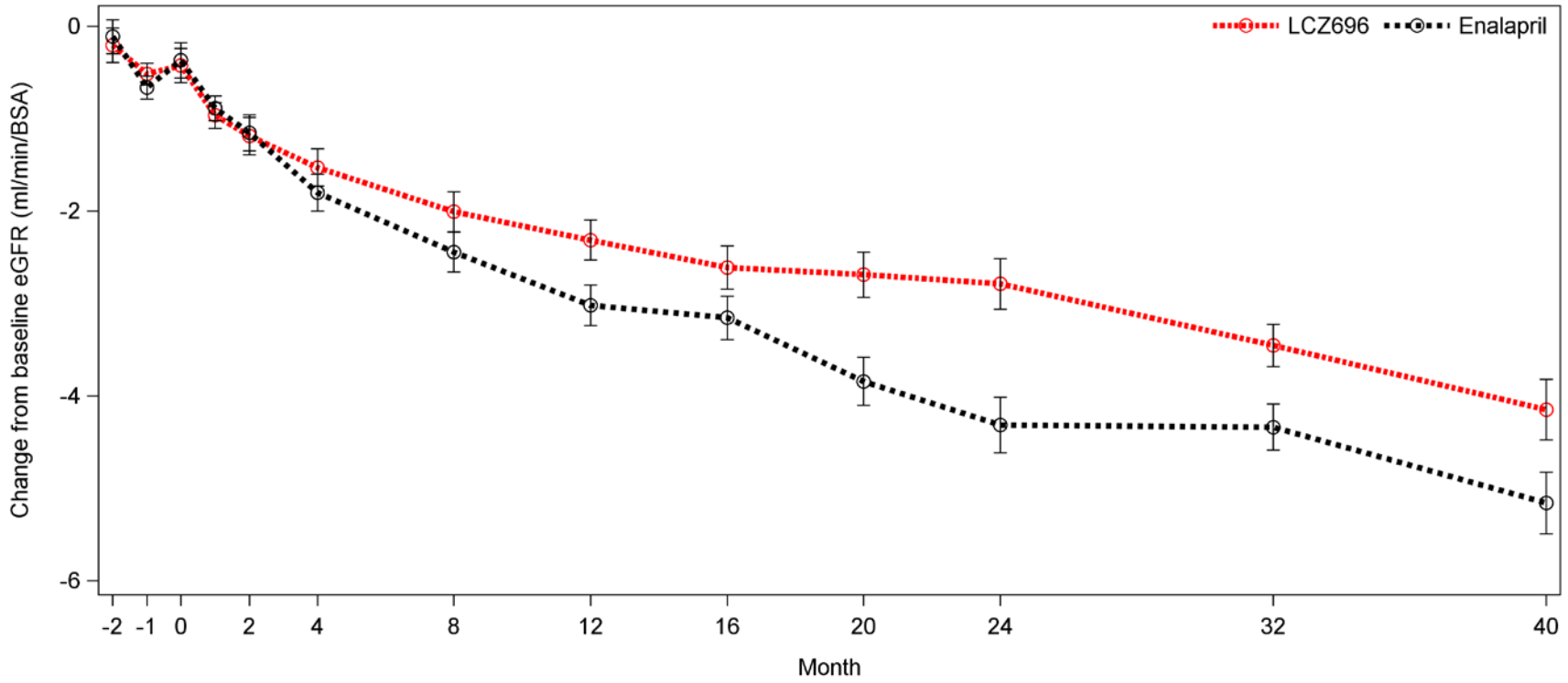
Table 86: Safety criteria for renal parameters during the double-blind period in PARADIGM-HF[a]

Study period (median drug exposure)	Run-in Period (15 days/29 days)		Double-blind period (24 months)	
Criteria	Enalapril N=9,798[a]	LCZ696 N=9,086[a]	Enalapril N=4,159[b]	LCZ696 N=4,136[b]
eGFR decline				
> 25% decrease from baseline	536 (5.5%)	811 (8.9%)	1497(36.0%)	1484(35.9%)
> 50% decrease from baseline	36 (0.4%)	42 (0.5%)	282(6.8%)	244(5.9%)
> 30 mL/min/1.73m^2	114 (1.2%)	188 (2.1%)	490(11.8%)	480(11.6%)
Serum creatinine increase				
> 50% increase from baseline	142 (1.4%)	198 (2.2%)	675(16.2%)	644(15.6%)
>0.5 mg/dL	9798 (100%)	9086 (100%)	4159 (100%)	4136(100%)
>2.0 mg/dL	264 (2.7%)	275 (3.0%)	484(11.6%)	447(10.8%)
>2.5 mg/dL	41 (0.4%)	44 (0.5%)	180(4.3%)	129(3.1%)
>3 mg/dL	11 (0.1%)	16 (0.2%)	81(2.0%)	59(1.4%)

[a] eGFR and serum creatinine at screening was used as the baseline
[b] Number of patients with a non-missing value at screening and during the study period
Reviewer's Table, Source: AIDENT, ALRS1-ALRS5 and response to FDA request dated 2/6/201

The time course for changes in eGFR (from baseline) is shown in Figure 22. There was a small but consistent decrease in eGFR in both arms (the median change at the study end was -4 and -3 mL/min/1.73m^2 in the enalapril and LCZ696 arms, respectively). The decrease in eGFR was slightly greater in the enalapril arm compared to the LCZ696 arm from Month 2 onwards.

Figure 22: Time course of change in eGFR from baseline (screening) in PARADIGM-HF



Reviewer' Figure, Data source: ALRS1-ALRS5 & AIDENT
The mean eGFR at baseline was similar between the two arms (~ 68 mL/min/1.73m^2). Standard error was plotted for each mean eGFR change from baseline by study group and time point. 0 indicates the start of the double-blind treatment. -2 and -1 indicate the time in the run-in period.

7.4.2.2 Potassium

A slightly higher percentage of subjects had a potassium <3.5 mmol/L in the LCZ696 arm compared to the enalapril arm during the double-blind period (7.5% vs. 5.8%) (Table 87). The percentage of subjects with a potassium >5.5 or 6 mmol/L was similar in the two treatment arms during both the run-in and double-blind periods.

Table 87: Notable abnormal potassium levels during the double-blind period in PARADIGM-HF[a]

Study period (median drug exposure)	Run-in period (15 days/29 days)		Double-blind period (24 months)	
Changes in potassium	Enalapril N=9,825[b]	LCZ696 N=9,096 [b]	Enalapril N=4,155[b]	LCZ696 N=4,129 [b]
<3.5 mmol/L	148 (1.5%)	199 (2.2%)	239(5.8%)	308 (7.5%)
>5.5 mmol/L	357(3.6%)	402 (4.4%)	701 (16.9%)	649(15.7%)
≥6.0 mmol/L	94 (1.0%)	103 (1.1%)	283 (6.8%)	231 (5.6%)

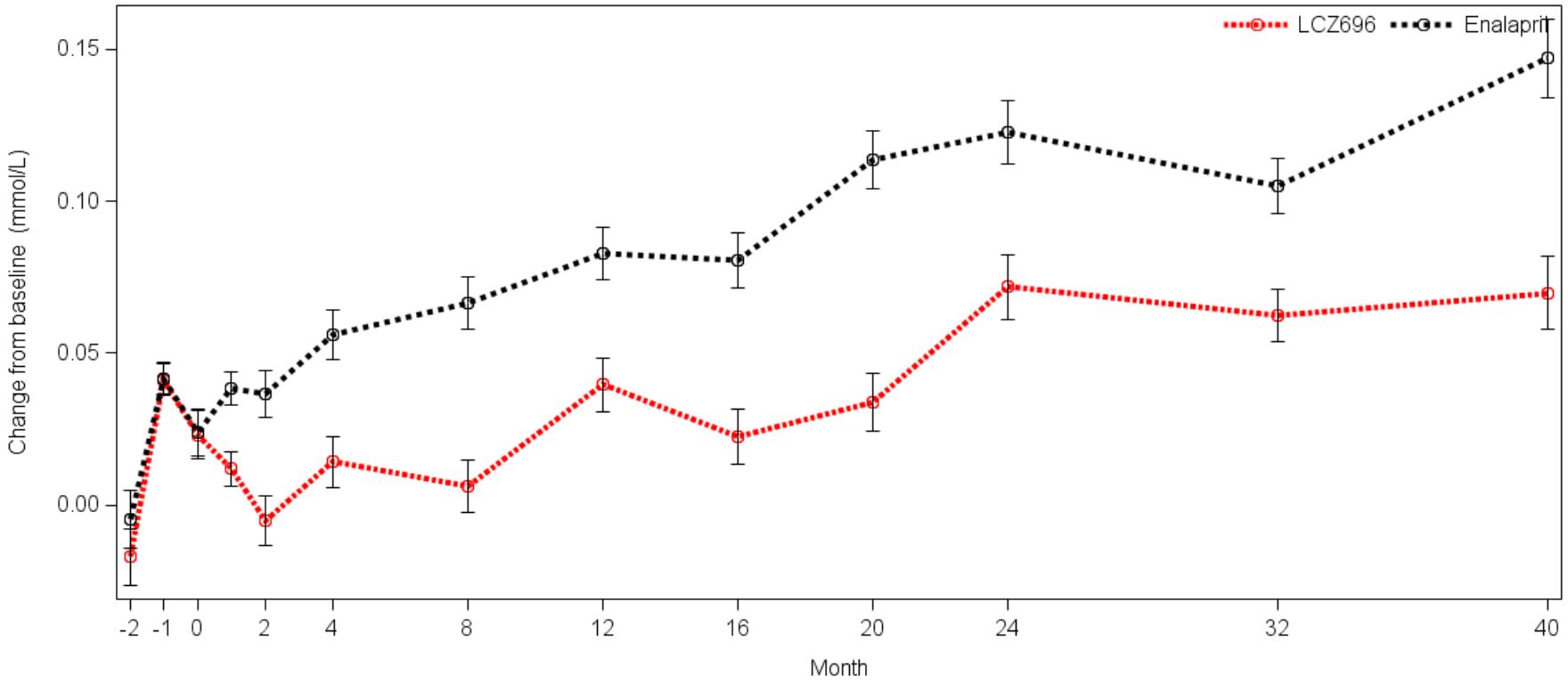
a Potassium at screening was used as the baseline
[b] Number of patients with a non-missing value during the study period
Reviewer's Table, Source: AIDENT, ALRS1-ALRS5 and response to FDA request dated 2/6/2015

The time course for changes in potassium (from baseline) is shown in Figure 23. There was a sharp increase in potassium level in the run-in period. In the first two months of the double-blind period, potassium levels dropped in the LCZ696 arm but consistently increased in the enalapril arm. Potassium levels steadily increased afterward in both treatment arms with a greater increase in the enalapril arm compared to the LCZ696 arm.

7.4.2.3 Other laboratory parameters

There were no meaningful differences between the treatment arms for other chemistry parameters.

Figure 23: Time course of change in potassium from baseline (screening) in PARADIGM-HF



Reviewer' Figure, Data source: ALRS1-ALRS5 & AIDENT
The mean potassium at baseline was similar between the two arms (~ 4.5 mmol/L). Standard error was plotted for each mean eGFR change from baseline by study group and time point. 0 indicates the start of the double-blind treatment. -2 and -1 indicate the time in the run-in period.

7.4.3 Vital Signs

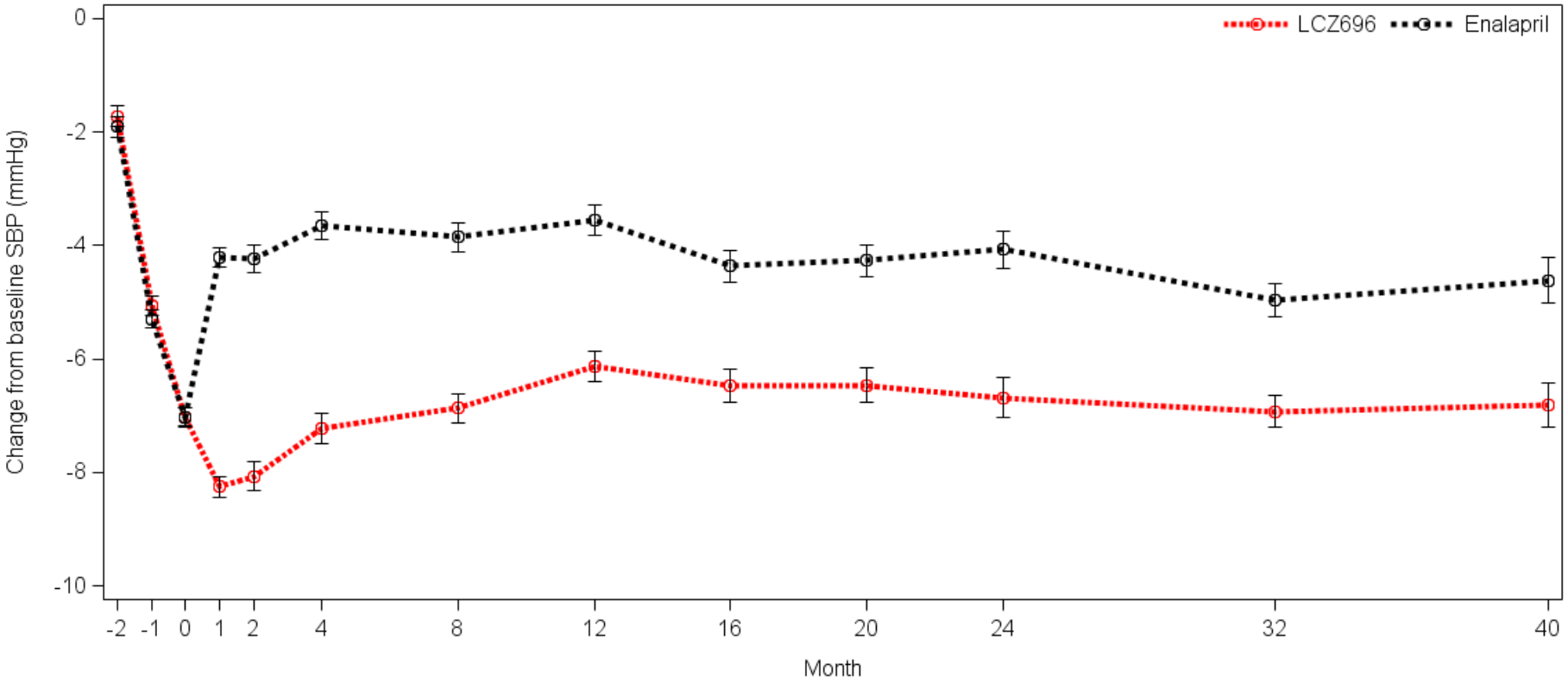
Consistent with the AE results, SBP and DBP were notable lower in the LCZ696 arm compared to the enalapril arm. The time course for changes in SBP (from the measurement taken at screening) shows that both arms experienced notable decreases in SBP during the run-in period (~7 mmHg decrease) (Figure 24). There was a rebound in SBP in the enalapril arm, perhaps due to coming off LCZ696; while SBP continued to decline in the LCZ696 arm during the first month of the double-blind period. After that, there were minor changes in SBP in both arms. The LCZ696 arm had consistently greater decreases in SBP from baseline (i.e., the screening measurement) compared to the enalapril arm. A similar but weaker trend was observed for DBP (data not shown). The categorical shift table (Table 88) shows that decreases in SBP of various thresholds or in association with symptoms occurred more frequently in the LCZ696 arm than in the enalapril arm in both the run-in and double-blind periods.

Table 88: Changes in SBP in PARADIGM-HF[a]

Study Period (median drug exposure)	Run-in period (15 days/29 days)		Double-blind period (24 months)	
SBP decrease	Enalapril N=10,004[a]	LCZ696 N=9,158[a]	Enalapril N=4,202[b]	LCZ696 N=4,184[b]
SBP < 90 mmHg	63 (0.1%)	112 (1.2%)	205 (4.9%)	321 (7.7%)
≥ 30 mmHg drop in SBP	510 (5.1%)	1078 (11.8%)	1031 (24.5%)	1325 (31.7%)
Simultaneously SBP <90 mmHg and ≥ 30 mmHg drop in SBP	22 (0.2%)	47 (0.5%)	96 (2.3%)	194 (4.6%)
SBP < 90 mmHg with symptomatic hypotension	36 (0.4%)	65 (0.7%)	62 (1.5%)	119 (2.8%)
≥ 30 mmHg drop in SBP with symptomatic hypotension	30 (0.3%)	65 (0.7%)	95 (2.3%)	203 (4.9%)

[a] SPB at screening was used as the baseline
[b] Number of patients with a non-missing value at screening and post-baseline values in the study period
Reviewer's Table, Data Source: AIDENT, AVSN and Response to FDA request dated 2/6/2015

Figure 24: Time course of change in SBP from baseline (screening) in PARADIGM-HF



Reviewer' Figure, Data source: AVSN & AIDENT
The mean SBP at baseline was similar between the two arms (~ 128 mmHg). Standard error was plotted for each mean SBP change from baseline by study group and time point. 0 indicates the start of the double-blind treatment. -2 and -1 indicate the time in the run-in period.

7.4.4 Electrocardiograms (ECGs)

The incidence of AEs/SAEs grouped under the Torsade de pointes/QT prolongations SMQ was similar in the two treatment arms (22.8 vs. 24.2% in the LCZ696 arm and enalapril arm, respectively). The Thorough QT study was negative (See Section 7.4.5).

7.4.5 Special Safety Studies/Clinical Trials

The FDA QT Inter-Disciplinary Review Team reviewed the Thorough QT study. According to their review, no significant QT prolongation was observed at LCZ696 doses of 400 mg and 1200 mg.

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

7.5.1 Time Dependency for Adverse Events

Time dependency for adverse events was explored for the primary safety topics of interest. See Section 7.4.5 for further discussion.

7.5.2 Drug-Demographic Interactions

See Section 7.4.5 for information on drug-demographic interactions for the primary safety topics of interest.

7.5.3 Drug-Disease Interactions

Renal elimination accounts for 52% to 68% of sacubitril excretion and ~13% of the excretion of valsartan and its metabolites. Evaluation of renal function subgroups (eGFR: < 60, 60-<90, ≥90 mL/min/1.73m^2) was performed for the primary safety topics of interest (see Section 7.4.5). As noted in Section 7.4.5, the incidence of hypotension, hyperkalemia and renal impairment was higher among subjects with lower eGFR in both treatment arms; thus HR was in general consistent across the renal function subgroups.

7.5.4 Drug-Drug Interactions

LCZ696 analytes (sacubitril, LBQ657, valsartan) are not significantly metabolized by CYP450 enzymes and do not significantly inhibit or induce CYP450 enzymes. Therefore, the drug interaction potential of LCZ696 with drugs associated with CYP450 enzymes is low. As noted in Section 7.3.5, concomitant use of MRA therapy did not seem to significantly affect the absolute risk of hypotension, hyperkalemia or renal impairment associated with LCZ696 as well as the relative risk of these events compared to enalapril.

Reviewer's Comments: It is difficult to evaluate potential interactions between LCZ696 and standard cardiovascular drugs used in PARADIGM-HF given that most subjects were on multiple drugs at the same time. Based on the available data, it does not appear that medications that are commonly used in the standard of care of subjects with HFrEF significantly alter the safety profile of LCZ696 relative to enalapril.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Cancer promotion was evaluated in PARADIGM-HF. In general, there were no imbalances between the two treatment arms (See Section 7.4.1).

7.6.2 Human Reproduction and Pregnancy Data

Because of the known fetal toxicity of agents that act directly on the RAAS, LCZ696 must not be used during pregnancy (See Section 4.3). In PARADIGM-HF, there were four pregnancies in the LCZ696 arm during the study; all were due to failure of contraception treatment. LCZ696 was stopped in all four cases. Two of the subjects had spontaneous abortions. One subject had a medical termination of the pregnancy and one pregnancy resulted in a normal baby. The study drug was restarted in the three cases in which the pregnancy was terminated. The investigators did not suspect a relationship between the outcome of the pregnancy and LCZ696 in any of these cases.

7.6.3 Pediatrics and Assessment of Effects on Growth

LCZ696 is not proposed for use in pediatric patients at the current time. Studies conducted in juvenile animals suggest a possible risk of growth retardation and decreased bone mineral density (BMD) (see Section 4.3). These findings are not considered relevant for the adult patient population. In PARADIGM-HF, the incidence of AEs grouped under the bone growth/BMD SMQ was similar in the two treatment arms (n=83/4203, 2.0% vs. n=80/4299, 1.9% in the LCZ696 and enalapril arms, respectively).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The incidence of overdose/accidental overdose AEs was low in both treatment groups in the double-blind period in PARADIGM-HF (n = 10/4203, 0.2% vs. n=18/4229, 0.4% in the LCZ696 and enalapril arms, respectively). Based on the pharmacology and structure of LCZ696 and analyses conducted as part of this review, there is no concern for drug abuse potential, withdrawal or rebound effects.

7.7 Additional Submissions / Safety Issues

The applicant submitted the required 120-Day Safety Update on 15 April, 2015. This update included new safety data from July 02, 2014 through February 28, 2015 (the safety cut-off date for the original NDA submission was July 01, 2014). The submission included data from two ongoing HF trials, two completed HTN studies and two ongoing studies in patients with HTN (see Table 89).

Table 89: Summary of completed and ongoing studies contributing safety data for 120-Day safety Update as of 28-Feb-2015

Study Number/ n Status	Title and Description
Heart failure trials	
CLCZ696D2301 (PARAGON) Planned (n=4300) Enrolled (n=132) **Status:** Ongoing	Phase 3 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 HF patients (NYHA Class II-IV) with preserved ejection fraction
CLCZ696B2317 Planned (n= (b) (4)) Enrolled (n=26) **Status:** Ongoing	Phase 3b multicenter study to evaluate safety and tolerability in patients with chronic HF and reduced ejection fraction from PARADIGM-HF receiving open-label LCZ696
Hypertension trials	
CLCZ696A2315[1,2] Randomized: LCZ 200 mg (n=479) LCZ 400 mg (n=473) Olm 20 mg (n=486) **Status:** Completed	Phase 3 multicenter, randomized, double-blind, active controlled study to evaluate the efficacy and safety of LCZ696 in comparison to olmesartan in patients with essential hypertension
CLCZ696A2318[1,2] Randomized: LCZ 200 mg (n=188) Olm 20 mg (n=188) **Status:** Completed	Phase 3 randomized, double-blind, parallel-group, active controlled, multicenter study to evaluate the efficacy and safety of LCZ696 200 mg in comparison with olmesartan 20 mg in patients with essential hypertension not adequately responsive to olmesartan 20 mg treatment
CLCZ696A2216[2] Planned (n= (b) (4)) Enrolled n = 454 **Status:** Ongoing	Phase 2 randomized, double-blind, active-controlled, multicenter study to evaluate the safety and efficacy of an LCZ696 regimen on arterial stiffness through assessment of central blood pressure in elderly patients with essential hypertension
Clinical pharmacology trials	
CLCZ696A2224[2] Planned (n= (b) (4)) Enrolled (n = 114) **Status:** Ongoing	Phase 2 randomized, double-blind, active-controlled, parallel group study to evaluate the effects of LCZ696 compared to olmesartan on regional aortic stiffness in subjects with essential hypertension

Source: Table 2-1 in the applicant's 120 Day Safety Update submitted on April-15-2015

The applicant provided unblinded safety data for deaths, non-fatal SAEs and AEs causing permanent study discontinuation for completed studies and blinded SAE and death data for ongoing studies. The applicant also evaluated the main safety topic of interest identified in PARADIGM-HF for the two completed unblinded HTN studies.

Overall, no new safety signals were seen and the safety profile of LCZ696 was consistent with that reported in the original NDA submission.

One additional confirmed angioedema event associated with LCZ696 was reported in HTN study CLCZ696A2315 (1/952, 0.1%). This case occurred in a 58-year-old Asian female with a 6-year history of essential hypertension. The patient did not have a past medical history of angioedema or HF. The most recent antihypertensive medication was valsartan. The patient experienced oral pruritus, facial swelling and nasal discomfort on Day 4, while on LCZ696 200 mg. She received treatment with levocetirizine. Study drug was permanently discontinued due to the event. The event was considered resolved without hospitalization on Day 8. The investigator assessed the event as suspected to be related to study drug. The AAC considered the event as angioedema of severity Grade I.

No case of angioedema (0/132 enrolled patients) was reported as of February 28, 2015 in the applicant's ongoing study in patients with HFpEF (PARAGON-HF). As of this date, 15 black patients from the US had entered the run-in period and 11 had been exposed to LCZ696.

8 Postmarket Experience

LCZ696 is not currently marketed in the United States or any other country.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

- LCZ696 should be approved for the treatment of heart failure (NYHA class II-IV) (b) (4)
- (b) (4)
-

(b) (4)

9.3 Advisory Committee Meeting

An advisory committee meeting was not held for this application.

9.4 Kansas City Cardiomyopathy Questionnaire

The following questions refer to your heart failure and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

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9.5 Concomittant Heart Failure Therapy in PARADIGM-HF

Table 90: Baseline beta-blocker and aldosterone antagonist use and mean daily dose (safety set[1])

	Enalapril (N=4229)				LCZ696 (N=4203)			
	Screening		Randomization		Screening		Randomization	
	n (%)	Mean [SD] mg	n (%)	Mean [SD] mg	n (%)	Mean [SD] mg	n (%)	Mean [SD] mg
Beta-blocker	3974 (94)		3946 (93)		3958 (94)		3928 (94)	
Carvedilol[2]	1677 (40)		1663 (39)		1654 (39)		1637 (40)	
Immediate release	1537 (36)	20.6 (15.9)	1521 (36)	20.7 (16.0)	1529 (36)	21.3 (16.2)	1504 (36)	21.4 (16.2)
Extended release	44 (1)	17.5 (15.6)	43 (1)	17.0 (15.4)	44 (1)	23.2 (19.7)	44 (1)	23.0 (19.8)
Other	96 (2)	39.0 (33.8)	99 (2)	39.3 (34.1)	81 (2)	38.5 (32.8)	89 (2)	37.0 (30.5)
Bisoprolol	1114 (26)	5.5 (6.4)	1116 (26)	5.5 (6.4)	1119 (27)	5.3 (3.4)	1120 (27)	5.3 (3.4)
Metoprolol[3]	917 (22)	72.6 (53.0)	900 (21)	73.4 (53.7)	939 (22)	78.7 (59.9)	925 (22)	78.5 (59.9)
Nebivolol	152 (4)	5.1 (3.3)	156 (4)	5.1 (3.4)	129 (3)	5.3 (4.0)	128 (3)	5.3 (4.2)
Atenolol	72 (2)	51.8 (32.3)	69 (2)	51.9 (32.1)	85 (2)	48.2 (28.9)	79 (2)	47.3 (25.9)
Other	58 (1)		56 (1)		53 (1)		57 (1)	
Aldosterone Antagonist	2530 (60)		2416 (57)		2400 (57)		2291 (55)	
Spironolactone	2331 (55)	30.1 (19.1)	2217 (52)	29.3 (16.8)	2224 (53)	30.4 (17.8)	2113 (50)	29.7 (17.1)
Eplerenone	172 (4)	28.6 (12.4)	173 (4)	28.3 (11.9)	154 (4)	28.8 (10.4)	158 (4)	28.3 (10.1)
Canrenone/canrenoate	29 (1)	46.6 (33.7)	28 (1)	40.9 (31.3)	24 (1)	35.9 (18.6)	22 (1)	36.9 (19.1)

Source: Applicant's analyses (*Response to Information Request – Clinical* dated February 17, 2015; April 3, 2015).
[1]Safety set excludes 4 subjects randomized to enalapril and 6 to LCZ696 who were never treated. Full analysis set excludes 21 enalapril and 22 LCZ696 subjects who were misrandomized (2 and 4, respectively) or were from sites excluded because of serious GCP violations.
[2]Investigator's did not report whether carvediol was immediate or extended release. For the purposes of this table, applicant considered carvedilol to be immediate release for reported total daily doses of 3.125, 6.25, 12.5, 25 and 50 mg and extended-release for total daily doses of 10, 20, 40 and 80 mg. "Other" includes doses not captured under those categories.
[3]Applicant is unable to distinguish immediate from extended-release formulations of metopro

Table 91: Subjects taking medications at or above specified levels at randomization (safety set[1])

	Enalapril n/N (%)	LCZ696 n/N (%)
Carvedilol IR ≥ 25 mg	639/1521 (42.0)	666/1504 (44.3)
≥ 50 mg	296/1521 (19.5)	311/1504 (20.7)
Metoprolol ≥ 100 mg	291/900 (32.3)	326/925 (35.2)
≥ 200 mg	64/900 (7.1)	89/925 (9.6)
Bisoprolol ≥ 5 mg	728/1116 (65.2)	745/1120 (66.5)
≥ 10 mg	231/1116 (20.7)	225/1120 (20.1)
Spironolactone ≥ 25 mg	1822/2217 (82.2)	1767/2113 (83.6)
≥ 50 mg	419/2217 (18.9)	396/2113 (18.7)

Source: Applicant's analyses (*Response to Information Request – Clinical* dated February 17, 2015 and April 3, 2015).
[1]Safety set excludes 4 subjects randomized to enalapril and 6 to LCZ696 who were never treated. Full analysis set excludes 21 enalapril and 22 LCZ696 subjects who were misrandomized (2 and 4, respectively) or were from sites excluded because of serious GCP violations.

9.6 Comparison of PARADIGM-HF subject characteristics with U.S. heart failure registry

Table 92: Comparison of PARADIGM-HF subjects with IMPROVE-HF registry

	PARADIGM-HF		IMPROVE-HF Registry[2] N=15177 (%)
	United States N=434 (%)	Overall N=8442 (%)	
Male	82	78	71
Age (years)	64	64	69
Race			
White	71	66	42
Black	26	5	9.2
Asian	0	18	--
Missing	--	--	47
Medical History			
Hypertension	89	71	62
Diabetes	50	35	34
Atrial fibrillation	38	37	31
Myocardial infarction	51	43	40
Ischemic etiology	61	60	65
Medication Use			
Beta-blocker	97	93	86
Aldosterone Antagonist	37	56	35
Diuretic	82	80	--
Digoxin	28	30	--
ICD (including CRT-D)	60	15	50
CRT-P	1	2	--
Baseline LVEF (mean [SD] %)	27	30	25
Screening SBP (mean [SD] mmHg)	124	128	120
Screening DBP (mean [SD] mmHg)	74	78	70
Heart rate	71	72	71
BNP (median [IQR] pmol/L)	69	73	112

Source: Reviewer's analysis of applicant's datasets (*vsn, ahis, dmg, avsn, alrs1, alrs2, alrs3, alrs4, alrs5, aident*).
[2]Fonarow, 2010: Registry of 34843 subjects with EF ≤ 35% from 167 U.S. outpatient cardiology practices; 15177 subjects were enrolled in a longitudinal cohort.

9.7 Results of Interim Analyses

Table 93: Results of interim analyses

	Enalapril n (%)	**LCZ696 n (%)**	**Hazard Ratio (95% CI; 1-sided p-value)**
First interim analysis (March 11, 2013)			
Primary composite endpoint	472/4231(11.2)	393/4203(9.4)	0.82 (0.72,0.93) 0.00154[1]
Cardiovascular death	243/4231 (5.7)	217/4203(5.2)	0.89 (0.74,1.07) 0.1061[1]
Second interim analysis (August 31, 2013)			
Primary composite endpoint	720/4231(17.0)	575/4205(13.7)	0.78 (0.70,0.87) 0.000004[2]
Cardiovascular death	394/4231 (9.3)	328/4205(7.8)	0.83 (0.72,0.96) 0.0059[2]
Third interim analysis (March 28, 2014)			
February 27, 2014 cut-off[2]			
Primary composite endpoint	920/4231(21.7)	752/4205(17.9)	0.80 (0.73,0.88) 0.000003[3]
Cardiovascular death	542/4231(12.8)	439/4205(10.4)	0.81 (0.71,0.91) 0.00035[3]
March 24, 2014 cut-off[2]			
Primary composite endpoint	953/4231(22.5)	791/4205(18.8)	0.81 (0.74,0.89) 0.000008[3]
Cardiovascular death	564/4231(13.3)	463/4205(11.0)	0.82 (0.72,0.92) 0.00059[3]

Source: Applicant's analyses (*Response to Information Request – Clinical* dated April 3, 2015).
[1]Stopping threshold 0.0001 required for both primary composite and cardiovascular death.
[2]Includes additional confirmed events occurring after February 27th but before March 24th. The DMC evaluated results using both cut-off dates for recommendation to terminate study.
[3]Stopping threshold 0.001 required for both primary composite and cardiovascular death.

9.8 MedDRA SMQs or grouped PTs for safety topics of interest

Hypotension

- Blood pressure decreased
- Blood pressure fluctuation
- Blood pressure inadequately controlled
- Blood pressure orthostatic abnormal
- Blood pressure systolic decreased
- Depressed level of consciousness
- Diastolic dysfunction
- Dizziness
- Dizziness exertional
- Dizziness postural
- Hypotension
- Loss of consciousness
- Orthostatic hypotension
- Presyncope
- Procedural hypotension
- Syncope

Hyperkalemia

- Hyperkalemia
- Blood potassium abnormal
- Blood potassium increased

Renal Impairment

- MedDRA 17.0 Acute Renal Failure SMQ

Cognitive Impairment

- MedDRA 17.0 Dementia SMQ

Gastric Lesions

- Gastritis HLT and additional MedDRA PTs including dyspepsia, abdominal pain upper and abdominal pain, gastroesophageal reflux disease, esophagitis and nausea
- MedDRA 17.0 Gastrointestinal Perforation, Ulcer, Hemorrhage, Obstruction SMQ

9.9 SMQ/NMQ definitions for the applicant's safety topics of interest

Category	Definition
Hypotension	NMQ Hypotension
Renal impairment	SMQ Acute renal failure
Hyperkalemia	PTs Hyperkalaemia, Hyperkaliuria, Pseudohyperkalaemia, Blood potassium, Blood potassium abnormal, Blood potassium increased
Angioedema	broad and narrow SMQ Angioedema
Developmental toxicity	SMQ Pregnancy and neonatal topics
Hypersensitivity reactions incl. pruritus	broad SMQ Hypersensitivity
Hepatotoxicity	NMQ Hepatotoxicty
Change in bone growth/bone mineral density	SMQ Osteoporosis/osteopenia high level grouping term (HLGT) Fractures
Cognitive impairment	broad and narrow SMQ Dementia
Stimulation of lipolysis	SMQ Hyperglycaemia/new onset diabetes mellitus
Gastric lesions	high level term (HLT) gastritis (excl infective) PTs Diarrhoea, Diarrhoea haemorrhagic, Post procedural diarrhea SMQ Gastrointestinal perforation, ulceration, haemorrhage or obstruction
QT prolongation	SMQ of Torsade de pointes/QT prolongation SMQ cardiac arrhythmias
Cancer promotion	SMQ Malignancies

Source: Table 9-6 in PARADIGM CSR. See Appendix for MedDRA PTs included in Hypotension NMQ and Hepatotoxicity NM

9.10 Visit schedule in PARADIGM-HF

Table 9-4 Evaluation and visit schedule

Phase		Screening	Single-blind active run-in				Double-blind treatment**															
			Enalapril run-in		LCZ696 run-in																	
Visit	D/S*	1	2A[14]	2[15]	3	4	5/777[T]	6	7	8	9	10	11	12	13	14	15	16	17	18	19	999°	778°°
Weeks (w) / Months (m)		-11 to -7w	-10 to -6w	-8 to -5w	-6 to -3w	-4 to -2w	0	2w	4w	8w	4m	8m	12m	16m	20m	24m	28m	32m	36m	40m	44m	Uns	EOS
Informed consent form	S	x																					
Call to IVRS[1]	S	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Inclusion/Exclusion criteria[2]	DS	x[2]		(x)	x	x	x																
Demography/Medical history (including alcohol and smoking history)	DS	x																					
HF History	DS	x																					
CV disease History	DS	x																					
Physical Exam[3]	S	x		(x)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Height (H) / Weight (W)	DS	H / W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W	W
Vital signs	DS	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Waist/hip circumference	DS						x[18]																x
NYHA Classification (HF signs and symptoms)	DS	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
HF and CV Medications	DS	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant Medications	DS	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Endpoint information	DS			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AEs / SAEs	DS		x	(x)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy tests[4]	DS	x					x						x			x			x			(x)	x
Plasma BNP and NT-proBNP[5]	DS	x																					
Plasma/serum biomarkers (including BNP & NT-proBNP) and biobanking [5]	DS		x[5]	x[5]	x[5]		x[18]		x			x											

Phase		Screening	Single-blind active run-in				Double-blind treatment**															
			Enalapril run-in		LCZ696 run-in																	
Visit	D/S*	1	2A[14]	2[15]	3	4	5/777[T]	6	7	8	9	10	11	12	13	14	15	16	17	18	19	999°	778°°
Weeks (w) / Months (m)		-11 to -7w	-10 to -6w	-8 to -5w	-6 to -3w	-4 to -2w	0	2w	4w	8w	4m	8m	12m	16m	20m	24m	28m	32m	36m	40m	44m	Uns	EOS
1st Urine morning void[6]	DS		x	x			x[18]		x			x											
PK sampling[7]	DS					x			x			x[16]											
Pharmacogenetic sampling	DS						x[17, 18]																
Local laboratory assessments[8]	DS			(x)	x	x	x															(x)	
Complete laboratory assessments	DS	x			x[19]		x			x[19]	x[19]		x			x			x				x
Abbreviated chemistry panel [9]	DS			(x)		x		x	x			x		x	x		x	x		x	x	(x)	
12-lead ECG evaluation	DS	x[13]					x[18]						x			x			x			(x)	x
Screening log	DS	x																					
Run-in completion log [10]	DS			(x)	x	x	x																
Run-in medication dispense	DS		x	x	x	x																	
Drug accountability	DS			(x)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)	x
Randomization	DS						x[19]																
Double-blind medication dispense	DS						x[19]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	(x)	
Urinalysis (local dipstick)[11]	S	x					x						x			x			x			(x)	x
Patient Global Assessment	DS										x	x	x			x			x				x
KCCQ [12]	DS						x[19]				x	x	x			x			x				x
EQ-5D	DS						x[19]				x	x	x			x			x				x
EOS information	DS																						x

Source: Table 9-4 in PARADIGM-HF

9.11 Incidence of safety topics of interest in the up-titration phase in TITRATION

Up-titration phase	Response variable	Stratum	LCZ696 Condensed (N=247) n/N (%)	LCZ696 Conservative (N=251) n/N (%)
I (From visit 3 to earlier of visit 4 or Censoring*)	Hypotension	High RAAS	1/120 (0.8)	4/127 (3.1)
		Low RAAS	10/127 (7.9)	2/124 (1.6)
		Total	11/247 (4.5)	6/251 (2.4)
	Hyperkalemia	High RAAS	4/120 (3.3)	3/127 (2.4)
		Low RAAS	1/127 (0.8)	1/124 (0.8)
		Total	5/247 (2.0)	4/251 (1.6)
	Renal dysfunction	High RAAS	1/120 (0.8)	3/127 (2.4)
		Low RAAS	3/127 (2.4)	1/124 (0.8)
		Total	4/247 (1.6)	4/251 (1.6)
II (From visit 4 to earlier of visit 5 or Censoring*)	Hypotension	High RAAS		1/127 (0.8)
		Low RAAS		7/124 (5.6)
		Total		8/251 (3.2)
	Hyperkalemia	High RAAS		1/127 (0.8)
		Low RAAS		1/124 (0.8)
		Total		2/251 (0.8)
	Renal dysfunction	High RAAS		0/127 (0.0)
		Low RAAS		1/124 (0.8)
		Total		1/251 (0.4)

- n : Total number of patients available at the start of the present phase with the specified AE since the last phase
- N : Total number of patients included in the analysis since the last phase.
- By design, the condensed regimen specifies up-titrating to LCZ696 200mg bid over 16 days from randomization (at visit 4), compared to up-titration over 37 days from randomization (at visit 5) following conservative regimen.

*For this analysis, censoring occurs at earlier of: treatment failure date, date of reaching blinded LCZ696 200mg bid, date of withdrawal of consent, date of lost to follow-up, last study visit date, date when patient died.

Source: The applicant's response to information request received on 5/1/2015

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

/s/

KIMBERLY A SMITH
05/15/2015

TZU-YUN C MCDOWELL
05/15/2015

ALIZA M THOMPSON
05/15/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 207620 **Applicant:** Novartis Pharmaceuticals Corporation **Stamp Date:** December 17, 2014

Drug Name: Entresto (sacubitril/valsartan) **NDA/BLA Type:** NDA

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?		x		As agreed upon at the pre-NDA meeting, the applicant has included components of the ISS in the summary of clinical safety.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		x		As agreed upon at the pre-NDA meeting, the applicant has included components of the ISE in the summary of clinical efficacy.
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title:			x	As agreed upon at the pre-IND meeting, the applicant did not perform phase 2 dose-ranging studies in

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Sample Size: Arms: Location in submission:				heart failure patients with a reduced EF. The target dose of 200 mg bid was chosen to provide valsartan exposure similar to valsartan 160 mg bid (the dose approved for heart failure) and approximately 90% neprilysin inhibition.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 PARADIGM-HF (CLC2696B2314) Indication: Treatment of heart failure (b) (4)	x			The application is based on a single study with a mortality outcome and low p-value.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	x			The applicant conducted a TQT study (B2123). A consult request was sent to DCRP-TQT on January 13, 2015.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	x			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been			x	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	Content Parameter	Yes	No	NA	Comment
	exposed as requested by the Division?				
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			As agreed upon at the pre-NDA meeting, the applicant submitted narratives for all deaths, SAEs of interest, and other specified AEs, e.g. angioedema
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Submitted a request for a waiver.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			The applicant submitted addendums on January 9 and 12, 2015 in response to information requests related to missing descriptions of variables in the analysis datasets.
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			The applicant submitted adjudication packages, as requested.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None at this time.

Kimberly Smith
Tzu-Yun McDowell — *see electronic signature*
Reviewing Medical Officer — Date

Aliza Thompson — *see electronic signature*
Clinical Team Leader — Date

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

/s/

KIMBERLY A SMITH
01/20/2015

TZU-YUN C MCDOWELL
01/20/2015

ALIZA M THOMPSON
01/20/2015

CLINICAL REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 29, 2014

Reviewer: Thomas A. Marciniak, M.D.
Medical Team Leader

NDA: 207-620

Drug: LCZ696

Subject: Data quality, cancer risk, and interactions in PARADIGM-HF

Summary and Recommendations

Because I have more experience than other Division reviewers with evaluating data quality, particularly completeness of follow-up, and cancer findings in large outcome trials, I have evaluated these aspects of the PARADIGM-HF trial of LCZ696. I am filing this review to record my evaluations. In addition, because another recent NDA showed interesting and highly relevant interactions between a new drug (ivabradine) and another class of drugs (loop diuretics) for treating heart failure (HF), I also evaluated similar interactions in PARADIGM. I summarize these three sets of evaluations immediately below followed by my recommendations and then by three sections providing the details justifying my recommendations.

I have the following observations regarding PARADIGM:

- The protocol, case report forms (CRFs), and conduct of PARADIGM have flaws that challenge the validity of its data. However, the flaws are similar to those of other recent outcome trials and (at least by my initial evaluation) not severe enough to reject outright the trial results.

- LCZ696 compared to enalapril shows a modestly increased risk of lung cancer (about 20%). This increased risk is consistent with the increased lung cancer risk with angiotensin receptor blocker (ARB) use seen in trials having adequate data submitted to the FDA. While the increased risk is not statistically significant in PARADIGM, PARADIGM is grossly underpowered to demonstrate a risk increase of this magnitude.

- LCZ696 does not show an interaction with loop diuretics. LCZ696 does show less favorable results for higher pre-randomization NYHA functional class.

I recommend the following:

1. The modest increased risk of lung cancer with LCZ696, and all ARBs,should be described in labeling, both for LCZ696 (if approved) and for other ARBs. Because the relabeling of ARBs for hypertension indications has substantial implications, as soon as possible the FDA should discuss the evidence for the increased lung cancer risk at an advisory committee meeting.

2. It is unclear whether ACE inhibitors (ACEI) also convey an increased risk of lung cancer. The FDA should analyze all ACEI outcome trials as I have analyzed the ARB trials.

3. The primary reviewers of the LCZ696 NDA submission need to evaluate the data quality, follow-up completeness, and interaction issues further to determine their importance for LCZ696 approval and, if approved, the impact upon labeling.

Data Quality and Completeness of Follow-up

The publication of the main results for the PARADIGM trial states that "Eleven patients in the LCZ696 group and 9 patients in the enalapril group were lost to follow-up . . ." Figure 1 of the publication records that the remainder of the patients had known final vital status (excluding 43 patients who were not randomized validly or from four sites closed prematurely because of GCP violations.) (McMurray, Packer et al. 2014)

COMMENT: I have invariably found that the lost-to-follow-up statistics reported in journal publications misrepresent the completeness of follow-up in recent outcome trials. PARADIGM is not an exception as I document below. There is no universal definition of what constitutes "lost-to-follow-up." For the validity of statistics by the intent-to-treat principle data are missing and validity is challenged regardless of whether the data are missing for patients being"lost", for withdrawal of consent, for site closures, or for sloppy follow-up. I assert that the most appropriate follow-up statistics to consider are the numbers of patients who have documented in the datasets any vital status follow-up (e.g., visit, phone, registry, etc.) on or after the earliest last follow-up date (31Mar14 for PARADIGM) and the numbers of patients who have a visit or other contact at which endpoint and adverse events were evaluated on or after the earliest last follow-up date. I provide these statistics for PARADIGM below.

However, before considering the follow-up rates we should evaluate whether the follow-up procedures and documents implemented for the trial were appropriate. The sources the FDA gets for evaluating the procedures and structures[1] for the trial are the protocol and the case report forms (CRFs). PARADIGM had serious limitations for both.

The serious limitation of the protocol regarding follow-up is the following specifications:

> "After randomization, study drug discontinuation for any reason does not constitute withdrawal from the study and should not lead to the patient being withdrawn from the study.

[1] A popular framework for evaluating, and assuring, quality is to consider three components contributing to quality: structure, process, and outcome. CRFs are structure components, the protocol is a process component, and the follow-up statistics are outcome components.

> On the contrary, even patients who have stopped taking study drug are expected to attend all the protocol specified study visits and perform all measurements as stipulated in the visit schedule. In case it is not possible for the patient to attend any visit(s), the site staff will keep in touch with the patient by means of regular phone contact to the patient himself/herself or to a person pre-designated by the patient according to the patient's study visit schedule. Data will continue to be collected about the patient's health status, including information on developing of **cardiovascular complications and vital status**." [bolding added]
>
> "If the patient does not attend the study visits, follow-up should continue according to the specified schedule by telephone to determine if **any of the health events/endpoint prespecified in the protocol** has occurred, except in the case that the patient specifically refuses such follow-up and withdraws his/her consent." [bolding added]

The serious limitation is that the protocol does not mandate follow-up for adverse events (AEs) other than the CV events specified in the protocol and vital status. Note that about 18% of patients discontinued LCZ696 during the trials, so telephone follow-up was not uncommon (see below.)

COMMENT: I find the approach for follow-up specified in the protocol completely unacceptable for the first major study of a new drug. Safety evaluations must not be limited to events "prespecified in the protocol." Some drug-related AEs, including both heart disease and cancer, may not manifest themselves until weeks or months after discontinuation of the drug. While the PARADIGM approach is particularly unacceptable for a new drug, it is also not appropriate for most drugs, new or old: For a single drug we virtually never have outcome trials of sufficient size and duration to demonstrate moderate increases of risk (e.g., 25-50%) for life-threatening disorders including cancer and heart disease.

This protocol limitation affects primarily non-CV AEs, such as cancer. It should not be a limiting factor for the primary and secondary CV endpoints. However, there are other protocol specifications, such as the dosing of enalapril and the management of other HF medications, that are challenging to the validity of the CV endpoints.

The PARADIGM CRFs also had serious limitations. While the visit CRFs did have adequate fields for describing the type of visit (e.g., phone or visit) and the source of information, the study completion CRF did not, as shown in Figure 1.

Figure 1: PARADIGM Study Completion CRF

While vital status ascertainment was virtually complete by the dates recorded on the study completion form (99.7%), it was not by documented contacts on the visit CRFs: About 5.3% of patients reported as alive at the end of study did not have a documented contact on or after the earliest last follow-up date.

Besides the study completion form problems, data collection for the most critical adverse events, i.e., those resulting in death, was inadequate. While the CRFs had a field for "Principal cause of death" during the single-blind run-in period, the CRFs used during the double-blind period did not have a similar field. Sites were to report death details on the routine adverse event CRFs. These limitations are problematic for AEs such as cancer. Similarly, the Death Adjudication Form collected categories of CV death but lacked a field for a text description of cause of death and recorded malignancy death only as a checkbox.

COMMENT: The vital status recording inadequacies are not unusual for current outcome trials. The numbers of patients with uncertain final vital status exceed the reported difference in numbers of deaths. The incomplete recordings of malignancies, along with the protocol limitation regarding AE follow-up, call into question the completeness of recording of malignancies in PARADIGM. However, the cross-comparisons of malignancy recordings on different CRFs are reasonably consistent as described in the ***Cancer Risk*** *section below.*

As noted above, while reportedly few patients were lost to follow-up, about 5.3% of patients reported alive did not have contacts on or after the earliest last follow-up date documented in the datasets. The rates were similar in both arms, slightly better for the LCZ696 arm. About 92% of the last contacts were patient visits. If one considers contacts at which AE information besides the CV endpoint may have been collected (e.g., dates of any reported AEs or patient visits or

hospitalizations), then about 92% of patients had complete follow-up. These latter rates were similar in both arms, again slightly better for the LCZ696 arm.

COMMENT: These rates of complete follow-up are typical of many recent outcome trials. While incomplete follow-up could distort the endpoint or AE rates, it is not sufficiently poor that we should reject the PARADIGM results outright.

Cancer Risk

For the evaluation of malignancies in PARADIGM I used the methodology I had developed for evaluating malignancies in ARB trials. I have included the pre-specified plan describing that methodology as Attachment 1. While follow-up completeness and the collection of AEs, including potential malignancies, was not optimal in PARADIGM, the follow-up rates in PARADIGM do not fail the criterion I had pre-specified in my methodology, i.e., incompleteness of follow-up does not exceed 10%.

Four PARADIGM datasets have some information regarding malignancies: AEV (adverse events); DTH1 (deaths—but malignancy flag only without site identified); HOS (hospitalizations); and CMD (concomitant medications—in a reason for medication variable.) I used all four of these datasets to ascertain malignancies in PARADIGM. I also cross-compared the AEV results to the other dataset results to estimate how complete was the AE reporting of malignancies. For solid cancers all but 8 (3.3%) had an AE report. I could not identify the site for 2 of 91 malignancy deaths (classified as malignancy deaths by either the site or the adjudication).

COMMENT: These statistics do not rule out by my pre-specified criteria analyzing and presenting the PARADIGM cancer results. Hence I do so below. However, I cannot detect problems such as failures to report malignancies during follow-up after treatment discontinuation and failures to report deaths so there is some uncertainty remaining regarding the PARADIGM cancer statistics.

I show in Table 1 the counts of patients with malignancy and brain tumor events by primary site and arm for PARADIGM.

Table 1: Patients with Malignancy and Brain Tumor Events in PARADIGM

primary site	enalapril	LCZ696
bile duct	0	2
bladder	10	14
breast	5	8
carcinoid	1	0
cervix	1	0
colon	26	24
esophagus	3	0
gi other	0	1
head & neck	4	2

primary site	enalapril	LCZ696
kidney	6	6
liver	2	2
lung	22	27
melanoma	1	4
mesothelioma	0	1
other	1	0
ovary	1	0
pancreas	3	6
prostate	20	16
sarcoma	1	0
stomach	6	4
testes	1	0
thyroid	1	1
unknown	3	4
uterus	0	2
solid cancer	118	122
non-melanoma skin	29	11
brain tumor	7	6
leukemia	2	4
lymphoma	2	3
myelodys	4	2
myeloma	2	1
hematologic malignancy	10	10

The double width rows in Table 1 are summary rows. Patients may be represented in more than one summary category, e.g., one patient may contribute to both the solid cancer and the non-melanoma skin cancer counts. Brain tumor includes both benign and malignant brain tumors as well as pituitary adenomas. (Please see Attachment 1 for further details and justification of this categorization of malignancies.)

The one summary category of malignancy that appears to be unbalanced between the two arms is "non-melanoma skin" (more precisely basal cell and squamous cell carcinomas of the skin). While solid cancers are approximately balanced between the two arms, lung cancers were slightly more frequent with LCZ696. All lung cancers occurred in patients without a history of lung cancer at baseline.

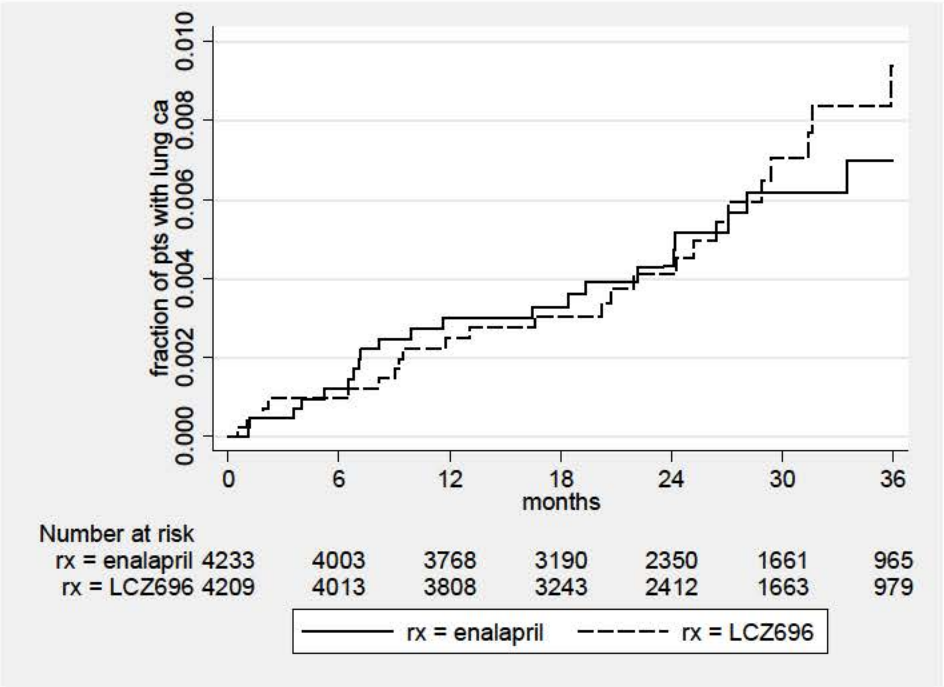
COMMENT: While the lower frequency of skin cancers with LCZ696 looks encouraging, I have seen many similar imbalances of skin cancers in other trials that were not confirmed in other trials of the same drug. I believe skin cancers are variably reported because they are rarely life-

threatening, unlike other malignancies. Any benefit of LCZ696 for skin cancers requires replication before acknowledging a claim.

The statistically insignificant lung cancer imbalance in PARADIGM in isolation would not be concerning. However, the point estimate of the increased risk of lung cancer with LCZ696 (about 20% by logistic or Cox regression) is similar to that seen with ARBs. I have included in Attachment 2 my patient-level meta-analyses of lung cancers in the ARB trials for which the datasets and CRFs have been submitted to the FDA. Because the risk with LCZ696 appears similar to that for other ARBs, I present other lung cancer statistics in PARADIGM below.

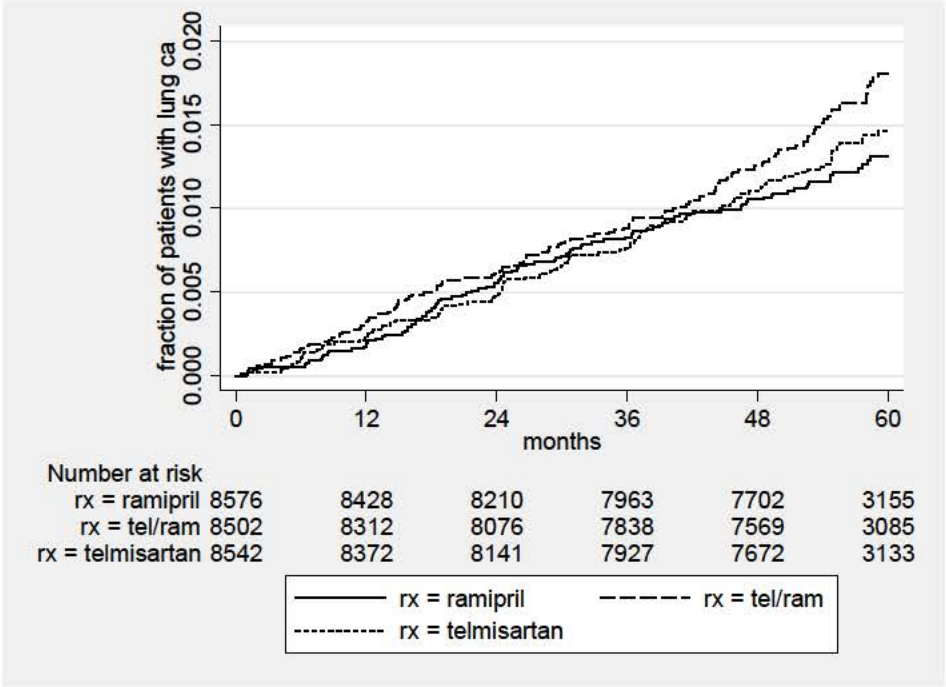
I show in Figure 2 the Kaplan-Meier plots of lung cancer incidence by arm for PARADIGM.

Figure 2: Lung Cancer Incidence in PARADIGM



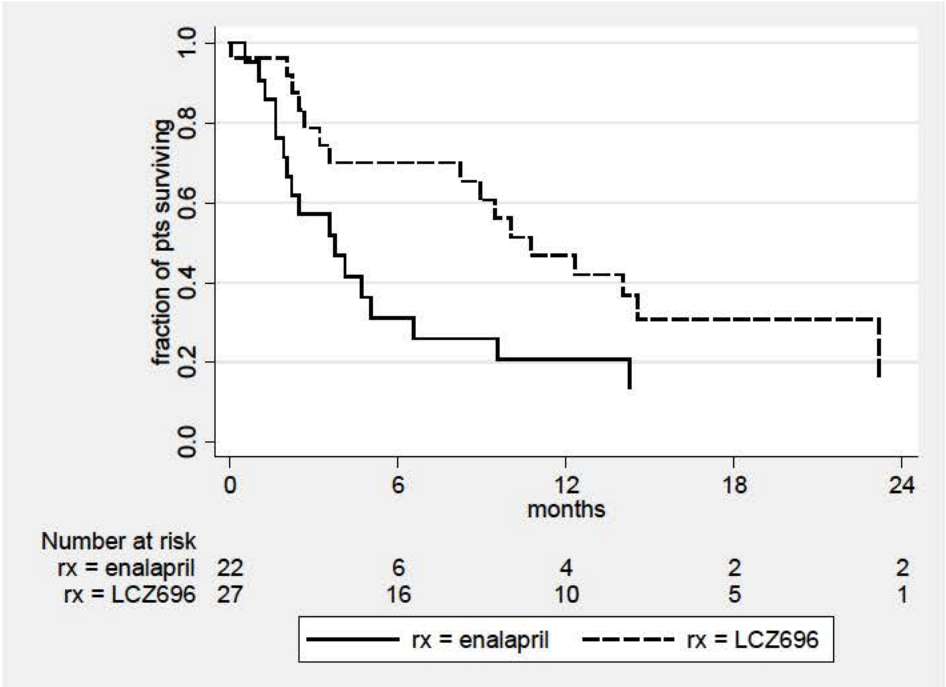
The divergence of the curves is not impressive but there may be a late divergence. For ARB trials particularly with placebo controls the lung cancer incidence curves diverge earlier, about 6 months. (See Figure 2 in Attachment 2.) However, the one large ARB outcome trial with an ACEI control arm (ONTARGET with telmisartan, ramipril, and combined telmisartan/ramipril arms) also shows delayed divergence of the curves as shown in Figure 3.

Figure 3: Lung Cancer Incidence in Telmisartan ONTARGET



Survival after a lung cancer event in PARADIGM was poor as shown in Figure 4.

Figure 4: Survival Following a Lung Cancer Event in PARADIGM



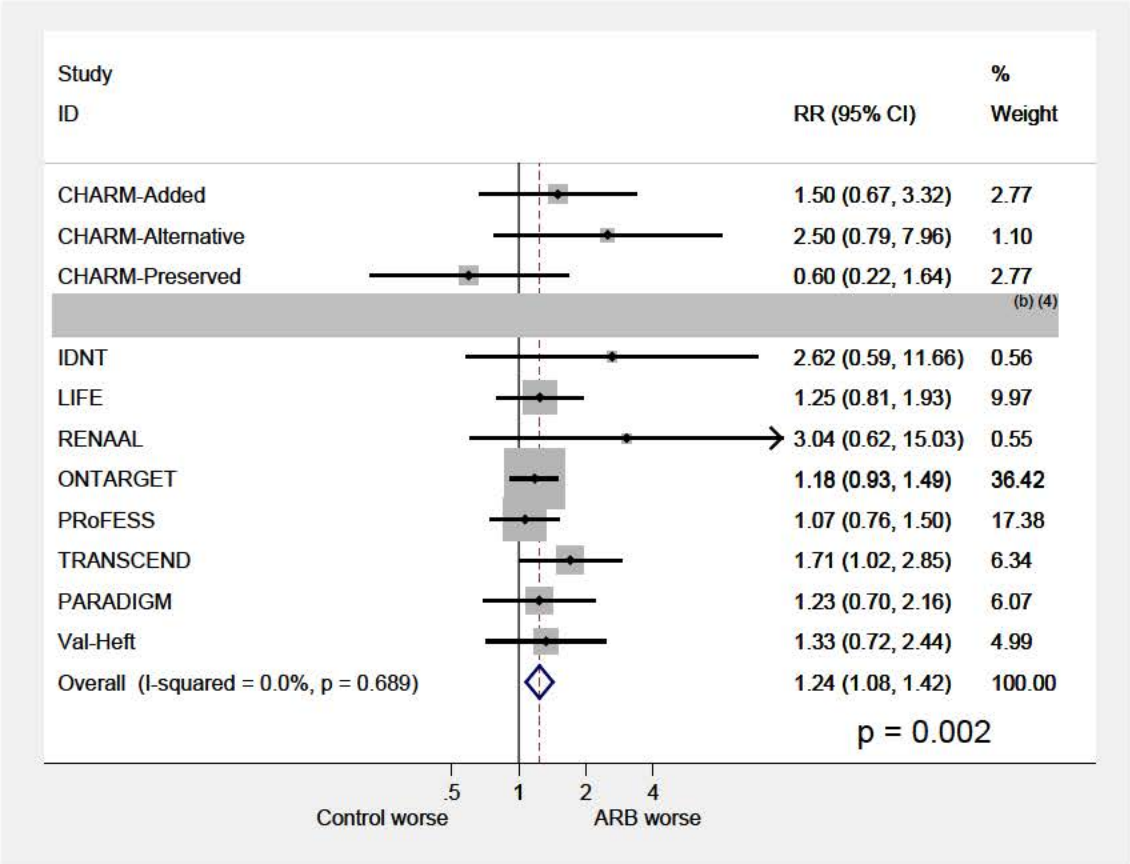
Survival after a lung cancer event in the LCZ696 arm of PARADIGM appears to be better than in the enalapril arm, at least early. However, survival beyond a year was poor in both arms, about 20-30%.

The vast majority (about 82%) of lung cancers occurred in smokers (including ex-smokers). The percentage was the same in both arms. There does not appear to be an interaction between LCZ696 and smoking for lung cancer (nor was there in the ARB trials—see Attachment 2.)

COMMENT: While the lung cancer differences in PARADIGM are statistically insignificant, the pattern of lung cancer statistics is similar to that seen in other trials involving ARBs. PARADIGM itself is grossly underpowered to detect a difference in lung cancer rates: With lung cancer rates and trial duration as observed in PARADIGM one would need a trial size of >150,000 patients to detect with 80% power an increase of 20% in lung cancers.

The ARB trials with adequate data are remarkably consistent as shown in Attachment 2. I have added PARADIGM to the primary meta-analysis in Attachment 2 and show the resulting meta-analysis in Figure 5.

Figure 5: Risk Ratios of Patients with Lung Cancer Events by ARB Trial Plus PARADIGM



RR = risk ratio for lung cancer ARB/control

I believe that the consistency of the lung cancer findings in the ARB trials is compelling evidence that ARB use is associated with an increased risk of lung cancer. Because this interpretation has been associated with controversy within the FDA, I've included as Attachment 3 a summary describing all of the reviews filed and communications issued regarding this topic. All of my reviews are available in the official CDER record system DARRTS, as are the other reviews.

For a HF indication for which LCZ696 reportedly has a mortality benefit, this modest increase in lung cancer risk is not concerning, particularly for non-smokers. (For the hypertension indication of ARBs the lung cancer risk is concerning, particularly for smokers.) Regardless, the lung cancer risk must be described in labeling so that patients and prescribers can make informed decisions. Smokers may wish to weigh the increased risk of lung cancer against the LCZ696 benefits. ACEIs appear to have a lower or null risk of increasing lung cancer rates and hence may be a good alternative for smokers. However, the risk of ACEIs is not as well characterized as that for ARBs so the FDA should analyze ACEI trials as I have analyzed the ARB trials.

Interactions

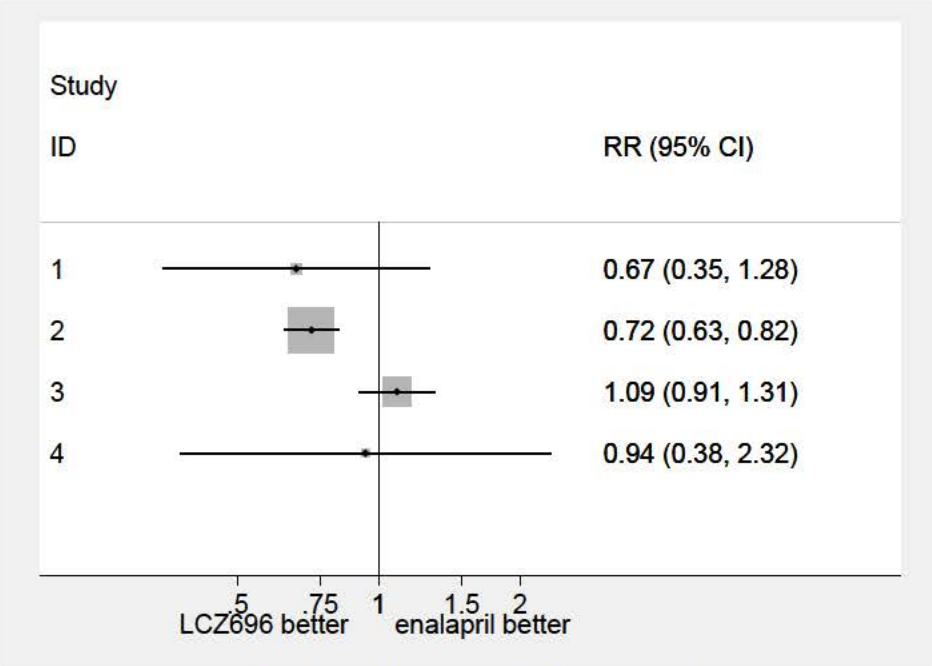
Another new HF drug, ivabradine, showed interesting and relevant interactions in its trials. I documented the potential interactions and their evidence in my CDTL review filed in DARRTS. (Marciniak 2014) The strongest interaction, but also the one that has engendered the most internal debate, is a qualitative interaction between ivabradine and loop diuretics for CV death (but not for HF hospitalizations—the ivabradine experience also suggests that we should analyze CV death and HF hospitalizations separately.) In patients with ischemic heart disease (IHD), including patients with HF not on a loop diuretic, ivabradine increases the risk of CV death; in patients on a loop diuretic ivabradine decreases the risk of CV death. I evaluated this interaction, and other ones, in PARADIGM and present the results below.

LCZ696 does not appear to interact with loop diuretics either for CV death or for HF hospitalizations (odds ratios [ORs] 0.87-0.93, p values 0.6-0.7) regardless of IHD etiology. (There is a significant interaction between IHD etiology and loop diuretics that I show below.) Because others have attributed the ivabradine-loop diuretic interaction to loop diuretics being related to HF severity and ivabradine working better in more severe HF (despite there being no evidence for the latter) and because understanding how LCZ696 efficacy relates to HF severity is important, I analyzed interactions between LCZ696 and NYHA class and LCZ696 and left ventricular ejection fraction (LVEF).

There is no interaction between LCZ696 and the LVEF recorded prior to randomization for either CV death or HF hospitalizations. There is a significant interaction between LCZ696 and NYHA class for HF hospitalizations (HR 1.5, $p = 0.001$) but not for CV death ($p>0.5$). I show the interaction graphically in Figure 6.

The point estimate for the risk ratio is unfavorable for LCZ696 in patients with NYHA class 3 HF prior to randomization. There are too few class 4 patients to understand the effect of LCZ696 in them.

Figure 6: Risk Ratios for HF Hospitalizations by NYHA Class in PARADIGM



RR = risk ratio for HF hospitalizations LCZ696/enalapril

I have commented on two interactions in PARADIGM, both for the HF hospitalization endpoint: the unfavorable interaction between LCZ696 and higher NYHA class and the unfavorable interaction between loop diuretic use and ischemic etiology. I show the quantitative statistics for these interactions in the Cox regression of time to first HF hospitalization in Table 2.

Table 2: Cox Regression of Time to First HF Hospitalization in PARADIGM

```
No. of subjects =         8441                     Number of obs    =      8441
No. of failures =         1196
Time at risk    =     207170.5
                                                   LR chi2(9)       =    202.82
Log likelihood  =   -10325.221                     Prob > chi2      =    0.0000

------------------------------------------------------------------------------
time to HF ho| Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      lcz696 |   .6915087   .0493421    -5.17   0.000     .6012579    .7953064
         age |    1.00766   .0027324     2.81   0.005     1.002319     1.01303
        male |   1.246821    .093085     2.95   0.003     1.077098    1.443288
       lvef0 |   .9698043   .0043708    -6.80   0.000     .9612754    .9784089
   1.nyh3to4 |   1.184298   .1018155     1.97   0.049      1.00065    1.401651
     nyh3to4#|
      lcz696 |
        1 1  |   1.567443    .194053     3.63   0.000     1.229733    1.997894
             |
 1.loopdiur0 |   1.413573   .1755179     2.79   0.005     1.108225    1.803054
  1.ischemic |   .7432048   .1091214    -2.02   0.043     .5573532    .9910295
             |
   loopdiur0#|
    ischemic |
        1 1  |   1.454897   .2326575     2.34   0.019     1.063442    1.990448
------------------------------------------------------------------------------
```

COMMENT: LCZ696 shows a different interaction pattern than that for ivabradine. We might expect so because we believe the mechanisms of action to be different. The different interaction patterns do suggest that the benefits of these two drugs should be complementary as we would also project from their differing mechanisms of action.

I do consider the LCZ696 interaction with NYHA class to be somewhat concerning: It seems strange to me that LCZ696 would have a benefit for CV death largely independent of NYHA class but less benefit at higher NYHA class for HF hospitalizations. Higher NYHA class is associated with both higher CV death and higher HF hospitalization rates. I have not analyzed these interaction issues thoroughly and I will leave their resolution to the primary NDA reviewers.

References

Marciniak, T. A. (2014). CDTL Review Memo, NDA 206-143, ivabradine.

McMurray, J. J. V., M. Packer, et al. (2014). "Angiotensin-Neprilysin Inhibition versus Enalapril in Heart Failure." New England Journal of Medicine **371**(11): 993-1004.

Analysis Plan for ARBs and Cancer
Version 1.2, August 18, 2012

Background

A recent published meta-analysis (M-A) re-raised the issue of whether angiotensin receptor blockers (ARBs) increase the risk of cancer. (Sipahi, Debanne et al. 2010) In response to publication of the M-A the FDA issued a drug safety communication on July 15, 2010, stating that the Agency's review was on-going. The Division entered a tracked safety issue (TSI) and assembled a team led by the Deputy Director for Safety (DDS) to perform the review. The DDS issued in August 2010 information requests to the developers of innovator ARBs marketed in the US to provide "study-level incidence by treatment arm of cancer (solid tumor only including skin cancer, not hematologic malignancy)" for trials with more than 100 patients and average follow-up of > 1 year. The drug companies submitted responses, among them Merck responses dated November 17, 2010, and February 2, 2011. The TSI team reviewed the responses and performed another M-A. Based on the TSI M-A the Agency issued another drug safety communication on June 2, 2011, stating that the relative risk of incident cancer in patients taking ARBs was 0.99 and the FDA also found no evidence of association between ARBs and cancer-related death, breast cancer, lung cancer, or prostate cancer.

However, the TSI M-A has many problems such that we cannot view it as a definitive answer to the questions of whether ARBs, or some ARBs, are associated with higher rates of cancer. Some of the problems with the TSI M-A are the following:

- The terms used for specific sites were not all inclusive of all malignancies, e.g., for lung cancers, lung cancers coded as malignant lung neoplasms were included but not ones coded as lung carcinomas. Yet the preliminary analyses of the LIFE study, one of the largest studies that prompted the latest round of meta-analyses, suggest that lung cancer is one of the tumors most affected and that ARBs could affect specific sites in different ways (see below.)

- The different sponsor submissions varied widely in how sponsors coded cancers, determined malignancy and new incidence determined, andcenosred cancer events. Several sponsors also had their staff assign a malignancy status to ambiguous cases. The variations in ascertaining cancer events and follow-up are great enough such that we should exclude some studies because of incomplete ascertainment of cancers or incomplete follow-up.

- The TSI M-A lumps studies with different controls together and lumps studies with and without concomitant use of ACE inhibitors (ACEIs). ARBs and ACEIs may affect some cancers similarly (see below).

- The TSI M-A included studies with patients on other drugs that affect cancer rates, e.g., immunosuppressives.

See the review "Losartan and Cancer" filed May 28, 2012, under the NDA 20-386 for more details regarding the problems with the TSI M-A.

An important issue is whether ARBs affect the incidence of all cancers or only specific ones. Most drugs affecting cancer rates have affected only specific sites (or a group of related sites) but the TSI M-A addresses primarily all solid cancers including skin cancers and secondarily breast, lung, and prostate (but inadequately for the latter as described above.) The losartan LIFE trial suggests that, rather than primarily affecting all solid cancers including skin cancers, ARBs may influence cancer rates in three different ways:

1. The strongest signal in LIFE regarding a specific cancer site is for lung cancer by Merck's SAE statistics (29:12 losartan:atenolol). The signal for all cancers is weaker and, in the absence of signals for most sites, appears to be related to the higher rates of lung (and prostate) cancers in the losartan arms. We need to analyze lung cancers separately as one primary hypothesis.

2. Prostate cancer SAE rates were also higher in the losartan arm in LIFE (58:42). In LIFE there is also a suggestion that gynecologic cancers were lower in the losartan arm, possibly implicating a hormonal mechanism. There is a plausible hormonal mechanism whereby ARBs (and ACEIs) could affect prostate cancers: ARBs and ACEIs initially decrease aldosterone levels but later there is "aldosterone breakthrough." If the aldosterone breakthrough is the result of a less specific adrenal stimulation that also increases adrenal androgen production, then an increase in prostate cancers would be expected. Hence, because the mechanism may be different, we should analyze prostate cancers separately taking into account that ACEIs may share the hormonal mechanism. As a secondary analysis we should combine lung and prostate cancer events.

3. Hematologic malignancy rates were lower in the losartan arm in LIFE. There is also a plausible mechanisms whereby ARBs (and ACEIs) could affect hematologic malignancies: Both ARBs and ACEIs suppress hematopoiesis slightly as evidenced by slightly decreased hemoglobin levels with chronic administration. This myelosuppression could also result in lower hematologic malignancy rates. We should analyze hematologic malignancy rates as a third primary hypothesis.

We have no evidence to assume that whatever is responsible for the increased lung cancer rates (if they are really increased) is an effect shared with ACEIs. However, we would expect that mechanisms 2 and 3 above, if real, are shared with ACEIs. Hence the studies included in MAs to address the different mechanisms should be different: For lung cancers (1 above) we may ignore the use of ACEIs as a control or as concomitant therapy for the primary analysis; for a secondary analysis excluding ACEI controls and concomitant ACEI use would be informative. For 2 and 3 above we must exclude ACEI use either as a control or as concomitant therapy (>10%--As a secondary analysis we can analyze trials have ACEI use of >10% by excluding the cases with ACEI use in both

arms.) Crossovers are also of concern and hence we should exclude trials with crossovers to open label ARB use of >10%.

The considerations for the different potential mechanisms are not limited to ACEI use: We must consider explicitly whether there is evidence for an ARB class effect or whether some ARBs could behave differently than others. We presume that mechanisms 2 and 3 are class effects of ARBs, i.e., all ARBs studied have shown aldosterone breakthrough and all ARBs have shown myelosuppression. For mechanisms 2 and 3 we have justification for analyzing all ARBs together (but dosage may be a consideration.) For 1 above we have no *a priori* reason justifying a class effect; conversely, because we do not understand the mechanism, we have no absolute *a priori* reasons to select out one or more of the ARBs. While ARBs do have different properties (e.g., lipophilicity, PPAR agonism) that we can use to group ARBs, we do not know which, if any, of these differing properties are important for cancer promotion. Hence, lacking a clearly justified *a priori* grouping, we default to grouping all ARBs together. However, we must be cognizant that grouping all ARBs may obscure a real signal for an appropriate subgroup and that a strong signal in two or more ARBs is greatly concerning.

In summary, the most important considerations for evaluating the risks of cancers with ARB administration are the following:

1. Assuring that the cancer ascertainments in the studies analyzed are as accurate and complete as possible and rejecting studies with incomplete ascertainment.

2. Selecting the appropriate studies, e.g., ones having appropriate controls and concomitant therapies, and the appropriate cancer sites for the suspected mechanisms.

3. Performing statistically valid meta-analyses.

Considerations 1 and 2 above are the ones that the TSI M-A does not handle appropriately, so I address them in detail below.

Plan

The general criteria used to screen trials initially for inclusion in the TSI M-A, similar to those used for the Sipaphi M-A, are reasonable. They are the following:

- Randomized, placebo-and active comparator-controlled studies for the ARBs
- Enrolled more than 100 patients
- Had a mean or median follow-up of > 1 year
- Collected cancer data (occurrence of cancer or cancer death) either as a prespecified endpoint or adverse event

However, while reasonable initial screening criteria, they are not adequate alone for selecting trials for inclusion in the M-As for two reasons: (1) As discussed above, the M-As for two of the cancer hypotheses should not include trials with ACEI control arms or

concomitant ACEI use. (2) If the cancer collection or follow-up for a trial is incomplete, then the trial may contribute more noise than useful information and we should not use it for the primary analyses. I recommend using these screening criteria with the two amplifications and I specify criteria for the latter below.

The time-consuming part of evaluating the risks of cancers with ARB administration is the work of assuring that the cancer ascertainments in the studies are accurate and complete. However, the time requirements are not excessive per study: I estimate that an experienced reviewer can complete the evaluation of one study in two to three days. Hence the total effort required for the 31 studies analyzed in the TSI M-A is about 62 to 93 man-days. Such an expenditure of effort would appear to be justified given the suggestive evidence from the losartan studies and the seriousness of increased cancer rates. While this level of effort is justified, it may be limited more by another requirement: To assure that cancer ascertainments are accurate and complete we need complete data for the trials, e.g., protocols, case report forms (CRFs), SAE reports, and datasets. I am able to identify submissions including these data for 16 of the 31 trials. (See Table 3 in Appendix 1.) Hence the appropriate next step may be to evaluate these trials completely.

We should consider requesting complete data for all 31 trials analyzed in the TSI M-A (b) (4) There are also other ARB studies listed in ClinicalTrials.gov that may also be relevant.) There is a risk of requesting the complete data for trials missing them now: Sponsors could claim not having complete data for trials with unfavorable results while submitting complete data for trials with neutral or favorable results. Hence I would consider an M-A on the trials for which we currently have complete data to be the most reliable. I would also request the data for the losartan trials (i.e., other than LIFE and RENAAL, for which we have NDA submissions) to determine whether the signal for losartan remains strong or diminishes (b) (4)

Individual Trial Evaluation

The following is the step-by-step procedure I recommend for evaluating each trial:

1. Collect the following metadata documents for the trial:
    a. Protocol
    b. Statistical analysis plan
    c. Blank annotated CRF
    d. DEFINE.PDF (or equivalent) file for data sets
    e. Study report
    f. Study design publication (if one)
    g. Major study results publication

2. Using the protocol, blank annotated CRF, DEFINE.PDF, and datasets determine which CRFs and datasets have baseline characteristics, randomization, cancer event information, history of cancer, smoking information, end of treatment date, and follow-up. Large outcome trials vary in where cancer event information is recorded. Besides the adverse event (AE) CRFs possible sources of cancer event information include death CRFs, end-of-study CRFs, hospitalization CRFs, endpoint CRFs, and cancer CRFs. An individual experienced in reviewing outcome trial data, including the datasets, should check all of these sources. For trials not specifying collection of all AEs the individual should make an initial assessment of whether the collection of cancer data is likely to be incomplete, including whether cancer site reporting is incomplete.

3. Using the protocol, study report, study publication, and datasets determine the end-of-study date to use as the censoring date for ITT analyses; also get the reported completeness of follow-up. If the reported completeness of follow-up exceeds 10 percent we will not use the trial for the primary analyses. Ten percent, of course, is a somewhat arbitrary number, although trials approaching this level of incompleteness have shown controversial results.

4. Collect the relevant datasets identified in 2 above and delete all treatment information from all datasets except a master dataset created from the baseline characteristics and randomization (treatment assignment) information. For cancer determinations use only datasets lacking the treatment assignments. CRFs typically do not have treatment assignments, with the exception of some PROBE design, open-label studies—not an issue for the 16 trials for which we currently have data. SAE reports occasionally have treatment assignments in the header or as an additional note at the end. Merge the cancer assignments into the master file after finalizing the cancer determinations.

5. Classify malignancies into sites based on the MedDRA "Neoplasms benign, malignant, and unspecified (incl cysts and polyps)" SOC with the following variations:
    a. Our concern is malignancies. Hence exclude benign neoplasms and attempt to determine the malignancy status of unspecified ones. Because unspecified neoplasms at different sites have different likelihoods of being malignant, use the guidance in Table 1 if the CRFs and SAE reports do not provide an unambiguous confirmation of malignancy. For the sites of interest for ARBs, i.e., lung, prostate, and hematologic, the most problematic cases are the lung tumors or lung masses that the records do not confirm as benign or malignant. Check all available records, e.g., CRFs, SAE reports, regarding these cases. Treatment can confirm malignancy, i.e., if the mass was treated with radiation therapy, it was likely malignant. If no other data are available, classify a lung mass as malignant if serious or severe and assume benign otherwise.
    b. While the sites of greatest interest for ARBs are lung, prostate, and hematologic, trying to classify all malignancies is worthwhile: We need to

resolve whether a neoplasm reported at one site is actually a metastasis from another site.

c. The MedDRA neoplasm SOC is predominantly anatomically oriented, although it does classify hematopoietic neoplasms and mesotheliomas separately. Classify hematopoietic neoplasms and mesotheliomas separately and also classify carcinoids and sarcomas separately, including fibrous malignant histiocytoma as a sarcoma. Cystosarcoma phyllodes is usually a benign breast tumor; classify it as a sarcoma if it is malignant.
d. Classify melanomas, including ocular melanomas, separately from all other skin cancers.
e. Brain tumors are not infrequently inadequately reported as benign vs. malignant. Benign brain tumors are also of substantial concern. Hence classify brain tumors into all brain tumors and malignant brain tumors.
f. Combine uncommon sites by anatomy using the site classification in Table 2. The sites in Table 2 link to MedDRA preferred terms that are used in analyzing the trial datasets (see below and Table 4 in Appendix 2.) Table 2 also includes "supersites" that group some sites for analysis purposes, e.g., the "gi" supersite is useful for analyzing gastrointestinal cancers that antiplatelet drugs may be expected to cause to bleed. The most relevant supersite for this effort is the "heme" supersite (hematologic malignancy). The "gyn" supersite (gynecologic malignancy or MedDRA reproductive neoplasms female malignant HLGT) is also relevant.
g. For this effort we are most concerned with lung, prostate, and hematologic malignancies so resolve suspected cases for these sites as completely and accurately as the available documentation permits.

Table 1: Guidance for Classifying Sites and Ambiguous Malignancy

term	guidance
adrenal mass/nodule	assume benign if not serious malignant if serious
bladder mass/lesion/tumor	classify as malignant
bowel/intestine (no small or large)	classify as colon
carcinoid	classify as carcinoid not by site
colon rectum cecum appendix	classify as colon
gall bladder	classify as bile duct
glioblastoma	classify as malignant brain
glioma	assume benign
hepatic nodule/mass/neoplasm/tumor	assume benign if not serious malignant if serious
lung neoplasm/mass/tumor/density etc.	base on characteristics eg seriousness check maximally
lung nodule	assume benign unless stated malignant
lymphoma	classify as lymphoma not by site
mesothelioma	classify as mesothelioma not by site
ovary mass/tumor	assume benign unless stated

term	guidance
	malignant
parotid/salivary gland	assume benign unless stated malignant and classify as head & neck
prostate nodule/enlargement	assume benign
refractory anemia	assume benign unless also stated as myelodysplasia
renal neoplasm/mass/tumor	assume malignant unless cyst
sarcoma	classify as sarcoma not by site
skin naevus/nodule/mole etc.	assume benign unless stated malignant
small intestine/GI	classify as gi
squamous cell carcinoma/scc	when site is not specified but the same patient has other skin cancers classify as skin cancer; check maximally for possible lung ca; classify as squamous if no other info
thrombocytosis/thrombocythemia	assume benign unless also stated as myelodysplasia
thyroid nodule/enlargement/tumor	assume benign unless stated malignant

Table 2: Sites for Grouping Malignancies for Analysis

site	supersite	comment
adrenal		
anus	gi	
bile duct	hepatobiliary	including gall bladder
bladder		including ureter & urethra
brain	brain	all & malignant separately
breast		
carcinoid	(gi)	include gi carcinoids in gi supersite
cervix	gyn	
colon	gi	
esophagus	gi	
eye		
germ cell		rare; resolve by gender
gi other	gi	small bowel & unspecified gi site
head & neck		
kidney		including renal pelvis
leukemia	heme	
liver	hepatobiliary	
lung		
lymphoma	heme	
melanoma		
mesothelioma		regardless of site

site	supersite	comment
myelodys	heme	
myeloma	heme	
other		
ovary	gyn	
pancreas		
penis		
pituitary	brain	benign or (rarely) malignant
prostate		
sarcoma		regardless of site
skin		
squamous		only if no other information
stomach	gi	
testes		
thyroid		
unknown		
uterus	gyn	
vagina	gyn	
vulva	gyn	

6. I have produced some automated tools for assisting with the classifying of cancer cases described in 5 above:
    a. A PTERMCA dataset links the MedDRA preferred terms to the sites in Table 2 as specified in Table 4 in Appendix 2. PTERMCA not only links MedDRA terms for malignancies in the neoplasm SOC but also unspecified malignancy terms in that SOC and procedures suggestive of a malignancy, e.g., colectomy, radiation therapy, etc. The latter are flagged with a binary variable CAUNCERTAIN. The PTERM variable also includes terms from older versions of MedDRA and other coding schemes. To use rename the preferred term variable to PTERM, convert to lowercase, and merge with PTERMCA.
    b. Not all datasets with cancer data have MedDRA coding and not all raw terms are correctly coded. Hence as a check I developed a Stata procedure GENCAMAYBE.DO to search the raw reported event terms for text strings suggestive of cancer. (The Stata procedure can easily be converted to a SAS program.) GENCAMAYBE sets a binary variable CAMAYBE if the raw term contains a string suggestive of cancer. To use rename the raw term variable to AETERM, convert to lowercase, and run GENCAMAYBE. GENCAMAYBE creates a binary flag variable CAMAYBE if the term suggests cancer.

7. I recommend classifying cancer cases operationally as follow:
    a. For each dataset having cancer information apply PTERMCA (if a preferred term is available) and GENCAMAYBE (if a raw term is available).

b. Create a new string variable CASITE. If PTERMCA was used, copy PTCASITE (preferred term cancer site) to CASITE if CAUNCERTAIN is not set.
c. Review all records for which PTCASITE is not null or CAUNCERTAIN or CAMAYBE are set. In my experience one can resolve most of the records without resorting to other documentation. Resolve with other documentation (CRFs, SAE reports, etc.) all possible potential lung, prostate, and heme malignancies. Populate CASITE for all confirmed or highly likely malignancies.
d. UNKNOWN is an appropriate value for CASITE if the reported term is "primary site unknown" or similar. However, if the only information available is that the case is a "cancer" or "malignancy" based on a checkbox on a hospitalization or death form, then enter CASITE as "malignancy". If one can not resolve most, i.e., 95 percent, of these unspecified malignancy cases from other records or documentation, then exclude the trial from the primary analyses.
e. Create binary flag variables for solid cancers excluding brain and non-melanoma skin, lung, prostate, and heme malignancies, assuring that the dates of diagnosis are within the censoring period (see below). Differentiate the flag variables by dataset source, e.g., CAALUNG for lung cancer from the AE dataset, CADLUNG for lung cancer from a DEATH dataset, etc. Merge the flag variables into a master dataset.
f. Generate global binary flag variables for solid cancer, lung, prostate, and heme malignancies using the binary flag variables from the individual dataset sources. Generate the global flags sequentially in the order of data sources AE, event or endpoint, hospitalization, treatment end, study end, and death. If more than a few cases, i.e., 5 percent of all cases, are detected only at study end or death, then exclude the trial from the primary analyses.
g. I believe one individual can perform all of the above evaluations in an unbiased fashion working from datasets without treatment identifiers. However, it is always worthwhile to have one individual's work checked by at least one additional individual. Ideally the second reviewer should have the same skills and experience as the primary reviewer, i.e., skills with dataset manipulations and experience with outcome trial data, preferably with cancer classifications. The time required for the second reviewer should be substantially less, e.g., one day per trial, than that for the first if the second reviewer works from the source documents collected by the first reviewer. If the two reviewers cannot reconcile their classifications of some cases, then we can consider two approaches to resolve: (1) Analyze each reviewer's assignments separately. I believe the results and conclusions will be similar. (2) Enlist a third reviewer to resolve the disputed cases.

8. In addition to the cancer site adjudicating the date of cancer diagnosis is important. I assert that, for the way cancers are reported in CV outcome trials, the

most appropriate definition is the date of first clinical diagnosis of cancer. Tumor registries typically use the date of first histologic diagnosis but CV trial data does not usually include the date of histologic diagnosis. Most cancer events occur during the course of the trial, i.e., "in the middle", so date of diagnosis is not usually problematic. For almost all cases we can use the start date of the AE or the date of hospital admission for a cancer hospitalization. One does have to check, if this date precedes the randomization, whether the start date represents the date of the first sign or symptom of the cancer, e.g., a cough for a lung cancer, or the date of diagnosis. If the AE start date is the first sign or symptom date, we need to determine the date of diagnosis from other sources.

One could exclude cancers at the start of a trial because they are unlikely to have any relationship to ARB use but for how long to exclude them is arbitrary; including them likely does not present a substantial amount of noise and avoids the arbitrary decision on exclusion period. For cancers reported at the end of the trial we could employ an absolute cutoff of the global study end date (see below.) However, a cancer reported one day after this date obviously could be treatment-related and dates have a reasonable amount of uncertainty—see my review of the LIFE study filed January 15, 2003, to NDA 20-386 for a detailed discussion of AE dates. Ideally we should examine cancer diagnoses (for entire studies, not by arm) at and shortly after study end dates. If cancer diagnoses are significantly more frequent around study end (as atrial fibrillation AEs were in LIFE), we should use a cutoff of study end plus the stabilization period—in LIFE for AEs the stabilization period was about 90 days. Until someone performs such analyses the global study end date is the appropriate cutoff to use for ITT analyses.

9. The final cancer case item to be considered is a flag whether the cancer is new (i.e., diagnosed after the randomization date) or recurrent (i.e., diagnosed on or before the randomization date.) While I agree new cancer rates may be informative, I believe that new and recurrent cancer rates are more informative and reliable for the following reasons: (1) Cancer patients typically die from recurrent disease, not their initial primary. Recurrent cancer is equally or more important clinically than new cancer. (2) CV outcome trials frequently record history of cancer as yes/no rather than for specific sites. Analyzing only new cancers will exclude trials with this limited history of cancer recording. (3) New and recurrent cancer rates correspond to our usual AE reporting of treatment-emergent events, e.g., we don't ignore an MI event because the patient also suffered an MI prior to randomization. I advise using treatment-emergent malignancy events for the primary analyses. I would use analyses of new malignancies as secondary analyses.

   Exclude trials without a recording of history of cancer from the new cancer M-As. For trials recording history of cancers by site classify the cancer new if there is no history of cancer for the same site. For ones recording only a yes/no response for history of cancer classify the cancer new if there is no history of cancer; if there is a history of cancer, check all records (particularly SAE reports) for mention of the

prior cancer site and classify the cancer new if the prior cancer site differs, not new otherwise.

10. The last data items that are useful for some analyses are censoring dates for each patient, i.e., the date of last follow-up and last treatment (the latter for on-treatment analyses.) Ideally we need to document two different dates of last follow-up for each patient: (1) the last date for which the records document reasonable ascertainment of events including cancer; and (2) the last date for which the records document vital status. Determining the date of last event follow-up can be difficult and time-consuming. Sponsors usually include a date of last treatment in study datasets and, because the dates of last treatment are usually reasonably well documented, I would use them unless we identify a systematic problem with the recordings for a trial, e.g., use of last dispensing date rather than a reported last administration date. The dates of last follow-up are more problematic and variably described. Because events alone are used for odds ratios, relative risks, and events without using censoring dates and because events largely determine the significance of hazard ratios and other time-to-event analyses, I favor determining initially only one last follow-up date, the vital status follow-up date.

Meta-Analyses

Before specifying the primary analyses there are some general statistical issues worth discussing:

1. This effort is a safety evaluation. For efficacy evaluations we have well-defined, pre-specified, specifically-collected primary endpoints in trials powered to detect reasonable differences between drugs and controls. For efficacy evaluations we insist upon strict statistical significance to guide the critical binary decision of allowing marketing or not. For safety evaluations we frequently start with *post hoc* observations, as is the case for this effort. We do not have data specifically collected to address the question and we do not have studies adequately powered to detect reasonable differences. Hence, while we may still use confidence intervals and p values to guide our safety decisions, we do not typically require strict statistical significance for safety data and we should consider patterns of problems, not just p values. Finally, while the critical efficacy decision is a binary one, we have different levels of action to address different levels of safety concerns. There are at least four levels of action to consider:
    a. Removing a drug from market. For this effort one might still insist upon having strict statistical significance of any result to justify removal.
    b. Including the findings in labeling and requiring an adequate post-marketing study to address the concerns. We typically take this action when the findings are concerning but not strictly statistically significant in any one study or available analysis.
    c. Including the findings in labeling without requiring a post-marketing study. We typically do not require any statistical significance for safety

findings, merely a difference between drug and control. Most of the safety results in existing labels fall into this category.

d. Doing nothing if no M-A confirms any concern.

We should consider all four of these levels of action for any results of these meta-analyses.

2. The index study for the hypotheses regarding lung, prostate, and hematologic malignancies is the LIFE study. Hence, for strict statistical significance one might exclude the LIFE study from the primary meta-analyses. However, for the identical situation with the Sipahi and TSI M-As, for which the CHARM study is considered the index study, neither M-A excluded the CHARM study in the primary analysis. Because LIFE contributes a minority of the patients to the all ARB M-As, I believe that including it in the overall M-As and excluding it for sensitivity analyses is reasonable.

3. For safety studies some prefer an on-treatment evaluation. I prefer an ITT evaluation because, just as for efficacy analyses, it preserves the randomization and minimizes the problems of informative censoring. However, just as for efficacy, if treatment discontinuations are common and follow-up thereafter is poor, either on-treatment or ITT safety evaluations will likely be biased; there is no statistical cure for poor study conduct. Hence for these M-As I am proposing excluding trials with poor cancer ascertainment and poor follow-up. I am proposing ITT for the primary M-As, i.e., randomization to the earlier of death or the global study end date. Because cancers may not manifest themselves or be diagnosed immediately, for secondary "on-treatment" M-As I propose treatment discontinuation plus 90 days (based on my LIFE trial analyses, see above. For ITT I do not recommend continuing beyond the global study end date unless a blinded analysis documents an appropriate stabilization period. However, follow-up is typically variable after the global study end date and I do have concerns that, if there was the potential for end-of-study unblinding, the extended follow-up may be biased.)

4. There are multiplicity issues for these M-As:
   a. I have proposed three different hypotheses. One, that ARBs may reduce hematologic malignancies, is clearly different from the other two in that it hypothesizes a benefit rather than a detriment. The other two are not as distinguishable. While I hypothesize different mechanisms for them, the increases in lung and prostate cancers could be the result of a common mechanism. I favor pursuing the two hypothesizes separately for this safety evaluation particularly because the prostate hypothesis may also be true for ACEIs, suggesting different trial inclusion criteria for the two hypotheses. Because I judge the signal to be stronger in LIFE for these two sites, weak or nonexistent for other sites, and weaker for all cancers, I would not base the primary M-A on all solid cancers.
   b. One approach for proceeding is to perform the proposed patient-level M-As, with the cancer ascertainment as described above, for the 16 trials for

which we have complete data. One might view such an M-A as an interim analysis, i.e., for suggestive or statistically significant results we should proceed to an M-A of all ARB trials for which we can obtain complete data. Because this is a safety evaluation I would not impose any strict statistical penalty for this interim analysis.

c. The more difficult multiplicity issue to address concerns how to resolve whether any positive results are an ARB class effect or an effect of some ARBs but not others. I think most people would be concerned if three ARBs showed a strong, statistically significant signal in an M-A of them alone but the other ARBs were neutral such that an all-ARBs M-A was not statistically significant. Because we have no strong *a priori* reason to hypothesize one or more ARBs as having greater cancer risk than the others, I would leave this issue to *post hoc* exploration.
d. Similarly, currently I cannot justify one of the secondary analyses discussed above (e.g., new malignancies only, on treatment rather than ITT, combined lung and prostate, etc.) as being more important than the others. I am not proposing secondary analysis plans preserving an overall alphas.
e. There are some cofactors that are of great interest. For lung cancers smoking history is critical and whether there is an interaction between treatment and smoking crucial to know. There is a suggestion of a gender effect, e.g., the one common male cancer, prostate, appears to be increased while common female cancers, breast and uterus, are not. Age and race are not specifically implicated for this effort but always of interest. I do not propose to include these cofactors in a analysis plan preserving an overall alpha but propose examining as descriptive factors if any primary analysis is significant.

5. Performing these patient-level evaluations would also open up the possibility of doing additional analyses not possible with the study-level M-As, in particular time-to-event and survival analyses. For the vast majority of clinical trial event analyses I have not encountered significant differences between the event incidence analyses, e.g., logistic regressions, and the time-to-event analyses, e.g., Cox regressions. I have found the subjective evaluation of the time-to-event and survival curves to be very informative. Because patient follow-up is variably defined and reported, I am not sure that there is any advantage to using a relative risk based on patient-years to one based on patients randomized. For the primary M-As I propose M-As of relative risks using fixed effects Mantel-Haenszel models analyzed using the metan package in Stata 12. The fixed effects Mantel-Haenszel model of relative risks is the default model of the metan package for binary outcome data such as cancer event occurrences.

6. Because I am hypothesizing a fixed effect, dosage becomes an issue for some trials. ARBs vary in potency so targeting or comparing mg dosages is not appropriate. Most trials performed a run-in or titrated to the maximum U.S. labeled dosage for hypertension but a few target half of this dosage. While

ideally we would like to know exposures and exposure-response relationships for the proposed mechanism (and for metabolites, etc.), U.S. maximum labeled dosage produce similar reductions in BP for all ARBs; percentage of maximum U.S. labeled dosage is a reasonable approach for standardizing potency. While, because we don't know the dose-response relationship for cancer activity (if one exists), I propose including the trials targeting half maximal dosage in the primary fixed effects M-A if they otherwise qualify, I also propose excluding them from secondary M-As to estimate the maximal treatment effect.

To summarize, my proposal for three primary M-As is the following:

- One primary M-A for each of the three hypotheses (lung, prostate, and hematologic)
- All M-As to use data from all 16 trials for which we currently have complete datasets and CRFs and which have reasonably complete cancer ascertainment and follow-up as defined above (If any FDA staff can identify other trials for which we currently have complete datasets and CRFs and which have reasonably complete cancer ascertainment and follow-up as defined above, I propose adding them to the analyses.)
- Cancer ascertainment as detailed above
- The M-As for prostate and hematologic malignancies excluding ACEI controls and trials with concomitant ACEI use
- Primary analyses of ITT relative risks using fixed effects Mantel-Haenszel models analyzed using the metan package of Stata 12

I argue that the proposed M-As, or variations on them proposed by other staff, will provide a more definitive answer to the question of whether ARBs affect cancer risk than any of the existing M-As, TSI or published. I believe the most critical factor is assuring that cancer ascertainment in the trials is as complete and accurate as possible. I will welcome discussion and proposals for variations on the statistical analyses and for secondary analysis plans preserving overall alpha.

Reference

Sipahi, I., S. M. Debanne, et al. (2010). "Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials." Lancet Oncol **11**(7): 627-36.

Revision History

Version	Date	Modifications
1.0	08/03/12	Original
1.1	08/09/12	1. Added LIFE lung and prostate ca statistics 2. Updated count of ARB trials with data in-house from 14 to 15 3. Added explicit ACEI exclusion criterion 4. Clarified use of dates of last treatment 5. Added discussion of ITT vs. on-treatment analyses 6. Added discussion of dosage issues
1.2	08/18/12	1. Added Revision History 2. Updated count of ARB trials with data in-house from 15 to 16 and added an appendix table identifying the 16 trials 3. Clarified that, if FDA staff identify other eligible trials, they will be added to the analyses 4. Added an appendix table of MedDRA preferred terms with site classifications 5. Specified relative risks, rather than odds ratios, for the primary M-As and the use of the metan package of Stata 12. NOTE: Clinicians and patients understand relative risks better than odds ratios. Switching from odds ratios to relative risks should have minimal to no impact upon the statistical significance of any M-A for these data; we will perform M-As using both measures and report both if there are more than minimal differences, e.g., p value difference ≥0.005. Relative risks are the default for binary outcomes for the metan package. 6. Corrected typos and awkward wording

Appendix 1

Table 3: Major ARB Trials with IND or NDA Data Submissions

ARB	Trial	IND or NDA
candesartan	CharmAdd	N20838S022
	CharmAlt	N20838S022
	CharmPres	N20838S022
irbesartan	(b) (4)	
	IDNT	N20757S021
	IRMA 2	N20757S021
losartan	LIFE	N20386S032
	RENAAL	N20386S028
olmesartan	(b) (4)	
telmisartan	ONTARGET	N20850S025
	PRoFESS	N20850S025
	TRANSCEND	N20850S025
valsartan	(b) (4)	
	Val-Heft	N20665S016
	VALIANT	N21283S011

Appendix 2

NOTE: Some of the MedDRA referred terms below are unspecified regarding malignancy status. Events coded to such unspecified terms need additional documentation to determine malignancy status. See Table 1 for guidance on classifying unspecified terms.

Table 4: MedDRA Preferred Terms and Sites

HLGT	Preferred Term	Site
breast neoplasms malignant and unspecified (incl nipple)	breast cancer	breast
	breast cancer female	breast
	breast cancer in situ	breast
	breast cancer male	breast
	breast cancer metastatic	breast
	breast cancer recurrent	breast
	breast cancer stage i	breast
	breast cancer stage ii	breast
	breast cancer stage iii	breast
	breast cancer stage iv	breast
	breast neoplasm	breast
	breast sarcoma	breast
	breast sarcoma metastatic	breast
	breast sarcoma recurrent	breast
	contralateral breast cancer	breast
	cystosarcoma phyllodes	breast
	inflammatory carcinoma of breast recurrent	breast
	inflammatory carcinoma of breast stage iii	breast
	inflammatory carcinoma of breast stage iv	breast
	inflammatory carcinoma of the breast	breast
	malignant nipple neoplasm	breast
	malignant nipple neoplasm female	breast
	malignant nipple neoplasm male	breast
	nipple neoplasm	breast
	paget's disease of the breast	breast
cancer-related morbidities	acanthosis nigricans	unknown
	acrokeratosis paraneoplastica	unknown
	bence jones proteinuria	myeloma
	cancer pain	unknown
	clonal evolution	unknown
	haemorrhagic tumour necrosis	unknown
	hypercalcaemia of malignancy	unknown
	infected neoplasm	unknown
	intracranial tumour haemorrhage	unknown
	leukostasis	unknown
	malignant ascites	unknown
	malignant dysphagia	unknown
	malignant pleural effusion	unknown
	meigs' syndrome	ovary

HLGT	Preferred Term	Site
	metastatic pain	unknown
	myasthenic syndrome	unknown
	necrolytic migratory erythema	unknown
	neoplasm swelling	unknown
	oncologic complication	unknown
	pancoast's syndrome	lung
	paraneoplastic cerebellar degeneration	unknown
	paraneoplastic dermatomyositis	unknown
	paraneoplastic pemphigus	unknown
	paraneoplastic retinopathy	unknown
	paraneoplastic syndrome	unknown
	pericardial effusion malignant	unknown
	pericarditis malignant	unknown
	polyneuropathy in malignant disease	unknown
	pseudomyxoma peritonei	unknown
	superior vena caval occlusion	unknown
	treatment related secondary malignancy	unknown
	trousseau's syndrome	unknown
	tumour associated fever	unknown
	tumour compression	unknown
	tumour embolism	unknown
	tumour flare	unknown
	tumour haemorrhage	unknown
	tumour local invasion	unknown
	tumour lysis syndrome	unknown
	tumour necrosis	unknown
	tumour pain	unknown
	tumour thrombosis	unknown
	tumour ulceration	unknown
endocrine neoplasms benign	pituitary tumour benign	pituitary
endocrine neoplasms malignant and unspecified	acth-producing pituitary tumour	pituitary
	adrenal carcinoma	adrenal
	adrenal cyst	adrenal
	adrenal gland cancer metastatic	adrenal
	adrenal neoplasm	adrenal
	adrenocortical carcinoma	adrenal
	apudoma	unknown
	carcinoid syndrome	carcinoid
	carcinoid tumour	carcinoid
	carcinoid tumour of the appendix	carcinoid
	carcinoid tumour of the caecum	carcinoid
	carcinoid tumour of the duodenum	carcinoid
	carcinoid tumour of the gastrointestinal tract	carcinoid
	carcinoid tumour of the pancreas	carcinoid
	carcinoid tumour of the prostate	carcinoid
	carcinoid tumour of the small bowel	carcinoid
	carcinoid tumour of the stomach	carcinoid

HLGT	Preferred Term	Site
	carcinoid tumour pulmonary	carcinoid
	craniopharyngioma	brain
	ectopic acth syndrome	unknown
	ectopic aldosterone secretion	unknown
	ectopic antidiuretic hormone secretion	unknown
	ectopic calcitonin production	unknown
	ectopic chorionic gonadotrophin secretion	unknown
	ectopic growth hormone secretion	unknown
	ectopic hormone secretion	unknown
	ectopic parathormone production	unknown
	ectopic prolactin secretion	unknown
	ectopic renin secretion	unknown
	endocrine neoplasm	other
	endocrine neoplasm malignant	other
	gastrinoma	gi other
	gastrinoma malignant	gi other
	glucagonoma	pancreas
	growth hormone-producing pituitary tumour	pituitary
	hormone-secreting ovarian tumour	ovary
	insulinoma	pancreas
	malignant neoplasm of islets of langerhans	pancreas
	malignant pituitary tumour	pituitary
	metastatic carcinoid tumour	carcinoid
	neuroendocrine carcinoma	other
	neuroendocrine tumour	other
	neurotensinoma	gi other
	pancreatic neuroendocrine tumour	pancreas
	paraganglion neoplasm	other
	paraganglion neoplasm malignant	other
	parathyroid tumour	other
	parathyroid tumour malignant	other
	phaeochromocytoma	other
	phaeochromocytoma malignant	other
	pituitary cancer metastatic	pituitary
	pituitary neoplasm malignant recurrent	pituitary
	pituitary tumour	pituitary
	pituitary tumour recurrent	pituitary
	prolactin-producing pituitary tumour	pituitary
	somatostatinoma	gi other
	thyroid cancer	thyroid
	thyroid cancer metastatic	thyroid
	thyroid neoplasm	thyroid
	thyroid stimulating hormone-producing pituitary tumour	pituitary
	vipoma	pancreas
gastrointestinal neoplasms malignant and	abdominal wall neoplasm	skin
	adenocarcinoma pancreas	pancreas
	anal cancer	anus

HLGT	Preferred Term	Site
unspecified	anal cancer metastatic	anus
	anal cancer recurrent	anus
	anal cancer stage 0	anus
	anal cancer stage i	anus
	anal cancer stage ii	anus
	anal cancer stage iii	anus
	anal cancer stage iv	anus
	anal neoplasm	anus
	colon cancer	colon
	colon cancer metastatic	colon
	colon cancer recurrent	colon
	colon cancer stage 0	colon
	colon cancer stage i	colon
	colon cancer stage ii	colon
	colon cancer stage iii	colon
	colon cancer stage iv	colon
	colon neoplasm	colon
	colorectal cancer	colon
	colorectal cancer metastatic	colon
	colorectal cancer recurrent	colon
	colorectal cancer stage i	colon
	colorectal cancer stage ii	colon
	colorectal cancer stage iii	colon
	colorectal cancer stage iv	colon
	colorectal carcinoma stage 0	colon
	desmoplastic small round cell tumour	sarcoma
	duodenal neoplasm	gi other
	erythroplasia of lip	skin
	gastric cancer	stomach
	gastric cancer recurrent	stomach
	gastric cancer stage 0	stomach
	gastric cancer stage i	stomach
	gastric cancer stage ii	stomach
	gastric cancer stage iii	stomach
	gastric cancer stage iv	stomach
	gastric neoplasm	stomach
	gastric sarcoma	stomach
	gastrointestinal cancer metastatic	gi other
	gastrointestinal carcinoma	gi other
	gastrointestinal carcinoma in situ	gi other
	gastrointestinal neoplasm	gi other
	gastrointestinal stromal tumour	gi other
	gastrooesophageal cancer	esophagus
	gingival cancer	head & neck
	hereditary non-polyposis colorectal cancer syndrome	colon
	intestinal adenocarcinoma	gi other
	large intestine carcinoma	colon

HLGT	Preferred Term	Site
	linitis plastica	stomach
	lip and/or oral cavity cancer	head & neck
	lip and/or oral cavity cancer recurrent	head & neck
	lip and/or oral cavity cancer stage 0	head & neck
	lip and/or oral cavity cancer stage i	head & neck
	lip and/or oral cavity cancer stage ii	head & neck
	lip and/or oral cavity cancer stage iii	head & neck
	lip and/or oral cavity cancer stage iv	head & neck
	lip neoplasm	head & neck
	lip neoplasm malignant stage unspecified	head & neck
	malignant anorectal neoplasm	anus
	malignant mesenteric neoplasm	other
	malignant palate neoplasm	head & neck
	malignant peritoneal neoplasm	unknown
	metastatic gastric cancer	stomach
	metastatic salivary gland cancer	head & neck
	mixed salivary tumour	head & neck
	muir-torre syndrome	colon
	neoplasm of appendix	colon
	oesophageal adenocarcinoma	esophagus
	oesophageal adenocarcinoma metastatic	esophagus
	oesophageal adenocarcinoma recurrent	esophagus
	oesophageal adenocarcinoma stage 0	esophagus
	oesophageal adenocarcinoma stage i	esophagus
	oesophageal adenocarcinoma stage ii	esophagus
	oesophageal adenocarcinoma stage iii	esophagus
	oesophageal adenocarcinoma stage iv	esophagus
	oesophageal cancer metastatic	esophagus
	oesophageal carcinoma	esophagus
	oesophageal carcinoma recurrent	esophagus
	oesophageal carcinoma stage 0	esophagus
	oesophageal neoplasm	esophagus
	oesophageal squamous cell carcinoma	esophagus
	oesophageal squamous cell carcinoma metastatic	esophagus
	oesophageal squamous cell carcinoma recurrent	esophagus
	oesophageal squamous cell carcinoma stage 0	esophagus
	oesophageal squamous cell carcinoma stage i	esophagus
	oesophageal squamous cell carcinoma stage ii	esophagus
	oesophageal squamous cell carcinoma stage iii	esophagus
	oesophageal squamous cell carcinoma stage iv	esophagus
	omentum neoplasm	other
	oral cavity cancer metastatic	head & neck
	oral neoplasm	head & neck
	oropharyngeal neoplasm	head & neck
	pancreatic carcinoma	pancreas
	pancreatic carcinoma metastatic	pancreas
	pancreatic carcinoma non-resectable	pancreas

HLGT	Preferred Term	Site
	pancreatic carcinoma recurrent	pancreas
	pancreatic carcinoma resectable	pancreas
	pancreatic carcinoma stage 0	pancreas
	pancreatic carcinoma stage i	pancreas
	pancreatic carcinoma stage ii	pancreas
	pancreatic carcinoma stage iii	pancreas
	pancreatic carcinoma stage iv	pancreas
	pancreatic neoplasm	pancreas
	pancreatic sarcoma	sarcoma
	peritoneal carcinoma	unknown
	peritoneal neoplasm	other
	peritoneal sarcoma	sarcoma
	rectal cancer	colon
	rectal cancer metastatic	unknown
	rectal cancer recurrent	colon
	rectal cancer stage 0	colon
	rectal cancer stage i	colon
	rectal cancer stage ii	colon
	rectal cancer stage iii	colon
	rectal cancer stage iv	colon
	rectal neoplasm	colon
	rectosigmoid cancer	colon
	rectosigmoid cancer recurrent	colon
	rectosigmoid cancer stage 0	colon
	rectosigmoid cancer stage i	colon
	rectosigmoid cancer stage ii	colon
	rectosigmoid cancer stage iii	colon
	rectosigmoid cancer stage iv	colon
	retroperitoneal cancer	other
	retroperitoneal neoplasm	unknown
	retroperitoneal neoplasm metastatic	other
	salivary gland cancer	head & neck
	salivary gland cancer recurrent	head & neck
	salivary gland cancer stage 0	head & neck
	salivary gland cancer stage i	head & neck
	salivary gland cancer stage ii	head & neck
	salivary gland cancer stage iii	head & neck
	salivary gland cancer stage iv	head & neck
	salivary gland neoplasm	head & neck
	small intestine carcinoma	gi other
	small intestine carcinoma metastatic	gi other
	small intestine carcinoma non-resectable	gi other
	small intestine carcinoma recurrent	gi other
	small intestine carcinoma resectable	gi other
	small intestine carcinoma stage 0	gi other
	small intestine carcinoma stage i	gi other
	small intestine carcinoma stage ii	gi other

HLGT	Preferred Term	Site
	small intestine carcinoma stage iii	gi other
	small intestine carcinoma stage iv	gi other
	tongue cancer metastatic	head & neck
	tongue carcinoma stage 0	head & neck
	tongue carcinoma stage i	head & neck
	tongue carcinoma stage ii	head & neck
	tongue carcinoma stage iii	head & neck
	tongue carcinoma stage iv	head & neck
	tongue neoplasm	head & neck
	tongue neoplasm malignant stage unspecified	head & neck
haematopoietic neoplasms (excl leukaemias and lymphomas)	blast cell proliferation	leukemia
	bone marrow leukaemic cell infiltration	leukemia
	bone marrow tumour cell infiltration	unknown
	epstein-barr virus associated lymphoproliferative disorder	lymphoma
	essential thrombocythaemia	myelodys
	haematological malignancy	unknown
	haematopoietic neoplasm	unknown
	leukoerythroblastosis	leukemia
	lymphatic system neoplasm	lymphoma
	lymphohistiocytosis	lymphoma
	lymphoproliferative disorder	lymphoma
	lymphoproliferative disorder in remission	lymphoma
	malignant histiocytosis	other
	malignant mast cell neoplasm	myeloma
	malignant splenic neoplasm	lymphoma
	myeloblastoma	other
	myelofibrosis	myelodys
	myeloid metaplasia	myelodys
	myeloproliferative disorder	myelodys
	polycythaemia vera	myelodys
	rosai-dorfman syndrome	lymphoma
	splenic neoplasm malignancy unspecified	lymphoma
	x-linked lymphoproliferative syndrome	lymphoma
hepatobiliary neoplasms malignant and unspecified	bile duct cancer	bile duct
	bile duct cancer non-resectable	bile duct
	bile duct cancer recurrent	bile duct
	bile duct cancer resectable	bile duct
	bile duct cancer stage 0	bile duct
	bile duct cancer stage i	bile duct
	bile duct cancer stage ii	bile duct
	bile duct cancer stage iii	bile duct
	bile duct cancer stage iv	bile duct
	biliary cancer metastatic	bile duct
	biliary neoplasm	bile duct
	gallbladder cancer	bile duct
	gallbladder cancer metastatic	bile duct
	gallbladder cancer non-resectable	bile duct

HLGT	Preferred Term	Site
	gallbladder cancer recurrent	bile duct
	gallbladder cancer stage 0	bile duct
	gallbladder cancer stage i	bile duct
	gallbladder cancer stage ii	bile duct
	gallbladder cancer stage iii	bile duct
	gallbladder cancer stage iv	bile duct
	hepatic angiosarcoma	sarcoma
	hepatic cancer metastatic	unknown
	hepatic cancer stage i	liver
	hepatic cancer stage ii	liver
	hepatic cancer stage iii	liver
	hepatic cancer stage iv	liver
	hepatic neoplasm	liver
	hepatic neoplasm malignant	liver
	hepatic neoplasm malignant non-resectable	liver
	hepatic neoplasm malignant recurrent	liver
	hepatic neoplasm malignant resectable	liver
	hepatobiliary carcinoma in situ	liver
	hepatobiliary neoplasm	liver
	hepatoblastoma	liver
	hepatoblastoma recurrent	liver
	liver carcinoma ruptured	liver
	malignant hepatobiliary neoplasm	liver
	malignant neoplasm of ampulla of vater	bile duct
	mixed hepatocellular cholangiocarcinoma	liver
leukaemias	5q minus syndrome	myelodys
	acute biphenotypic leukaemia	leukemia
	acute leukaemia	leukemia
	acute leukaemia in remission	leukemia
	acute lymphocytic leukaemia	leukemia
	acute lymphocytic leukaemia (in remission)	leukemia
	acute lymphocytic leukaemia recurrent	leukemia
	acute megakaryocytic leukaemia	leukemia
	acute megakaryocytic leukaemia (in remission)	leukemia
	acute monocytic leukaemia	leukemia
	acute monocytic leukaemia (in remission)	leukemia
	acute myeloid leukaemia	leukemia
	acute myeloid leukaemia (in remission)	leukemia
	acute myeloid leukaemia recurrent	leukemia
	acute myelomonocytic leukaemia	leukemia
	acute promyelocytic leukaemia	leukemia
	aleukaemic leukaemia	leukemia
	b precursor type acute leukaemia	leukemia
	b-cell type acute leukaemia	leukemia
	blast cell crisis	leukemia
	blast crisis in myelogenous leukaemia	leukemia
	burkitt's leukaemia	leukemia

HLGT	Preferred Term	Site
	chloroma	leukemia
	chloroma (in remission)	leukemia
	chronic eosinophilic leukaemia	leukemia
	chronic leukaemia	leukemia
	chronic leukaemia in remission	leukemia
	chronic lymphocytic leukaemia	leukemia
	chronic lymphocytic leukaemia (in remission)	leukemia
	chronic lymphocytic leukaemia recurrent	leukemia
	chronic lymphocytic leukaemia refractory	leukemia
	chronic lymphocytic leukaemia stage 0	leukemia
	chronic lymphocytic leukaemia stage 1	leukemia
	chronic lymphocytic leukaemia stage 2	leukemia
	chronic lymphocytic leukaemia stage 3	leukemia
	chronic lymphocytic leukaemia stage 4	leukemia
	chronic lymphocytic leukaemia transformation	leukemia
	chronic myeloid leukaemia	leukemia
	chronic myeloid leukaemia (in remission)	leukemia
	chronic myeloid leukaemia transformation	leukemia
	chronic myelomonocytic leukaemia	leukemia
	chronic myelomonocytic leukaemia (in remission)	leukemia
	eosinophilic leukaemia	leukemia
	erythraemic myelosis (in remission)	leukemia
	erythroleukaemia	leukemia
	hairy cell leukaemia	leukemia
	juvenile chronic myelomonocytic leukaemia	leukemia
	large granular lymphocytosis	leukemia
	leukaemia	leukemia
	leukaemia basophilic	leukemia
	leukaemia cutis	leukemia
	leukaemia granulocytic	leukemia
	leukaemia in remission	leukemia
	leukaemia monocytic	leukemia
	leukaemia recurrent	leukemia
	leukaemic infiltration brain	leukemia
	leukaemic infiltration extramedullary	leukemia
	leukaemic infiltration gingiva	leukemia
	leukaemic infiltration hepatic	leukemia
	leukaemic infiltration pulmonary	leukemia
	leukaemic retinopathy	leukemia
	lymphocytic leukaemia	leukemia
	lymphoid leukaemia (in remission)	leukemia
	mastocytic leukaemia	leukemia
	mature b-cell type acute leukaemia	leukemia
	monocytic leukaemia in remission	leukemia
	myelodysplastic syndrome	myelodys
	myelodysplastic syndrome transformation	other
	myelodysplastic syndrome unclassifiable	other

HLGT	Preferred Term	Site
	myeloid leukaemia	leukemia
	myeloid leukaemia in remission	leukemia
	natural killer-cell leukaemia	leukemia
	neonatal leukaemia	leukemia
	prolymphocytic leukaemia	leukemia
	refractory anaemia	myelodys
	refractory anaemia with an excess of blasts	myelodys
	refractory anaemia with ringed sideroblasts	myelodys
	refractory cytopenia with multilineage dysplasia	myelodys
	refractory cytopenia with multilineage dysplasia and ringed sideroblasts	myelodys
	t-cell chronic lymphocytic leukaemia	leukemia
	t-cell prolymphocytic leukaemia	leukemia
	t-cell type acute leukaemia	leukemia
	trisomy 12	lymphoma
lymphomas hodgkin's disease	hodgkin's disease	lymphoma
	hodgkin's disease lymphocyte depletion stage i site unspecified	lymphoma
	hodgkin's disease lymphocyte depletion stage i subdiaphragm	lymphoma
	hodgkin's disease lymphocyte depletion stage i supradiaphragm	lymphoma
	hodgkin's disease lymphocyte depletion stage ii site unspecified	lymphoma
	hodgkin's disease lymphocyte depletion stage ii subdiaphragm	lymphoma
	hodgkin's disease lymphocyte depletion stage ii supradiaphragm	lymphoma
	hodgkin's disease lymphocyte depletion type recurrent	lymphoma
	hodgkin's disease lymphocyte depletion type refractory	lymphoma
	hodgkin's disease lymphocyte depletion type stage iii	lymphoma
	hodgkin's disease lymphocyte depletion type stage iv	lymphoma
	hodgkin's disease lymphocyte depletion type stage unspecified	lymphoma
	hodgkin's disease lymphocyte predominance stage i site unspec	lymphoma
	hodgkin's disease lymphocyte predominance stage i subdiaphragm	lymphoma
	hodgkin's disease lymphocyte predominance stage i supradiaphragm	lymphoma
	hodgkin's disease lymphocyte predominance stage ii site unspec	lymphoma
	hodgkin's disease lymphocyte predominance stage ii subdiaphragm	lymphoma
	hodgkin's disease lymphocyte predominance stage ii supradiaphragm	lymphoma
	hodgkin's disease lymphocyte predominance type recurrent	lymphoma
	hodgkin's disease lymphocyte predominance type refractory	lymphoma
	hodgkin's disease lymphocyte predominance type stage	lymphoma

HLGT	Preferred Term	Site
	iii	
	hodgkin's disease lymphocyte predominance type stage iv	lymphoma
	hodgkin's disease lymphocyte predominance type stage unspecified	lymphoma
	hodgkin's disease mixed cellularity recurrent	lymphoma
	hodgkin's disease mixed cellularity refractory	lymphoma
	hodgkin's disease mixed cellularity stage i site unspecified	lymphoma
	hodgkin's disease mixed cellularity stage i subdiaphragmatic	lymphoma
	hodgkin's disease mixed cellularity stage i supradiaphragmatic	lymphoma
	hodgkin's disease mixed cellularity stage ii subdiaphragmatic	lymphoma
	hodgkin's disease mixed cellularity stage ii supradiaphragmatic	lymphoma
	hodgkin's disease mixed cellularity stage iii	lymphoma
	hodgkin's disease mixed cellularity stage iv	lymphoma
	hodgkin's disease mixed cellularity stage unspecified	lymphoma
	hodgkin's disease nodular sclerosis recurrent	lymphoma
	hodgkin's disease nodular sclerosis refractory	lymphoma
	hodgkin's disease nodular sclerosis stage i site unspecified	lymphoma
	hodgkin's disease nodular sclerosis stage i subdiaphragmatic	lymphoma
	hodgkin's disease nodular sclerosis stage i supradiaphragmatic	lymphoma
	hodgkin's disease nodular sclerosis stage ii subdiaphragmatic	lymphoma
	hodgkin's disease nodular sclerosis stage ii supradiaphragmatic	lymphoma
	hodgkin's disease nodular sclerosis stage iii	lymphoma
	hodgkin's disease nodular sclerosis stage iv	lymphoma
	hodgkin's disease nodular sclerosis stage unspecified	lymphoma
	hodgkin's disease recurrent	lymphoma
	hodgkin's disease refractory	lymphoma
	hodgkin's disease stage i	lymphoma
	hodgkin's disease stage ii	lymphoma
	hodgkin's disease stage iii	lymphoma
	hodgkin's disease stage iv	lymphoma
	hodgkin's disease unclassifiable	lymphoma
lymphomas nec	central nervous system lymphoma	lymphoma
	disseminated large cell lymphoma	lymphoma
	lymph node cancer metastatic	breast
	lymphocytic lymphoma	lymphoma
	lymphoma	lymphoma
	lymphoma aids related	lymphoma
	lymphoma transformation	lymphoma
	malignant lymphoid neoplasm	lymphoma

HLGT	Preferred Term	Site
	malignant lymphoma unclassifiable high grade	lymphoma
	malignant lymphoma unclassifiable low grade	lymphoma
lymphomas non-hodgkin's b-cell	b-cell lymphoma	lymphoma
	b-cell lymphoma recurrent	lymphoma
	b-cell lymphoma refractory	lymphoma
	b-cell lymphoma stage i	lymphoma
	b-cell lymphoma stage ii	lymphoma
	b-cell lymphoma stage iii	lymphoma
	b-cell lymphoma stage iv	lymphoma
	b-cell small lymphocytic lymphoma	lymphoma
	b-cell small lymphocytic lymphoma recurrent	lymphoma
	b-cell small lymphocytic lymphoma refractory	lymphoma
	b-cell small lymphocytic lymphoma stage i	lymphoma
	b-cell small lymphocytic lymphoma stage ii	lymphoma
	b-cell small lymphocytic lymphoma stage iii	lymphoma
	b-cell small lymphocytic lymphoma stage iv	lymphoma
	b-cell unclassifiable lymphoma high grade	lymphoma
	b-cell unclassifiable lymphoma low grade	lymphoma
	burkitt's lymphoma	lymphoma
	burkitt's lymphoma recurrent	lymphoma
	burkitt's lymphoma refractory	lymphoma
	burkitt's lymphoma stage i	lymphoma
	burkitt's lymphoma stage ii	lymphoma
	burkitt's lymphoma stage iii	lymphoma
	burkitt's lymphoma stage iv	lymphoma
	diffuse large b-cell lymphoma	lymphoma
	diffuse large b-cell lymphoma recurrent	lymphoma
	diffuse large b-cell lymphoma refractory	lymphoma
	diffuse large b-cell lymphoma stage i	lymphoma
	diffuse large b-cell lymphoma stage ii	lymphoma
	diffuse large b-cell lymphoma stage iii	lymphoma
	diffuse large b-cell lymphoma stage iv	lymphoma
	extranodal marginal zone b-cell lymphoma (malt type)	lymphoma
	extranodal marginal zone b-cell lymphoma (malt type) recurrent	lymphoma
	extranodal marginal zone b-cell lymphoma (malt type) refractory	lymphoma
	extranodal marginal zone b-cell lymphoma (malt type) stage i	lymphoma
	extranodal marginal zone b-cell lymphoma (malt type) stage ii	lymphoma
	extranodal marginal zone b-cell lymphoma (malt type) stage iii	lymphoma
	extranodal marginal zone b-cell lymphoma (malt type) stage iv	lymphoma
	follicle centre lymphoma diffuse small cell lymphoma	lymphoma
	follicle centre lymphoma diffuse small cell lymphoma recurrent	lymphoma
	follicle centre lymphoma diffuse small cell lymphoma	lymphoma

HLGT	Preferred Term	Site
	refractory	
	follicle centre lymphoma diffuse small cell lymphoma stage i	lymphoma
	follicle centre lymphoma diffuse small cell lymphoma stage ii	lymphoma
	follicle centre lymphoma diffuse small cell lymphoma stage iii	lymphoma
	follicle centre lymphoma diffuse small cell lymphoma stage iv	lymphoma
	follicle centre lymphoma, follicular grade i, ii, iii	lymphoma
	follicle centre lymphoma, follicular grade i, ii, iii recurrent	lymphoma
	follicle centre lymphoma, follicular grade i, ii, iii refractory	lymphoma
	follicle centre lymphoma, follicular grade i, ii, iii stage i	lymphoma
	follicle centre lymphoma, follicular grade i, ii, iii stage ii	lymphoma
	follicle centre lymphoma, follicular grade i, ii, iii stage iii	lymphoma
	follicle centre lymphoma, follicular grade i, ii, iii stage iv	lymphoma
	high grade b-cell lymphoma burkitt-like lymphoma	lymphoma
	high grade b-cell lymphoma burkitt-like lymphoma recurrent	lymphoma
	high grade b-cell lymphoma burkitt-like lymphoma refractory	lymphoma
	high grade b-cell lymphoma burkitt-like lymphoma stage i	lymphoma
	high grade b-cell lymphoma burkitt-like lymphoma stage ii	lymphoma
	high grade b-cell lymphoma burkitt-like lymphoma stage iii	lymphoma
	high grade b-cell lymphoma burkitt-like lymphoma stage iv	lymphoma
	lymphoma cutis	lymphoma
	lymphoplasmacytoid lymphoma/immunocytoma	lymphoma
	lymphoplasmacytoid lymphoma/immunocytoma recurrent	lymphoma
	lymphoplasmacytoid lymphoma/immunocytoma refractory	lymphoma
	lymphoplasmacytoid lymphoma/immunocytoma stage i	lymphoma
	lymphoplasmacytoid lymphoma/immunocytoma stage ii	lymphoma
	lymphoplasmacytoid lymphoma/immunocytoma stage iii	lymphoma
	lymphoplasmacytoid lymphoma/immunocytoma stage iv	lymphoma
	mantle cell lymphoma	lymphoma
	mantle cell lymphoma recurrent	lymphoma
	mantle cell lymphoma refractory	lymphoma
	mantle cell lymphoma stage i	lymphoma
	mantle cell lymphoma stage ii	lymphoma
	mantle cell lymphoma stage iii	lymphoma
	mantle cell lymphoma stage iv	lymphoma
	nodal marginal zone b-cell lymphoma	lymphoma
	nodal marginal zone b-cell lymphoma recurrent	lymphoma
	nodal marginal zone b-cell lymphoma refractory	lymphoma

HLGT	Preferred Term	Site
	nodal marginal zone b-cell lymphoma stage i	lymphoma
	nodal marginal zone b-cell lymphoma stage ii	lymphoma
	nodal marginal zone b-cell lymphoma stage iii	lymphoma
	nodal marginal zone b-cell lymphoma stage iv	lymphoma
	precursor b-lymphoblastic lymphoma	lymphoma
	precursor b-lymphoblastic lymphoma recurrent	lymphoma
	precursor b-lymphoblastic lymphoma refractory	lymphoma
	precursor b-lymphoblastic lymphoma stage i	lymphoma
	precursor b-lymphoblastic lymphoma stage ii	lymphoma
	precursor b-lymphoblastic lymphoma stage iii	lymphoma
	precursor b-lymphoblastic lymphoma stage iv	lymphoma
	primary effusion lymphoma	lymphoma
	primary mediastinal large b-cell lymphoma	lymphoma
	primary mediastinal large b-cell lymphoma recurrent	lymphoma
	primary mediastinal large b-cell lymphoma refractory	lymphoma
	primary mediastinal large b-cell lymphoma stage i	lymphoma
	primary mediastinal large b-cell lymphoma stage ii	lymphoma
	primary mediastinal large b-cell lymphoma stage iii	lymphoma
	primary mediastinal large b-cell lymphoma stage iv	lymphoma
	splenic marginal zone lymphoma	lymphoma
	splenic marginal zone lymphoma recurrent	lymphoma
	splenic marginal zone lymphoma refractory	lymphoma
	splenic marginal zone lymphoma stage i	lymphoma
	splenic marginal zone lymphoma stage ii	lymphoma
	splenic marginal zone lymphoma stage iii	lymphoma
	splenic marginal zone lymphoma stage iv	lymphoma
	waldenstrom's macroglobulinaemia	myeloma
	waldenstrom's macroglobulinaemia recurrent	myeloma
	waldenstrom's macroglobulinaemia refractory	myeloma
	waldenstrom's macroglobulinaemia stage i	myeloma
	waldenstrom's macroglobulinaemia stage ii	myeloma
	waldenstrom's macroglobulinaemia stage iii	myeloma
	waldenstrom's macroglobulinaemia stage iv	myeloma
lymphomas non-hodgkin's t-cell	adult t-cell lymphoma/leukaemia	leukemia
	adult t-cell lymphoma/leukaemia recurrent	leukemia
	adult t-cell lymphoma/leukaemia refractory	leukemia
	adult t-cell lymphoma/leukaemia stage i	leukemia
	adult t-cell lymphoma/leukaemia stage ii	leukemia
	adult t-cell lymphoma/leukaemia stage iii	leukemia
	adult t-cell lymphoma/leukaemia stage iv	leukemia
	anaplastic large cell lymphoma t- and null-cell types	lymphoma
	anaplastic large cell lymphoma t- and null-cell types recurrent	lymphoma
	anaplastic large cell lymphoma t- and null-cell types refractory	lymphoma
	anaplastic large cell lymphoma t- and null-cell types stage i	lymphoma
	anaplastic large cell lymphoma t- and null-cell types	lymphoma

HLGT	Preferred Term	Site
	stage ii	
	anaplastic large cell lymphoma t- and null-cell types stage iii	lymphoma
	anaplastic large cell lymphoma t- and null-cell types stage iv	lymphoma
	angiocentric lymphoma	lymphoma
	angiocentric lymphoma recurrent	lymphoma
	angiocentric lymphoma refractory	lymphoma
	angiocentric lymphoma stage i	lymphoma
	angiocentric lymphoma stage ii	lymphoma
	angiocentric lymphoma stage iii	lymphoma
	angiocentric lymphoma stage iv	lymphoma
	angioimmunoblastic t-cell lymphoma	lymphoma
	angioimmunoblastic t-cell lymphoma recurrent	lymphoma
	angioimmunoblastic t-cell lymphoma refractory	lymphoma
	angioimmunoblastic t-cell lymphoma stage i	lymphoma
	angioimmunoblastic t-cell lymphoma stage ii	lymphoma
	angioimmunoblastic t-cell lymphoma stage iii	lymphoma
	angioimmunoblastic t-cell lymphoma stage iv	lymphoma
	extranodal nk/t-cell lymphoma, nasal type	lymphoma
	hepatosplenic t-cell lymphoma	lymphoma
	intestinal t-cell lymphoma	lymphoma
	intestinal t-cell lymphoma recurrent	lymphoma
	intestinal t-cell lymphoma refractory	lymphoma
	intestinal t-cell lymphoma stage i	lymphoma
	intestinal t-cell lymphoma stage ii	lymphoma
	intestinal t-cell lymphoma stage iii	lymphoma
	intestinal t-cell lymphoma stage iv	lymphoma
	mycosis fungoides	lymphoma
	mycosis fungoides recurrent	lymphoma
	mycosis fungoides refractory	lymphoma
	mycosis fungoides stage i	lymphoma
	mycosis fungoides stage ii	lymphoma
	mycosis fungoides stage iii	lymphoma
	mycosis fungoides stage iv	lymphoma
	natural killer-cell lymphoblastic lymphoma	lymphoma
	peripheral t-cell lymphoma unspecified	lymphoma
	peripheral t-cell lymphoma unspecified recurrent	lymphoma
	peripheral t-cell lymphoma unspecified refractory	lymphoma
	peripheral t-cell lymphoma unspecified stage i	lymphoma
	peripheral t-cell lymphoma unspecified stage ii	lymphoma
	peripheral t-cell lymphoma unspecified stage iii	lymphoma
	peripheral t-cell lymphoma unspecified stage iv	lymphoma
	precursor t-lymphoblastic lymphoma/leukaemia	leukemia
	precursor t-lymphoblastic lymphoma/leukaemia recurrent	leukemia
	precursor t-lymphoblastic lymphoma/leukaemia refractory	leukemia

HLGT	Preferred Term	Site
	precursor t-lymphoblastic lymphoma/leukaemia stage i	leukemia
	precursor t-lymphoblastic lymphoma/leukaemia stage ii	leukemia
	precursor t-lymphoblastic lymphoma/leukaemia stage iii	leukemia
	precursor t-lymphoblastic lymphoma/leukaemia stage iv	leukemia
	t-cell lymphoma	lymphoma
	t-cell lymphoma recurrent	lymphoma
	t-cell lymphoma refractory	lymphoma
	t-cell lymphoma stage i	lymphoma
	t-cell lymphoma stage ii	lymphoma
	t-cell lymphoma stage iii	lymphoma
	t-cell lymphoma stage iv	lymphoma
	t-cell unclassifiable lymphoma high grade	lymphoma
	t-cell unclassifiable lymphoma low grade	lymphoma
lymphomas non-hodgkin's unspecified histology	immunoblastic lymphoma	lymphoma
	leukaemic lymphoma	leukemia
	non-hodgkin's lymphoma	lymphoma
	non-hodgkin's lymphoma recurrent	lymphoma
	non-hodgkin's lymphoma refractory	lymphoma
	non-hodgkin's lymphoma stage i	lymphoma
	non-hodgkin's lymphoma stage ii	lymphoma
	non-hodgkin's lymphoma stage iii	lymphoma
	non-hodgkin's lymphoma stage iv	lymphoma
	non-hodgkin's lymphoma transformed recurrent	lymphoma
	non-hodgkin's lymphoma unspecified histology aggressive	lymphoma
	non-hodgkin's lymphoma unspecified histology aggressive recurrent	lymphoma
	non-hodgkin's lymphoma unspecified histology aggressive refractory	lymphoma
	non-hodgkin's lymphoma unspecified histology aggressive stage i	lymphoma
	non-hodgkin's lymphoma unspecified histology aggressive stage ii	lymphoma
	non-hodgkin's lymphoma unspecified histology aggressive stage iii	lymphoma
	non-hodgkin's lymphoma unspecified histology aggressive stage iv	lymphoma
	non-hodgkin's lymphoma unspecified histology indolent	lymphoma
	non-hodgkin's lymphoma unspecified histology indolent stage i	lymphoma
	non-hodgkin's lymphoma unspecified histology indolent stage ii	lymphoma
	non-hodgkin's lymphoma unspecified histology indolent stage iii	lymphoma
	non-hodgkin's lymphoma unspecified histology indolent stage iv	lymphoma
	plasmablastic lymphoma	lymphoma
mesotheliomas	mesothelioma	mesothelioma
	mesothelioma malignancy unspecified	mesothelioma
	mesothelioma malignant	mesothelioma

HLGT	Preferred Term	Site
	mesothelioma malignant advanced	mesothelioma
	mesothelioma malignant recurrent	mesothelioma
	pericardial mesothelioma malignant advanced	other
	pericardial mesothelioma malignant localised	other
	pericardial mesothelioma malignant recurrent	other
	peritoneal mesothelioma malignant	other
	peritoneal mesothelioma malignant advanced	other
	peritoneal mesothelioma malignant recurrent	other
	pleural mesothelioma	mesothelioma
	pleural mesothelioma malignant	mesothelioma
	pleural mesothelioma malignant advanced	mesothelioma
	pleural mesothelioma malignant recurrent	mesothelioma
metastases	lymphangiosis carcinomatosa	unknown
	metastases to abdominal cavity	unknown
	metastases to abdominal wall	unknown
	metastases to adrenals	unknown
	metastases to biliary tract	unknown
	metastases to bladder	unknown
	metastases to bone	unknown
	metastases to bone marrow	unknown
	metastases to breast	unknown
	metastases to central nervous system	unknown
	metastases to chest wall	unknown
	metastases to diaphragm	unknown
	metastases to eustachian tube	unknown
	metastases to eye	unknown
	metastases to fallopian tube	unknown
	metastases to gallbladder	unknown
	metastases to gastrointestinal tract	unknown
	metastases to heart	unknown
	metastases to kidney	unknown
	metastases to large intestine	unknown
	metastases to larynx	unknown
	metastases to liver	unknown
	metastases to lung	unknown
	metastases to lymph nodes	unknown
	metastases to meninges	unknown
	metastases to mouth	unknown
	metastases to muscle	unknown
	metastases to nasal sinuses	unknown
	metastases to neck	unknown
	metastases to nervous system	unknown
	metastases to oesophagus	unknown
	metastases to ovary	unknown
	metastases to pancreas	unknown
	metastases to penis	unknown
	metastases to perineum	unknown

HLGT	Preferred Term	Site
	metastases to peripheral nervous system	unknown
	metastases to peripheral vascular system	unknown
	metastases to peritoneum	unknown
	metastases to pharynx	unknown
	metastases to pituitary gland	pituitary
	metastases to placenta	unknown
	metastases to pleura	unknown
	metastases to prostate	unknown
	metastases to rectum	unknown
	metastases to reproductive organ	unknown
	metastases to retroperitoneum	unknown
	metastases to salivary gland	unknown
	metastases to skin	unknown
	metastases to small intestine	unknown
	metastases to soft tissue	unknown
	metastases to spine	unknown
	metastases to spleen	unknown
	metastases to stomach	unknown
	metastases to testicle	unknown
	metastases to the mediastinum	unknown
	metastases to the respiratory system	unknown
	metastases to thorax	unknown
	metastases to thyroid	unknown
	metastases to trachea	unknown
	metastases to urinary tract	unknown
	metastases to uterus	unknown
	metastasis	unknown
miscellaneous and site unspecified neoplasms malignant and unspecified	abdominal neoplasm	unknown
	adenocarcinoma	unknown
	adenoid cystic carcinoma	other
	angiosarcoma	sarcoma
	angiosarcoma metastatic	sarcoma
	angiosarcoma non-metastatic	sarcoma
	angiosarcoma recurrent	sarcoma
	basosquamous carcinoma	skin
	cancer in remission	unknown
	carcinoma in situ	unknown
	cardiac neoplasm malignant	other
	cardiac neoplasm unspecified	other
	cardiac teratoma	other
	cartilage neoplasm	sarcoma
	choriocarcinoma	other
	congenital teratoma	other
	ear neoplasm	skin
	ear neoplasm malignant	skin
	erythroplasia	skin
	extragonadal primary embryonal carcinoma	other

HLGT	Preferred Term	Site
	extragonadal primary germ cell cancer	germ cell
	extragonadal primary germ cell tumour mixed stage i	germ cell
	extragonadal primary germ cell tumour mixed stage ii	germ cell
	extragonadal primary germ cell tumour mixed stage iii	germ cell
	extragonadal primary malignant teratoma	other
	extragonadal primary non-seminoma	other
	extragonadal primary non-seminoma stage i	other
	extragonadal primary non-seminoma stage ii	other
	extragonadal primary non-seminoma stage iii	other
	extragonadal primary non-seminoma stage iv	other
	extragonadal primary seminoma (pure) stage i	testes
	extragonadal primary seminoma (pure) stage ii	testes
	extragonadal primary seminoma (pure) stage iii	testes
	extragonadal primary seminoma (pure) stage iv	testes
	germ cell cancer	germ cell
	gestational trophoblastic tumour	uterus
	granular cell tumour	unknown
	haemangiopericytoma	sarcoma
	head and neck cancer	head & neck
	malignant haemangiopericytoma	sarcoma
	malignant haemangiopericytoma metastatic	sarcoma
	malignant haemangiopericytoma non-metastatic	sarcoma
	malignant haemangiopericytoma recurrent	sarcoma
	malignant hydatidiform mole	uterus
	malignant melanoma of sites other than skin	melanoma
	malignant middle ear neoplasm	other
	malignant neoplasm of auricular cartilage	sarcoma
	malignant neoplasm progression	unknown
	malignant pericardial neoplasm	other
	malignant transformation	unknown
	metastatic neoplasm	unknown
	metastatic squamous cell carcinoma	squamous
	mucoepidermoid carcinoma	head & neck
	neoplasm	unknown
	neoplasm malignant	unknown
	neoplasm progression	unknown
	neoplasm recurrence	unknown
	otic cancer metastatic	other
	pelvic neoplasm	unknown
	pericardial neoplasm	other
	pseudosarcoma	esophagus
	queyrat erythroplasia	penis
	recurrent cancer	unknown
	signet-ring cell carcinoma	colon
	small cell carcinoma	unknown
	smooth muscle cell neoplasm	sarcoma
	squamous cell carcinoma	squamous

HLGT	Preferred Term	Site
	stewart-treves syndrome	sarcoma
	teratoma	unknown
	tumour invasion	unknown
	vascular neoplasm	other
	yolk sac tumour site unspecified	other
nervous system neoplasms benign	astrocytoma, low grade	brain
	brain neoplasm benign	brain
	brain stem glioma benign	brain
	craniopharyngioma benign	brain
	haemangioblastoma	brain
	meningioma benign	brain
	oligodendroglioma benign	brain
	spinal meningioma benign	brain
nervous system neoplasms malignant and unspecified nec	aesthesioneuroblastoma	head & neck
	anaplastic astrocytoma	brain
	astrocytoma	brain
	astrocytoma malignant	brain
	brain cancer metastatic	unknown
	brain neoplasm	brain
	brain neoplasm malignant	brain
	brain stem glioma	brain
	brain teratoma	brain
	carotid body tumour	other
	central nervous system dermoid tumour	brain
	central nervous system leukaemia	leukemia
	central nervous system neoplasm	brain
	cerebellar tumour	brain
	cerebral neuroblastoma	brain
	choroid plexus carcinoma	other
	cns germinoma	brain
	ependymoma	brain
	ependymoma malignant	brain
	ganglioneuroblastoma	other
	glioblastoma	brain
	glioblastoma multiforme	brain
	glioma	brain
	gliomatosis cerebri	brain
	glioneuronal tumour	other
	gliosarcoma	sarcoma
	haemangiopericytoma of meninges	sarcoma
	intracranial meningioma malignant	melanoma
	malignant cranial nerve neoplasm	brain
	malignant glioma	brain
	malignant neoplasm of spinal cord	brain
	malignant nervous system neoplasm	other
	malignant oligodendroglioma	brain
	medulloblastoma	brain

HLGT	Preferred Term	Site
	medulloblastoma recurrent	brain
	melanomatous meningitis	melanoma
	meningeal neoplasm	brain
	meningioma	brain
	meningioma malignant	brain
	metastatic glioma	brain
	mixed astrocytoma-ependymoma	brain
	mixed oligo-astrocytoma	brain
	neonatal neuroblastoma	other
	nervous system neoplasm	other
	neurilemmoma	other
	neurilemmoma malignant	lung
	neuroblastoma	other
	neuroblastoma recurrent	other
	neuroectodermal neoplasm	other
	nongerminomatous germ cell tumour of the cns	brain
	non-secretory adenoma of pituitary	pituitary
	oligodendroglioma	brain
	optic nerve glioma	eye
	peripheral nervous system neoplasm	other
	pineal germinoma	brain
	pineal neoplasm	brain
	pineal parenchymal neoplasm malignant	brain
	pinealoblastoma	brain
	pinealoma	brain
	pineocytoma	brain
	primitive neuroectodermal tumour	other
	secretory adenoma of pituitary	pituitary
	spinal cord neoplasm	unknown
	spinal meningioma malignant	brain
ocular neoplasms	carcinoma in situ of eye	eye
	choroid melanoma	melanoma
	choroid neoplasm	other
	conjunctival melanoma	melanoma
	conjunctival neoplasm	eye
	conjunctival primary acquired melanosis	eye
	extraocular retinoblastoma	eye
	eyelid tumour	skin
	intraocular melanoma	melanoma
	intraocular retinoblastoma	eye
	iris neoplasm	eye
	iritic melanoma	melanoma
	lacrimal duct neoplasm	eye
	malignant melanoma of eyelid	melanoma
	malignant neoplasm of choroid	eye
	malignant neoplasm of conjunctiva	eye
	malignant neoplasm of cornea	eye

HLGT	Preferred Term	Site
	malignant neoplasm of eye	eye
	malignant neoplasm of eyelid	skin
	malignant neoplasm of lacrimal duct	eye
	malignant neoplasm of lacrimal gland	eye
	malignant neoplasm of orbit	eye
	malignant neoplasm of retina	eye
	metastatic ocular melanoma	melanoma
	neoplasm of cornea unspecified malignancy	eye
	neoplasm of orbit	eye
	ocular cancer metastatic	eye
	ocular haemangiopericytoma	eye
	ocular neoplasm	eye
	optic nerve neoplasm	eye
	optic tract glioma	eye
	retinal melanoma	melanoma
	retinal neoplasm	eye
	retinoblastoma	eye
	retinoblastoma bilateral	eye
	retinoblastoma unilateral	eye
	retro-orbital neoplasm	eye
plasma cell neoplasms	gammopathy	myeloma
	heavy chain disease	myeloma
	leukaemia plasmacytic	leukemia
	leukaemia plasmacytic (in remission)	leukemia
	light chain disease	myeloma
	multiple myeloma	myeloma
	myeloma recurrence	myeloma
	paraproteinaemia	myeloma
	plasmacytoma	myeloma
renal and urinary tract neoplasms malignant and unspecified	bladder adenocarcinoma recurrent	bladder
	bladder adenocarcinoma stage 0	bladder
	bladder adenocarcinoma stage i	bladder
	bladder adenocarcinoma stage ii	bladder
	bladder adenocarcinoma stage iii	bladder
	bladder adenocarcinoma stage iv	bladder
	bladder adenocarcinoma stage unspecified	bladder
	bladder cancer	bladder
	bladder cancer recurrent	bladder
	bladder cancer stage 0, with cancer in situ	bladder
	bladder cancer stage 0, without cancer in situ	bladder
	bladder cancer stage i, with cancer in situ	bladder
	bladder cancer stage i, without cancer in situ	bladder
	bladder cancer stage ii	bladder
	bladder cancer stage iii	bladder
	bladder cancer stage iv	bladder
	bladder neoplasm	bladder
	bladder squamous cell carcinoma recurrent	bladder

HLGT	Preferred Term	Site
	bladder squamous cell carcinoma stage 0	bladder
	bladder squamous cell carcinoma stage i	bladder
	bladder squamous cell carcinoma stage ii	bladder
	bladder squamous cell carcinoma stage iii	bladder
	bladder squamous cell carcinoma stage iv	bladder
	bladder squamous cell carcinoma stage unspecified	bladder
	bladder transitional cell carcinoma	bladder
	bladder transitional cell carcinoma recurrent	bladder
	bladder transitional cell carcinoma stage 0	bladder
	bladder transitional cell carcinoma stage i	bladder
	bladder transitional cell carcinoma stage ii	bladder
	bladder transitional cell carcinoma stage iii	bladder
	bladder transitional cell carcinoma stage iv	bladder
	carcinoma in situ of bladder	bladder
	clear cell sarcoma of the kidney	sarcoma
	hereditary leiomyomatosis renal cell carcinoma	kidney
	hereditary papillary renal carcinoma	kidney
	malignant neoplasm of paraurethral glands	bladder
	malignant neoplasm of renal pelvis	kidney
	malignant urinary tract neoplasm	bladder
	metastatic carcinoma of the bladder	bladder
	metastatic renal cell carcinoma	kidney
	nephroblastoma	kidney
	non-renal cell carcinoma of kidney	kidney
	renal cancer	kidney
	renal cancer metastatic	kidney
	renal cancer recurrent	kidney
	renal cancer stage i	kidney
	renal cancer stage ii	kidney
	renal cancer stage iii	kidney
	renal cancer stage iv	kidney
	renal cell carcinoma	kidney
	renal cell carcinoma recurrent	kidney
	renal cell carcinoma stage i	kidney
	renal cell carcinoma stage ii	kidney
	renal cell carcinoma stage iii	kidney
	renal cell carcinoma stage iv	kidney
	renal neoplasm	kidney
	rhabdoid tumour of the kidney	kidney
	transitional cell cancer of renal pelvis and ureter metastatic	bladder
	transitional cell cancer of the renal pelvis and ureter	bladder
	transitional cell cancer of the renal pelvis and ureter localised	bladder
	transitional cell cancer of the renal pelvis and ureter recurrent	bladder
	transitional cell cancer of the renal pelvis and ureter regional	bladder

HLGT	Preferred Term	Site
	transitional cell carcinoma	bladder
	ureteral neoplasm	bladder
	ureteric cancer	bladder
	ureteric cancer local	bladder
	ureteric cancer metastatic	bladder
	ureteric cancer recurrent	bladder
	ureteric cancer regional	bladder
	urethral cancer	bladder
	urethral cancer local	bladder
	urethral cancer metastatic	bladder
	urethral cancer recurrent	bladder
	urethral cancer regional	bladder
	urethral neoplasm	bladder
	urinary tract carcinoma in situ	bladder
	urinary tract neoplasm	bladder
reproductive and genitourinary neoplasms gender unspecified nec	buschke-lowenstein's tumour	other
	genitourinary tract neoplasm	unknown
reproductive neoplasms female malignant and unspecified	adenocarcinoma of the cervix	cervix
	adenosquamous carcinoma of the cervix	cervix
	borderline ovarian tumour	ovary
	cervix cancer metastatic	cervix
	cervix carcinoma	cervix
	cervix carcinoma recurrent	cervix
	cervix carcinoma stage 0	cervix
	cervix carcinoma stage i	cervix
	cervix carcinoma stage ii	cervix
	cervix carcinoma stage iii	cervix
	cervix carcinoma stage iv	cervix
	cervix neoplasm	cervix
	clear cell endometrial carcinoma	uterus
	endometrial cancer	uterus
	endometrial cancer metastatic	uterus
	endometrial cancer recurrent	uterus
	endometrial cancer stage 0	uterus
	endometrial cancer stage i	uterus
	endometrial cancer stage ii	uterus
	endometrial cancer stage iii	uterus
	endometrial cancer stage iv	uterus
	endometrial neoplasm	uterus
	endometrial sarcoma	uterus
	endometrial sarcoma metastatic	uterus
	endometrial sarcoma recurrent	uterus
	erythroplasia of vulva	skin
	fallopian tube cancer	ovary
	fallopian tube cancer metastatic	uterus

HLGT	Preferred Term	Site
	fallopian tube cancer stage i	uterus
	fallopian tube cancer stage ii	uterus
	fallopian tube cancer stage iii	uterus
	fallopian tube cancer stage iv	uterus
	fallopian tube neoplasm	uterus
	female reproductive neoplasm	unknown
	female reproductive tract carcinoma in situ	unknown
	genital neoplasm malignant female	unknown
	malignant neoplasm of placenta	uterus
	malignant neoplasm of uterine adnexa	ovary
	malignant ovarian cyst	ovary
	metastatic uterine cancer	uterus
	mucinous endometrial carcinoma	uterus
	mueller's mixed tumour	uterus
	ovarian cancer	ovary
	ovarian cancer metastatic	ovary
	ovarian cancer recurrent	ovary
	ovarian dysgerminoma stage i	ovary
	ovarian dysgerminoma stage ii	ovary
	ovarian dysgerminoma stage iii	ovary
	ovarian dysgerminoma stage iv	ovary
	ovarian dysgerminoma stage unspecified	ovary
	ovarian embryonal carcinoma	ovary
	ovarian epithelial cancer	ovary
	ovarian epithelial cancer metastatic	ovary
	ovarian epithelial cancer recurrent	ovary
	ovarian epithelial cancer stage i	ovary
	ovarian epithelial cancer stage ii	ovary
	ovarian epithelial cancer stage iii	ovary
	ovarian epithelial cancer stage iv	ovary
	ovarian germ cell cancer	ovary
	ovarian germ cell cancer stage i	ovary
	ovarian germ cell cancer stage ii	ovary
	ovarian germ cell cancer stage iii	ovary
	ovarian germ cell cancer stage iv	ovary
	ovarian germ cell choriocarcinoma stage i	ovary
	ovarian germ cell choriocarcinoma stage ii	ovary
	ovarian germ cell choriocarcinoma stage iii	ovary
	ovarian germ cell choriocarcinoma stage iv	ovary
	ovarian germ cell embryonal carcinoma stage i	ovary
	ovarian germ cell embryonal carcinoma stage ii	ovary
	ovarian germ cell embryonal carcinoma stage iii	ovary
	ovarian germ cell embryonal carcinoma stage iv	ovary
	ovarian germ cell endodermal sinus tumour stage i	ovary
	ovarian germ cell endodermal sinus tumour stage ii	ovary
	ovarian germ cell endodermal sinus tumour stage iii	ovary
	ovarian germ cell endodermal sinus tumour stage iv	ovary

HLGT	Preferred Term	Site
	ovarian germ cell polyembryoma stage i	ovary
	ovarian germ cell polyembryoma stage ii	ovary
	ovarian germ cell polyembryoma stage iii	ovary
	ovarian germ cell polyembryoma stage iv	ovary
	ovarian germ cell teratoma stage i	ovary
	ovarian germ cell teratoma stage ii	ovary
	ovarian germ cell teratoma stage iii	ovary
	ovarian germ cell teratoma stage iv	ovary
	ovarian granulosa-theca cell tumour	ovary
	ovarian low malignant potential tumour	ovary
	ovarian neoplasm	ovary
	ovarian stromal cancer	ovary
	paget's disease of the vulva	skin
	papillary serous endometrial carcinoma	uterus
	placental neoplasm	other
	small cell carcinoma of the cervix	cervix
	squamous cell carcinoma of the cervix	cervix
	squamous endometrial carcinoma	uterus
	uterine cancer	uterus
	uterine carcinoma in situ	uterus
	uterine neoplasm	uterus
	vaginal cancer	vagina
	vaginal cancer metastatic	vagina
	vaginal cancer recurrent	vagina
	vaginal cancer stage 0	vagina
	vaginal cancer stage i	vagina
	vaginal cancer stage ii	vagina
	vaginal cancer stage iii	vagina
	vaginal cancer stage iva	vagina
	vaginal cancer stage ivb	vagina
	vaginal neoplasm	vagina
	vulval cancer	vulva
	vulval cancer metastatic	vulva
	vulval cancer recurrent	vulva
	vulval cancer stage 0	vulva
	vulval cancer stage i	vulva
	vulval cancer stage ii	vulva
	vulval cancer stage iii	vulva
	vulval cancer stage iv	vulva
	vulval neoplasm	vulva
reproductive neoplasms male malignant and unspecified	carcinoma in situ of penis	penis
	erythroplasia of penis	skin
	genital neoplasm malignant male	prostate
	male reproductive tract carcinoma in situ	prostate
	male reproductive tract neoplasm	prostate
	malignant neoplasm of epididymis	testes
	malignant neoplasm of seminal vesicle	testes

HLGT	Preferred Term	Site
	malignant neoplasm of spermatic cord	testes
	neoplasm prostate	prostate
	paget's disease of penis	penis
	penile malignant neoplasm	penis
	penile neoplasm	penis
	penis carcinoma	penis
	penis carcinoma metastatic	penis
	penis carcinoma recurrent	penis
	penis carcinoma stage i	penis
	penis carcinoma stage ii	penis
	penis carcinoma stage iii	penis
	penis carcinoma stage iv	penis
	prostate cancer	prostate
	prostate cancer metastatic	prostate
	prostate cancer recurrent	prostate
	prostate cancer stage 0	prostate
	prostate cancer stage i	prostate
	prostate cancer stage ii	prostate
	prostate cancer stage iii	prostate
	prostate cancer stage iv	prostate
	scrotal cancer	skin
	seminoma	testes
	teratoma of testis	testes
	testicular cancer metastatic	testes
	testicular choriocarcinoma	testes
	testicular choriocarcinoma stage i	testes
	testicular choriocarcinoma stage ii	testes
	testicular choriocarcinoma stage iii	testes
	testicular embryonal carcinoma	testes
	testicular embryonal carcinoma stage i	testes
	testicular embryonal carcinoma stage ii	testes
	testicular embryonal carcinoma stage iii	testes
	testicular germ cell cancer	testes
	testicular germ cell cancer metastatic	testes
	testicular germ cell tumour mixed stage i	testes
	testicular germ cell tumour mixed stage ii	testes
	testicular germ cell tumour mixed stage iii	testes
	testicular malignant teratoma stage i	testes
	testicular malignant teratoma stage ii	testes
	testicular malignant teratoma stage iii	testes
	testicular neoplasm	testes
	testicular seminoma (pure)	testes
	testicular seminoma (pure) stage i	testes
	testicular seminoma (pure) stage ii	testes
	testicular seminoma (pure) stage iii	testes
	testicular yolk sac tumour stage i	testes
	testicular yolk sac tumour stage ii	testes

HLGT	Preferred Term	Site
	testicular yolk sac tumour stage iii	testes
	testis cancer	testes
respiratory and mediastinal neoplasms malignant and unspecified	adenosquamous cell lung cancer	lung
	adenosquamous cell lung cancer recurrent	lung
	adenosquamous cell lung cancer stage 0	lung
	adenosquamous cell lung cancer stage i	lung
	adenosquamous cell lung cancer stage ii	lung
	adenosquamous cell lung cancer stage iii	lung
	adenosquamous cell lung cancer stage iv	lung
	bronchial carcinoma	lung
	bronchial neoplasm	lung
	bronchioloalveolar carcinoma	lung
	carcinoma in situ of trachea	lung
	diaphragm neoplasm	other
	epiglottic carcinoma	head & neck
	glottis carcinoma	head & neck
	hypopharyngeal cancer	head & neck
	hypopharyngeal cancer recurrent	head & neck
	hypopharyngeal cancer stage 0	head & neck
	hypopharyngeal cancer stage i	head & neck
	hypopharyngeal cancer stage ii	head & neck
	hypopharyngeal cancer stage iii	head & neck
	hypopharyngeal cancer stage iv	head & neck
	hypopharyngeal neoplasm	head & neck
	large cell carcinoma of the respiratory tract stage unspecified	lung
	large cell lung cancer recurrent	lung
	large cell lung cancer stage 0	lung
	large cell lung cancer stage i	lung
	large cell lung cancer stage ii	lung
	large cell lung cancer stage iii	lung
	large cell lung cancer stage iv	lung
	laryngeal cancer	head & neck
	laryngeal cancer recurrent	head & neck
	laryngeal cancer stage 0	head & neck
	laryngeal cancer stage i	head & neck
	laryngeal cancer stage ii	head & neck
	laryngeal cancer stage iii	head & neck
	laryngeal cancer stage iv	head & neck
	laryngeal neoplasm	head & neck
	lung adenocarcinoma	lung
	lung adenocarcinoma metastatic	lung
	lung adenocarcinoma recurrent	lung
	lung adenocarcinoma stage 0	lung
	lung adenocarcinoma stage i	lung
	lung adenocarcinoma stage ii	lung
	lung adenocarcinoma stage iii	lung

HLGT	Preferred Term	Site
	lung adenocarcinoma stage iv	lung
	lung cancer metastatic	lung
	lung carcinoma cell type unspecified recurrent	lung
	lung carcinoma cell type unspecified stage 0	lung
	lung carcinoma cell type unspecified stage i	lung
	lung carcinoma cell type unspecified stage ii	lung
	lung carcinoma cell type unspecified stage iii	lung
	lung carcinoma cell type unspecified stage iv	lung
	lung infiltration malignant	unknown
	lung neoplasm	lung
	lung neoplasm malignant	lung
	lung squamous cell carcinoma recurrent	lung
	lung squamous cell carcinoma stage 0	lung
	lung squamous cell carcinoma stage i	lung
	lung squamous cell carcinoma stage ii	lung
	lung squamous cell carcinoma stage iii	lung
	lung squamous cell carcinoma stage iv	lung
	lung squamous cell carcinoma stage unspecified	lung
	malignant mediastinal neoplasm	lung
	malignant neoplasm of pleura	mesothelioma
	malignant neoplasm of thorax	unknown
	malignant respiratory tract neoplasm	lung
	maxillofacial sinus neoplasm	head & neck
	mediastinum neoplasm	lung
	metastatic bronchial carcinoma	lung
	nasal cavity cancer	head & neck
	nasal neoplasm	head & neck
	nasal sinus cancer	head & neck
	nasopharyngeal cancer	head & neck
	nasopharyngeal cancer recurrent	head & neck
	nasopharyngeal cancer stage 0	head & neck
	nasopharyngeal cancer stage i	head & neck
	nasopharyngeal cancer stage ii	head & neck
	nasopharyngeal cancer stage iii	head & neck
	nasopharyngeal cancer stage iv	head & neck
	neoplasm of thymus	other
	non-small cell lung cancer	lung
	non-small cell lung cancer metastatic	lung
	non-small cell lung cancer recurrent	lung
	non-small cell lung cancer stage 0	lung
	non-small cell lung cancer stage i	lung
	non-small cell lung cancer stage ii	lung
	non-small cell lung cancer stage iii	lung
	non-small cell lung cancer stage iiia	lung
	non-small cell lung cancer stage iiib	lung
	non-small cell lung cancer stage iv	lung
	oropharyngeal cancer recurrent	head & neck

HLGT	Preferred Term	Site
	oropharyngeal cancer stage 0	head & neck
	oropharyngeal cancer stage i	head & neck
	oropharyngeal cancer stage ii	head & neck
	oropharyngeal cancer stage iii	head & neck
	oropharyngeal cancer stage iv	head & neck
	oropharyngeal cancer stage unspecified	head & neck
	pancoast's tumour	lung
	paranasal sinus and nasal cavity malignant neoplasm	head & neck
	paranasal sinus and nasal cavity malignant neoplasm recurrent	head & neck
	paranasal sinus and nasal cavity malignant neoplasm stage 0	head & neck
	paranasal sinus and nasal cavity malignant neoplasm stage i	head & neck
	paranasal sinus and nasal cavity malignant neoplasm stage ii	head & neck
	paranasal sinus and nasal cavity malignant neoplasm stage iii	head & neck
	paranasal sinus and nasal cavity malignant neoplasm stage iv	head & neck
	paranasal sinus neoplasm	head & neck
	pharyngeal cancer metastatic	head & neck
	pharyngeal cancer recurrent	head & neck
	pharyngeal cancer stage 0	head & neck
	pharyngeal cancer stage i	head & neck
	pharyngeal cancer stage ii	head & neck
	pharyngeal cancer stage iii	head & neck
	pharyngeal cancer stage iv	head & neck
	pharyngeal cancer stage unspecified	head & neck
	pharyngeal neoplasm	head & neck
	pleura carcinoma	other
	pleural neoplasm	other
	pleural sarcoma	sarcoma
	postcricoid cancer	head & neck
	respiratory tract carcinoma in situ	lung
	respiratory tract neoplasm	lung
	sinus cancer metastatic	head & neck
	small cell lung cancer extensive stage	lung
	small cell lung cancer limited stage	lung
	small cell lung cancer metastatic	lung
	small cell lung cancer recurrent	lung
	small cell lung cancer stage unspecified	lung
	throat cancer	head & neck
	thymic cancer metastatic	other
	thymoma	other
	thymoma malignant	other
	thymoma malignant recurrent	other

HLGT	Preferred Term	Site
	tonsil cancer	head & neck
	tonsillar neoplasm	head & neck
	tracheal cancer	lung
	tracheal neoplasm	lung
	vocal cord neoplasm	head & neck
skeletal neoplasms malignant and unspecified	bone cancer metastatic	unknown
	bone giant cell tumour	sarcoma
	bone neoplasm	sarcoma
	bone neoplasm malignant	unknown
	bone sarcoma	sarcoma
	chondrosarcoma	sarcoma
	chondrosarcoma metastatic	sarcoma
	chondrosarcoma recurrent	sarcoma
	chordoma	brain
	ewing's sarcoma	sarcoma
	ewing's sarcoma metastatic	sarcoma
	ewing's sarcoma recurrent	sarcoma
	giant cell tumour of tendon sheath	sarcoma
	osteosarcoma localised	sarcoma
	osteosarcoma metastatic	sarcoma
	osteosarcoma recurrent	sarcoma
	peripheral neuroepithelioma of bone	other
	peripheral neuroepithelioma of bone metastatic	other
	peripheral neuroepithelioma of bone recurrent	other
skin neoplasms malignant and unspecified	acral lentiginous melanoma stage i	melanoma
	acral lentiginous melanoma stage ii	melanoma
	acral lentiginous melanoma stage iii	melanoma
	acral lentiginous melanoma stage iv	melanoma
	acral lentiginous melanoma stage unspecified	melanoma
	atypical fibroxanthoma	skin
	basal cell carcinoma	skin
	basosquamous carcinoma of skin	skin
	bowen's disease	skin
	carcinoma in situ of skin	skin
	dysplastic naevus syndrome	skin
	extramammary paget's disease	skin
	lentigo maligna recurrent	melanoma
	lentigo maligna stage i	melanoma
	lentigo maligna stage ii	melanoma
	lentigo maligna stage iii	melanoma
	lentigo maligna stage iv	melanoma
	lentigo maligna stage unspecified	melanoma
	malignant melanoma	melanoma
	malignant melanoma in situ	melanoma
	malignant melanoma stage i	melanoma
	malignant melanoma stage ii	melanoma
	malignant melanoma stage iii	melanoma

HLGT	Preferred Term	Site
	malignant melanoma stage iv	melanoma
	mastocytoma	skin
	melanoma recurrent	melanoma
	metastatic malignant melanoma	melanoma
	neoplasm skin	skin
	neuroendocrine carcinoma of the skin	skin
	paget's disease of skin	skin
	porocarcinoma	other
	skin cancer	skin
	skin cancer metastatic	skin
	skin neoplasm bleeding	skin
	squamous cell carcinoma of skin	skin
	superficial spreading melanoma stage i	melanoma
	superficial spreading melanoma stage ii	melanoma
	superficial spreading melanoma stage iii	melanoma
	superficial spreading melanoma stage iv	melanoma
	superficial spreading melanoma stage unspecified	melanoma
soft tissue neoplasms malignant and unspecified (excl sarcomas)	amyloidoma	unknown
	inflammatory myofibroblastic tumour	unknown
	malignant fibrous histiocytoma	sarcoma
	malignant fibrous histiocytoma metastatic	sarcoma
	malignant fibrous histiocytoma non-metastatic	sarcoma
	malignant fibrous histiocytoma recurrent	sarcoma
	malignant soft tissue neoplasm	sarcoma
	peripheral neuroepithelioma	other
	peripheral neuroepithelioma of soft tissue	other
	tendon neoplasm	sarcoma
soft tissue sarcomas	alveolar soft part sarcoma	sarcoma
	alveolar soft part sarcoma metastatic	sarcoma
	alveolar soft part sarcoma non-metastatic	sarcoma
	alveolar soft part sarcoma recurrent	sarcoma
	congenital fibrosarcoma	sarcoma
	dermatofibrosarcoma	sarcoma
	epithelioid sarcoma	sarcoma
	epithelioid sarcoma metastatic	sarcoma
	epithelioid sarcoma non-metastatic	sarcoma
	epithelioid sarcoma recurrent	sarcoma
	extra-osseous ewing's sarcoma	sarcoma
	extra-osseous ewing's sarcoma metastatic	sarcoma
	extra-osseous ewing's sarcoma nonmetastatic	sarcoma
	extra-osseous ewing's sarcoma recurrent	sarcoma
	extraskeletal chondrosarcoma	sarcoma
	extraskeletal chondrosarcoma metastatic	sarcoma
	extraskeletal chondrosarcoma non-metastatic	sarcoma
	extraskeletal chondrosarcoma recurrent	sarcoma
	extraskeletal osteosarcoma	sarcoma
	extraskeletal osteosarcoma metastatic	sarcoma

HLGT	Preferred Term	Site
	extraskeletal osteosarcoma non-metastatic	sarcoma
	extraskeletal osteosarcoma recurrent	sarcoma
	fibrosarcoma	sarcoma
	fibrosarcoma metastatic	sarcoma
	fibrosarcoma non-metastatic	sarcoma
	kaposi's sarcoma	sarcoma
	kaposi's sarcoma aids related	sarcoma
	kaposi's sarcoma classical type	sarcoma
	leiomyosarcoma	sarcoma
	leiomyosarcoma metastatic	sarcoma
	leiomyosarcoma non-metastatic	sarcoma
	leiomyosarcoma recurrent	sarcoma
	liposarcoma	sarcoma
	liposarcoma metastatic	sarcoma
	liposarcoma non-metastatic	sarcoma
	liposarcoma recurrent	sarcoma
	lymphangiosarcoma	sarcoma
	malignant mesenchymoma	other
	malignant mesenchymoma metastatic	other
	malignant mesenchymoma non-metastatic	other
	malignant mesenchymoma recurrent	other
	malignant muscle neoplasm	sarcoma
	neurofibrosarcoma	sarcoma
	neurofibrosarcoma metastatic	sarcoma
	neurofibrosarcoma non-metastatic	sarcoma
	neurofibrosarcoma recurrent	sarcoma
	rhabdomyosarcoma	sarcoma
	rhabdomyosarcoma recurrent	sarcoma
	sarcoma	sarcoma
	sarcoma metastatic	sarcoma
	sarcoma of skin	sarcoma
	sarcoma uterus	uterus
	sarcomatosis	sarcoma
	small intestine leiomyosarcoma	sarcoma
	spindle cell sarcoma	sarcoma
	synovial sarcoma	sarcoma
	synovial sarcoma metastatic	sarcoma
	synovial sarcoma non-metastatic	sarcoma
	synovial sarcoma recurrent	sarcoma
	testicular leiomyosarcoma	sarcoma
	undifferentiated sarcoma	sarcoma
	urinary bladder sarcoma	sarcoma
	uterine leiomyosarcoma	uterus

Attachment: Comments on Plan

From: Stockbridge, Norman L
Sent: Monday, August 20, 2012 6:04 AM
To: Marciniak, Thomas
Cc: Southworth, Mary Ross; Temple, Robert; Unger, Ellis
Subject: FW: Emailing: ARB ca review plan v1p2.doc

Attachments: ARB ca review plan v1p2.doc

I am replying by forwarding, so some other interested parties have a chance to comment on your proposed patient-level meta-analysis plan if they choose.

For my part, I think you did well in anticipating my major concerns--blinding, multiplicity, what studies to include, what to lump or split, and how the results might influence regulatory decision-making. We aren't likely to agree about how exactly those issues are handled, but I think you did well by addressing each.

As I noted in an email on Aug 4, I do not consider this 90-person-day effort to be worthwhile given the results of the subject-level meta-analysis, so, despite your assertions to the contrary (email of Aug 10), this project is not part of your assigned work. If nonetheless, it obtains findings you think would be of interest, I am sure all of us will be open to reviewing its results.

I assume that, pending completion of your meta-analysis project, there is nothing further you wish to include in reviews of ARB-cancer TSI. We will proceed with steps to close it.
Regards,
Norman

-----Original Message-----
From: Marciniak, Thomas
Sent: Sunday, August 19, 2012 2:31 PM
To: Stockbridge, Norman L
Subject: Emailing: ARB ca review plan v1p2.doc

I've attached an updated plan. Note that it now includes a revision history (at the end of the text following the Reference.) I'll file it after you return from leave pending your final comments.

Tom

-----Original Message-----
From: Marciniak, Thomas
Sent: Friday, August 03, 2012 4:13 PM
To: Stockbridge, Norman L
Subject: Emailing: ARB ca review plan v1p0.doc

Attachments: ARB ca review plan v1p0.doc

There is still much work to do on the stats side of the analysis plan, but I believe the cancer ascertainment plans are most critical and there is plenty to comment uon.

Tom

From: Marciniak, Thomas
Sent: Friday, August 31, 2012 3:08 PM
To: Unger, Ellis
Cc: Southworth, Mary Ross; Temple, Robert; Stockbridge, Norman L
Subject: RE: Emailing: ARB ca review plan v1p2.doc

To address Ellis' comments:

o First, this would represent a lot of man-hours, so I have to assume that there is a paucity of work in the Division at this point, or that you will be doing this mostly after hours.

You are faced with a serious, unanswered question of whether drugs taken by millions of Americans increase cancer rates and you're concerned about 62 to 93 man-days for my entire plan and half of that for trials for which we currently have data? You have already wasted more effort than that on your ill-conceived and poorly executed TSI meta-analysis. Whether or not there is a paucity of work in the Division at this point may be one of your concerns; mine is protecting the public health particularly regarding those drugs for which I have primary responsibility.

O Second, when we get into writing analytic plans, and specifically plans for adjudicating clinical endpoints, the plan/protocol might need to be reviewed at a high level – i.e., the OND IO or higher. There is a MAPP on this, I believe. You should consult that MAPP before you start any work to see if it applies here. If it applies, the protocol will need to go up to for review and comment before you begin.

Your second email indicates that the MAPP is not applicable. I have submitted my plan for comments, but please note the limitations regarding higher level review that I describe in my response to your last comment.

O Third, if you were to go ahead with this and find a RR of, say 1.3, I doubt there would be much enthusiasm for basing a regulatory decision (labeling or otherwise) on that. People would have various opinions on where the meaningful threshold is, but it might be worth asking for some input before you start.

How do you know what the RR is until you do an adequate study? And astonishingly, you would ignore a 30% increase in cancer rates for any drug, much less drugs for which there are many alternatives? I believe that we must inform patients and providers if there is any risk and that they, not you, should make the decisions. Furthermore, even if the population RR is 1.3 we should expect that risks in subgroups will vary and that some have substantially higher risks than 30% or special concerns. For lung cancer interaction with smoking is always a concern. Prostate cancer is only a problem for males.

O Finally, given you familiarity with some of the trial data, any decision YOU make regarding inclusion and exclusion of trials can be called into question after the fact. It

doesn't matter that your criteria are reasonable and defensible, because you can know the effect that your criteria will have on the trials to be included/excluded before you begin.

Anyone can always call analyses in question after the fact, but that is precisely why I submitted my plan prospectively. You also appear to be making your usual prejudicial assumptions: First, all of us have a familiarity with some of the trial data but I am the only one who appears to believe that the "trial data" we have is questionable—why else would I be insisting upon analyses from the raw data? So, I don't know the trial results and I don't know the inclusion and exclusion criteria for the trials. Second, you are implying that I have manipulated the inclusion and exclusion criteria to achieve some prejudicial result or goal. My only goal is to answer as best possible the question of whether ARBs affect cancer rates. I have no commitment to a positive or negative answer to that question as you do (see my final comments below.) It is always dismaying that, when you wish to disagree with a reviewer, you accuse them of biases while you readily accept sponsor assertions—despite sponsors literally having billions of dollars of incentives to bias the results.

Finally, you have issued a final FDA Drug Safety Communication declaring unequivocally that "treatment with an ARB medication does not increase the risk of cancer." You have based this unequivocal statement on the substantially flawed TSI meta-analysis. So the "YOU" that has a problem with credibility currently is a plural you: You and everybody else in the management chain from Dr. Southworth through Dr. Hamburg. Your emails and meeting discussions have the appearance of discouraging me from pursuing a legitimate safety concern while my efforts reveal facts that reflect poorly upon your performance. I suggest that it is more appropriate for you to encourage my efforts in the interest of public health.

Tom

-----Original Message-----
From: Unger, Ellis
Sent: Tuesday, August 21, 2012 2:41 PM
To: Marciniak, Thomas
Cc: Southworth, Mary Ross; Temple, Robert; Stockbridge, Norman L
Subject: RE: Emailing: ARB ca review plan v1p2.doc

Here's a link to the MAPP.

http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM229716.pdf

It turns out that the MAPP covers new NDAs and BLAs, and so is not really applicable here. It's a good thing to keep in mind, however.

Ellis

-----Original Message-----
From: Unger, Ellis
Sent: Monday, August 20, 2012 11:04 PM
To: Marciniak, Thomas
Cc: Southworth, Mary Ross; Temple, Robert; Stockbridge, Norman L
Subject: RE: Emailing: ARB ca review plan v1p2.doc

Tom, et al,

I've gone through the protocol only fairly quickly, but I have a few comments.

First, this would represent a lot of man-hours, so I have to assume that there is a paucity of work in the Division at this point, or that you will be doing this mostly after hours.

Second, when we get into writing analytic plans, and specifically plans for adjudicating clinical endpoints, the plan/protocol might need to be reviewed at a high level – i.e., the OND IO or higher. There is a MAPP on this, I believe. You should consult that MAPP before you start any work to see if it applies here. If it applies, the protocol will need to go up to for review and comment before you begin.

Third, if you were to go ahead with this and find a RR of, say 1.3, I doubt there would be much enthusiasm for basing a regulatory decision (labeling or otherwise) on that. People would have various opinions on where the meaningful threshold is, but it might be worth asking for some input before you start.

Finally, given you familiarity with some of the trial data, any decision YOU make regarding inclusion and exclusion of trials can be called into question after the fact. It doesn't matter that your criteria are reasonable and defensible, because you can know the effect that your criteria will have on the trials to be included/excluded before you begin.

Ellis

-----Original Message-----
From: Stockbridge, Norman L
Sent: Monday, August 20, 2012 6:04 AM
To: Marciniak, Thomas
Cc: Southworth, Mary Ross; Temple, Robert; Unger, Ellis
Subject: FW: Emailing: ARB ca review plan v1p2.doc

I am replying by forwarding, so some other interested parties have a chance to comment on your proposed patient-level meta-analysis plan if they choose.

For my part, I think you did well in anticipating my major concerns--blinding, multiplicity, what studies to include, what to lump or split, and how the results might

influence regulatory decision-making. We aren't likely to agree about how exactly those issues are handled, but I think you did well by addressing each.

As I noted in an email on Aug 4, I do not consider this 90-person-day effort to be worthwhile given the results of the subject-level meta-analysis, so, despite your assertions to the contrary (email of Aug 10), this project is not part of your assigned work. If nonetheless, it obtains findings you think would be of interest, I am sure all of us will be open to reviewing its results.

I assume that, pending completion of your meta-analysis project, there is nothing further you wish to include in reviews of ARB-cancer TSI. We will proceed with steps to close it.
Regards,
Norman

-----Original Message-----
From: Marciniak, Thomas
Sent: Sunday, August 19, 2012 2:31 PM
To: Stockbridge, Norman L
Subject: Emailing: ARB ca review plan v1p2.doc

I've attached an updated plan. Note that it now includes a revision history (at the end of the text following the Reference.) I'll file it after you return from leave pending your final comments.

Tom

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

/s/

THOMAS A MARCINIAK
08/31/2012
Original version 1.0 submitted to Dr. Stockbridge on August 3, 2012.

CLINICAL REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: March 7, 2013

Reviewer: Thomas A. Marciniak, M.D.
Medical Team Leader

TSI: 935

Drugs: Angiotensin receptor blockers (ARBs)

Subject: Risk of cancer

Summary

BACKGROUND: A published meta-analysis raised the question of whether use of angiotensin receptor blockers (ARBs) is associated with an increased risk of cancer.

METHODS: To identify all malignancy adverse events I followed a pre-specified analysis plan to analyze the raw data from all 16 large ARB clinical outcomes trials submitted to the FDA. Using the malignancy determinations I performed pre-specified patient-level meta-analyses of incidences of lung, prostate, and hematologic malignancy events and Kaplan-Meier analyses and Cox regressions (stratified by trial and including baseline cofactors) of incidence rates and of survival after malignancy diagnosis.

RESULTS: I excluded five trials from the primary analyses because they failed the pre-specified criteria for completeness of follow-up and malignancy reporting. The pooled risk ratio for lung cancer comparing the ARB arms to the control arms in the 11 trials with adequate data was 1.24 (95% confidence interval 1.08-1.43, p = 0.003). The increased risk of lung cancer with ARBs was robust to meta-analyses excluding the index trial, including all four of the excluded trials that had malignancy site reporting, and analyzing new diagnoses alone. Kaplan-Meier analyses estimated about 0.8 excess lung cancer cases per year per 1,000 patients treated. Cox regressions estimated about a 4-fold higher risk in ex-smokers and an 11-fold higher risk in current smokers

compared to non-smokers regardless of ARB use. Survival after a lung cancer event was dismal, about 34 percent at one year regardless of initial ARB use. The meta-analyses for prostate and hematologic malignancies were inconclusive. Solid cancer rates (excluding non-melanoma skin cancers and brain tumors) were slightly but not significantly increased with ARB use.

CONCLUSION: ARB use is associated with an increased risk of lung cancer.

Introduction

In 2010 a meta-analysis published by Sipahi *et al.* raised the question of whether use of angiotensin receptor blockers (ARBs) is associated with an increased risk of cancer. (Sipahi, Debanne et al. 2010) Sipahi *et al.* analyzed cancer data from publications and from the FDA website for 61,590 patients from five trials and observed that patients randomized to ARBs had a significantly increased risk of new cancers (risk ratio (RR) 1.08, 95% confidence interval (CI) 1.01-1.15). They also analyzed specific solid cancer sites and found that only new lung cancers were significantly more frequent in the ARB arms (RR 1.25, 95% CI 1.05-1.49). They concluded that their findings warranted further investigation.

The Sipahi *et al.* meta-analysis stimulated other meta-analyses and observational studies addressing similar issues. Bangalore *et al.* analyzed 70 antihypertensive trials with 324,168 patients. (Bangalore, Kumar et al. 2011) Regarding ARBs they found no difference in cancer risk, although they observed an increased cancer risk with the combination of ARBs with angiotensin converting enzyme inhibitors (ACEI) by a fixed effect meta-analysis but not by a random effects one. The ARB Trialists Collaboration analyzed 15 ARB trials with 138,769 patients and found no excess cancer risk with ARB use. (ARB Trialists Collaboration 2011) The FDA conducted a trial-level meta-analysis of 31 trials and approximately 156,000 patients and concluded that ARB treatment does not increase the risk of cancer. (FDA 2011)

All of the published meta-analyses have severe limitations regarding trials included and the information available on cancer cases in publically available trial data. For example, regarding trials included, the ARB Trialists Collaboration analyzed only the LIFE trial for losartan, omitting three other major losartan trials because they were not able to obtain the data. Regarding information on cancer cases, Bangalore *et al.* counted seven cancer cases for the losartan RENAAL trial and referenced the main RENAAL publication. (Brenner, Cooper et al. 2001) However the main RENAAL publication does not include statistics on cancer cases. I queried the meta-analysis authors and they confirmed that they had obtained the RENAAL cancer incidences from a 2008 meta-analysis. (Coleman, Baker et al. 2008) The latter meta-analysis also referenced only the main RENAAL publication. Upon query the author of the 2008 meta-analysis quoted the source as a RENAAL substudy publication. (Remuzzi, Ruggenenti et al. 2004) However, the RENAAL substudy publication tabulated cancer cases only for adverse events leading to patient withdrawal. Because cancer is not a reason for withdrawing ARB

treatment, counting only withdrawals grossly underestimates cancer incidence (as confirmed by the RENAAL data submission to the FDA.)

The FDA meta-analysis did not correct the flaws present in the meta-analyses using published data. The FDA requested summary trial data from the drug companies but did not specify details on how to classify incident cases, ambiguous cases, or censoring periods and did not mandate submission of data for all relevant trials. Furthermore, the FDA meta-analysis of lung cancers was seriously flawed in that it did not count lung carcinomas as lung cancers but was inappropriately limited to lung cancers coded as "malignant lung neoplasm".

Sipahi was unaware of these flaws in the FDA meta-analysis but publically criticized it for not exploring exposure-risk relationships in a patient-level analysis. (Wood 2011) I agree with Sipahi that as serious a question as whether widely-used antihypertensives increase cancer risk deserves the most discriminating analysis possible. I proceeded with a patient-level meta-analysis of the raw data in long-term ARB trials submitted to the FDA as recommended in an editorial on the Sipahi *et al.* meta-analysis. (Nissen 2010)

My experience with ARBs and cancer predates the Sipahi *et al.* meta-analysis: I had performed the primary clinical review of the losartan LIFE trial submitted to the FDA in 2002. (Marciniak 2003) I observed then that there was a numeric but not statistically significant excess of lung cancers in the losartan arm in that trial. I also observed that there was a less prominent numeric excess of prostate cancers in the losartan arm. Re-examining the LIFE data after the publication of the Sipahi *et al.* meta-analysis I observed additionally that hematologic malignancies were less frequent in the losartan arm. I hypothesized that the latter result, if real, might be related to the same mechanism responsible for the slight suppression of hematopoiesis observed with both ARBs and ACEIs. (Leshem-Rubinow, Steinvil et al. 2012) I hypothesized also that the excess of prostate cancers, if real, might be related to an increase in adrenal androgen levels resulting from the same mechanism responsible for aldosterone breakthrough following chronic ARB or ACEI use. (Bomback and Klemmer 2007)

Hence I targeted the following three independent hypotheses in patient-level meta-analyses:

1. That ARB use increases the risk of lung cancer. Because I had no *a priori* hypothesis that ACEIs share this effect, I pre-specified for the primary analysis of lung cancers ignoring the use of ACEIs both as controls and in the ARB arms.

2. That ARB use increases the risk of prostate cancer. For this hypothesis I pre-specified criteria for eliminating trials only with ACEI control arms or with substantial use of ACEIs during the trial. Because of resource limitations, i.e., I performed this work without official FDA support, I did not analyze the data by concomitant ACEI use in the ARB arms.

3. That ARB use decreases the risk of hematologic malignancies. Regarding ACEI use I proposed analyzing this hypothesis identically to that regarding prostate cancer.

Because previous meta-analyses had also targeted all cancers, I also analyzed all solid cancers excluding non-melanoma skin cancers and brain tumors. I excluded hematologic malignancies because I hypothesize that ARBs may decrease them, non-melanoma skin cancers because of their less serious nature compared to other solid cancers and because they are under-reported, and brain tumors because their malignancy status is frequently not reported and because most ARBs do not cross the blood-brain barrier.

Methods

Trial Selection

I adopted the same general criteria for trial size and duration used by the Sipahi *et al.* and FDA meta-analyses: randomized, placebo-and active comparator-controlled studies for the ARBs; enrolled more than 100 patients; had a mean or median follow-up longer than one year; and collected cancer data either as a prespecified endpoint or adverse event. I considered only trials for which the sponsors had submitted complete data (i.e., protocols, case report forms, and datasets) to the FDA.

Regarding trial data I looked for data on all cancer-related events, not just deaths, and for data on the primary site of the cancer, because the hypotheses involve specific sites and not all cancers. I prespecified excluding trials from the primary analyses if more than five percent of all cancers were detected only at study end or death or if the primary sites were not reported for more than five percent of the cancers (other than cancers reported explicitly as unknown primaries). Because I have concerns about the validity of any results from trials having poor follow-up and I have documented serious problems with them in previous reviews, I prespecified excluding trials from the primary analyses if completeness of follow-was less than 90 percent. For the hypotheses regarding prostate cancer and hematologic malignancies, which postulate similar effects for both ARBs and ACEIs, I prespecified excluding trials from the primary analyses if the trials had only ACEI control arms or if the concomitant use of ACEIs in the trials exceeded 10 percent.

Consulting with other FDA staff I identified 16 ARB trials with data submitted to the FDA and meeting the general criteria for trial size and duration. I excluded five of these 16 trials from the primary analyses because of incomplete follow-up or incomplete cancer ascertainment (see Appendix 1) and included 11 trials in the meta-analysis of lung cancer. I excluded six of the 11 trials from the meta-analyses of prostate and hematologic malignancies because of ACEI use. I list the trials used in the primary meta-analyses in Table 1 and those excluded in Table 2**.**

Table 1: Trials Included in the Primary Meta-Analyses

ARB	Trial	Reference	NDA	N	Prostate/heme analyses?
candesartan	Charm-Added	(McMurray, Ostergren et al. 2003)	20838 S022	2548	No, ACEI use ~100%
	Charm-Alternative	(Granger, McMurray et al. 2003)	20838 S022	2028	Yes
	Charm-Preserved	(Yusuf, Pfeffer et al. 2003)	20838 S022	3023	No, ACEI use ~20%
irbesartan	(b) (4)				
	IDNT	(Lewis, Hunsicker et al. 2001)	20757 S021	1716	Yes
losartan	LIFE	(Dahlof, Devereux et al. 2002)	20386 S032	9193	Yes
	RENAAL	(Brenner, Cooper et al. 2001)	20386 S028	1513	Yes
telmisartan	ONTARGET	(Yusuf, Teo et al. 2008)	20850 S025	25620	No, ACEI control arm
	PRoFESS	(Yusuf, Diener et al. 2008)	20850 S025	20332	No, ACEI use ~31%
	TRANSCEND	(Yusuf, Teo et al. 2008)	20850 S025	5926	Yes
valsartan	Val-Heft	(Cohn and Tognoni 2001)	20665 S016	5010	No, ACEI use ~93%

Table 2: Trials Excluded from the Primary Meta-Analyses

ARB	Trial	Reference	IND/NDA	N	Reason Excluded
irbesartan	IRMA 2	(Parving, Lehnert et al. 2001)	N20757 S021	611	Incomplete follow-up
olmesartan	[redacted] (b) (4)				
valsartan	[redacted] (b) (4)				
	VALIANT	(Pfeffer, McMurray et al. 2003)	N21283 S011	14679	Incomplete cancer reporting

The 11 trials for the lung cancer meta-analysis include 85,925 patients and studied five different ARBs while the five trials for the prostate and hematologic malignancies meta-analyses include 20,376 patients and studied four ARBs. The five excluded trials total 29,832 patients and studied three ARBs. Two FDA-approved ARBs, azilsartan and eprosartan, did not have any eligible trials submitted to the FDA. The FDA approved azilsartan in 2011 and its sponsor has not conducted large outcome trials with it. [redacted] (b) (4) The other FDA-approved ARB not included in the primary meta-analyses, olmesartan, had two trials with FDA data submissions meeting the general criteria but failing the criterion for completeness of follow-up.

Cancer Ascertainment

From the study protocols, case report forms (CRFs), and dataset documentation I identified all CRFs and datasets having data regarding cancers. The CRFs having cancer data included adverse event forms, serious adverse event forms, endpoint forms, procedure forms, end of treatment forms, disposition forms, and death forms depending upon the particular study. I used computer string searches to identify possible cancer cases from the investigator-reported verbatim terms in the corresponding datasets and string matches to standard cancer terms if coded terms were available. The string searches included misspellings and ambiguous terms, (e.g., "kancer", "lung mass") and I designed them to be sensitive rather than specific. Blinded to treatment assignment I manually reviewed all possible cancer cases, consulting primarily the investigator-reported verbatim terms and comments but reviewing the full case report forms for ambiguous cases. I assigned a primary cancer site, e.g., "lung", "prostate", if the case had adequate documentation of malignancy or seriousness and of the primary site. If medical histories included cancer sites I assigned cancer sites using the same approach.

For the post-randomization cancer events I assigned a date of first clinical diagnosis of the cancer or cancer recurrence. I used date of first clinical diagnosis because date of histologic diagnosis is frequently not available in trial CRFs. I identified both initial diagnoses of cancers, i.e., incident new cancers, as well as recurrences of cancers originally diagnosed prior to randomization, distinguishing the new cancers when possible. I consider cancer recurrences to be as clinically relevant as incident new cancers because cancer patients die more frequently from the local or metastatic recurrence than from the original primary.

Finally, I identified for each trial the earliest last follow-up date, e.g., the global study end date or the primary endpoint censoring date. I counted cancer events by the intent-to-treat (ITT) principle if they occurred on or after the randomization date and before or on the earliest last follow-up date. I did not attempt to censor the cancers occurring shortly after randomization despite the realization that they are highly unlikely to be related to study drug use; I do not have an *a priori* justification for a censoring date and, being infrequent, counting them does not appear to affect substantially the meta-analyses. I relied upon the incidence curves to show any differences in early vs. later rates. I favor and pre-specified the ITT approach because it is the only approach that preserves the randomization and, if the effect size is less than two-fold, the majority of cancers will be numerically unrelated to the study drug use. Furthermore, cancers frequently require weeks to diagnose but cause adverse effects leading earlier to study drug discontinuation. I would consider an on-treatment analysis allowing an adequate time for delayed diagnoses as a sensitivity analysis but, because of resource limitations, I did not assign dates of last treatment and perform on-treatment analyses.

Statistical Analysis

I performed all statistical analyses using Stata 12. For the meta-analyses I used the *metan* package. (Harris, Bradburn et al. 2008) Because I hypothesized similar effects for all ARBs, I performed fixed-effect meta-analyses of risk ratios evaluated by the Mantel-Haenszel method. I evaluated heterogeneity with the I^2 statistic.

To show the time course of cancer development I generated Kaplan-Meier plots of time to first cancer event occurrences. I also generated Kaplan-Meir plots of survival after first clinical diagnosis of a new or recurrent cancer. I used crude survival rather than cause-specific survival, i.e., deaths due to cancer, because I believe that cancer usually contributes to the demise of patients with recurrent or metastatic cancer. I estimated statistical significance of the time courses of cancer development and survival following cancer diagnosis by log rank tests stratified by study. I explored the effects of baseline factors by Cox regressions stratified by study. For the Cox regressions I tested the proportional hazards assumptions by graphs and statistics of Schoenfeld residuals produced by the Stata 12 *estat phtest* command.

Results

Lung Cancer

I identified new or recurrent lung cancer events during the censoring periods in 805 of the 85,925 patients in the eleven trials. The pooled RR comparing the ARB arms to the control arms is 1.24 (95% CI 1.08-1.43, p = 0.003). I show the forest plot of RRs by trial in Figure 1. The I^2 statistic did not suggest significant heterogeneity (p > 0.6). All of the trials except one, CHARM-Preserved, showed an excess of lung cancers in the ARB arms. The CI for the CHARM-Preserved risk ratio overlaps with the risk ratio CIs for all eleven trials and for the ten trials excluding CHARM-Preserved. Because LIFE was the index study suggesting an effect of an ARB upon lung cancer, I performed a second meta-analysis excluding LIFE. The pooled RR excluding LIFE is also 1.24 (95% CI 1.07-1.44, p = 0.005). As sensitivity analyses I performed meta-analyses including the trials excluded from the primary analyses. For a meta-analysis including the one irbesartan study excluded (IRMA 2), the pooled RR remains 1.24 and the p value is 0.003. For a meta-analysis including all 15 trials that collected the cancer sites for all malignancies, i.e., all except VALIANT, the pooled RR is 1.16 and the p value is 0.026.

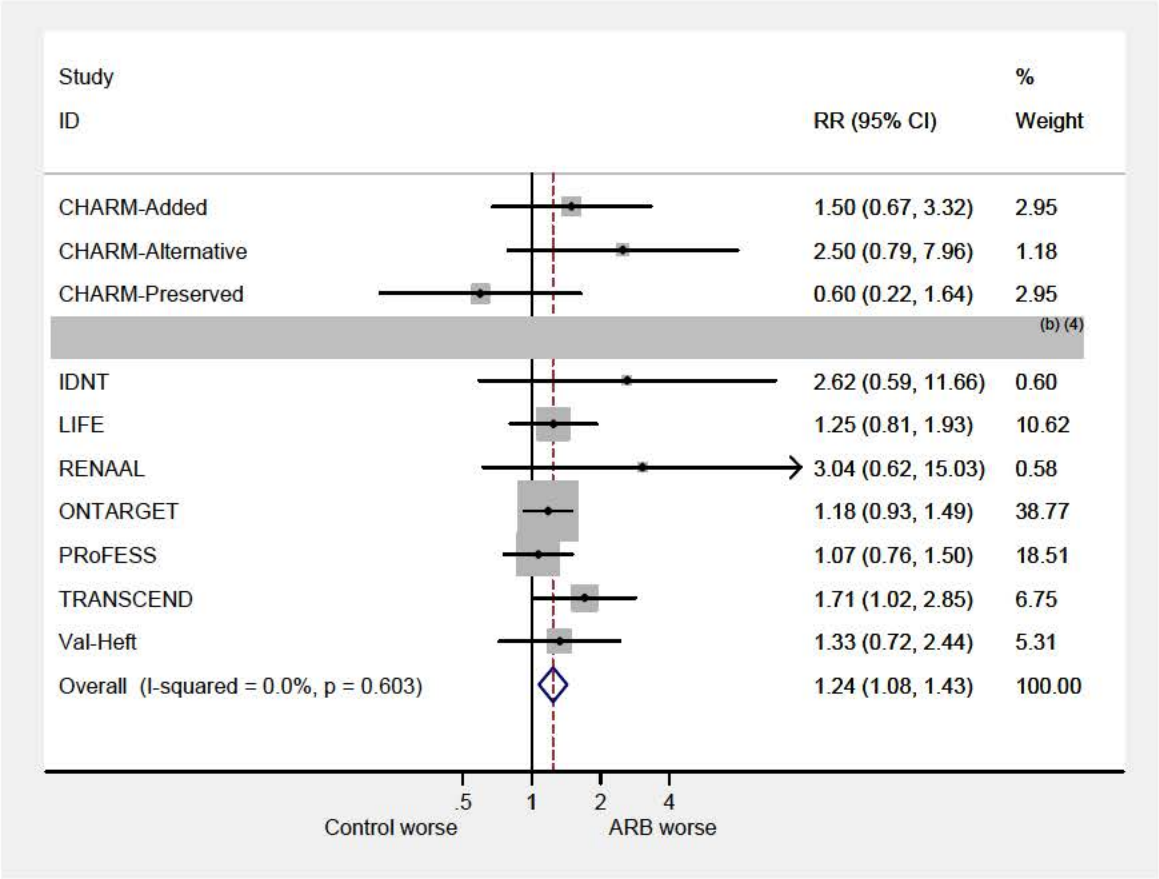
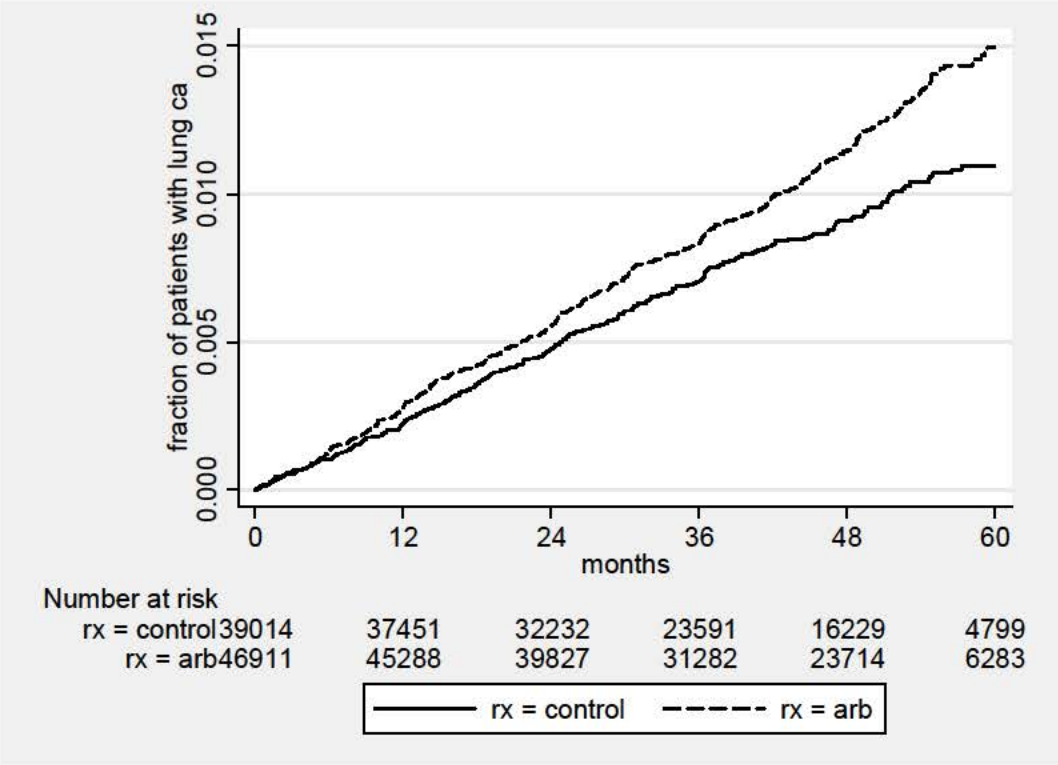


Figure 1: Risk Ratios of Patients with Lung Cancer Events by Trial

I identified new lung cancers during the censoring periods in 645 of the 63,877 patients in the nine trials that captured histories of cancer sites. (PRoFESS did not capture histories of cancer sites. IDNT may have in concomitant diagnoses but the sponsor did not submit to the FDA a dataset with them.) About 97% of the first lung cancer events were new lung cancers in these nine trials. The pooled RR is 1.32 (95% CI 1.12-1.59, p = 0.001). The pooled RR excluding LIFE is 1.33 (95% CI 1.12-1.59, p = 0.001).

I also analyzed new or recurrent lung cancer events separately for the trials excluding most ACEI use (i.e., the trials I use for the prostate cancer and hematologic malignancy meta-analyses) and for the trials including substantial ACEI use. For the five trials excluding most ACEI use the pooled RR is 1.57 (95% CI 1.16-2.13, p = 0.003). For the six trials having substantial ACEI use the pooled RR is 1.16 (95% CI 0.99-1.36, p = 0.074).

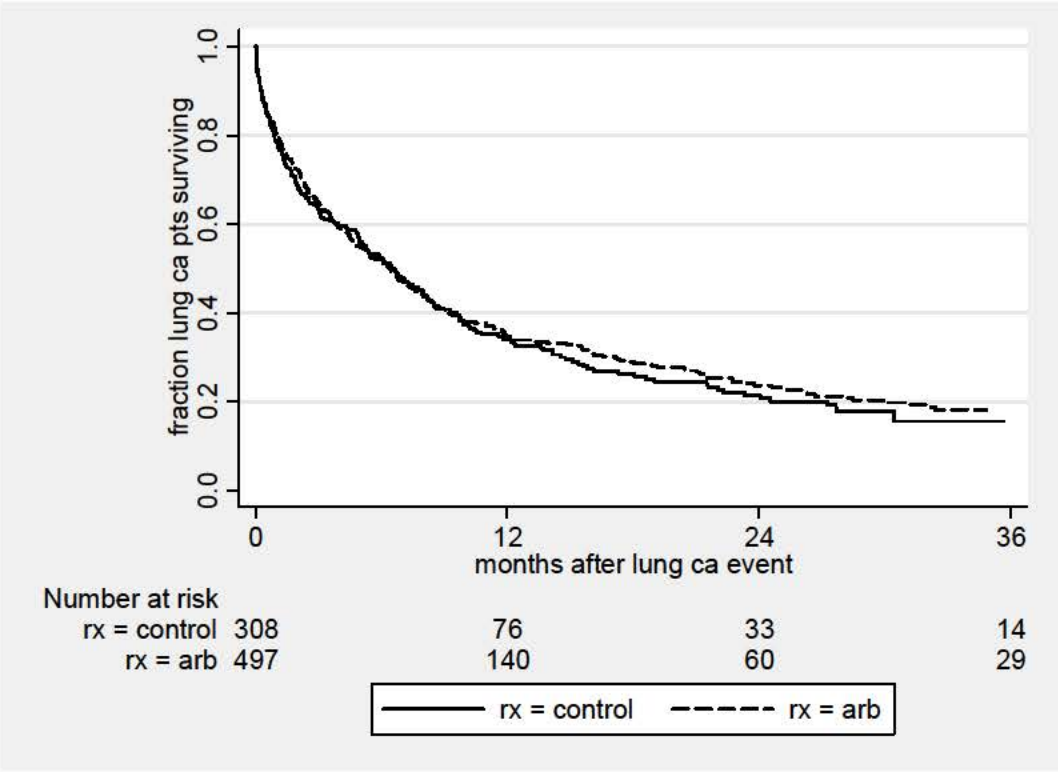
I show the Kaplan-Meier plot of times to first lung cancer events (new or recurrent) in Figure 2. The incidence curves start to diverge at about nine months and then continue to diverge throughout the five years of follow-up in the longest trials. At five years the cumulative hazard estimate is 1.5% for the ARB arms and 1.1% for the control arms, an absolute risk difference of about 0.4%, i.e., about 0.8 excess lung cancer cases per year per 1,000 patients treated.



p = 0.0033 by log rank stratified by study

Figure 2: Times to First Lung Cancer Events

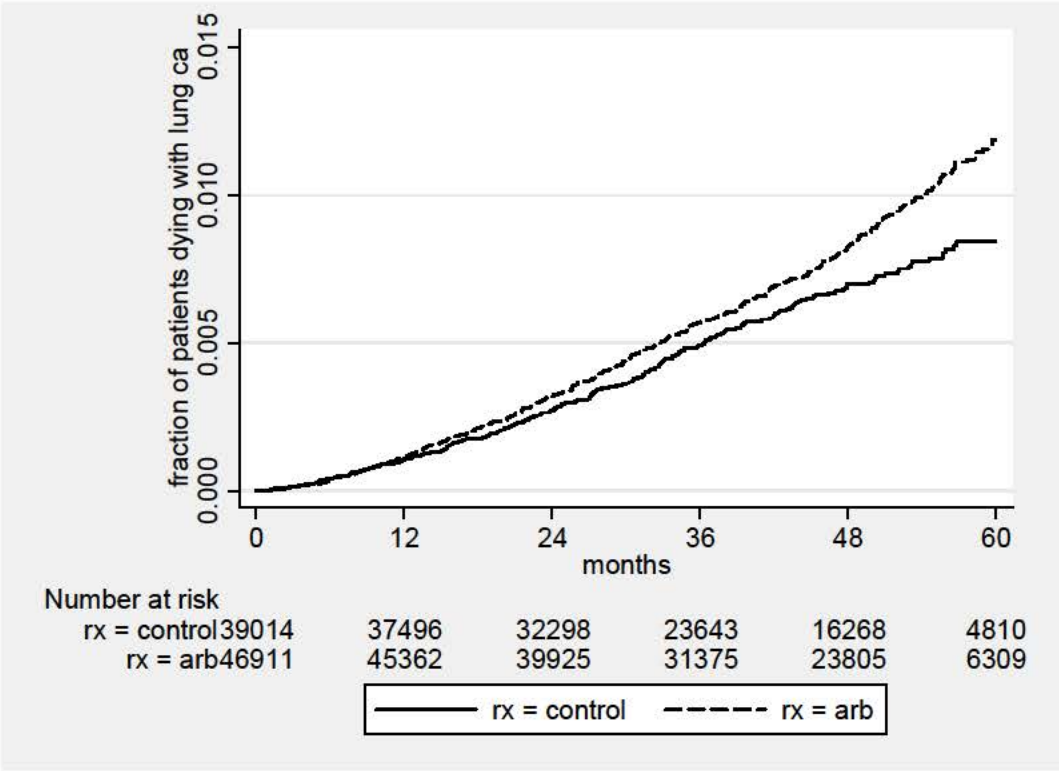
Having a lung cancer event portends a poor prognosis in these studies, similarly poor in the ARB and control arms. I show the Kaplan-Meier plots for survival after a lung cancer event in Figure 3. Survival is dismal, about 34% at one year.



p > 0.7 by log rank stratified by study

Figure 3: Survival after a Lung Cancer Event

Because lung cancer events were more frequent with ARB use while survival after a lung cancer event was similar regardless of ARB use, patients dying with lung cancer were more frequent in the ARB arms. I show the Kaplan-Meier plots for times to patients dying with lung cancer in Figure 4. The hazard ratio (HR) by Cox regression for dying with lung cancer is 1.27 (95% CI 1.08-1.51, p = 0.005).



p = 0.005 by log rank stratified by study

Figure 4: Times to Dying with Lung Cancer

I explored the effects of baseline cofactors upon lung cancer events with Cox regressions stratified by study. The Cox regression including only treatment as a factor produces results similar to the meta-analysis, HR 1.27 (95% CI 1.1-1.46, p = 0.001). For this Cox regression the proportional hazards assumption is not rejected (p > 0.3). I show the results of a Cox regression including treatment and cofactors of age, sex, and smoking status (for the 10 studies having data on smoking, i.e., except Val-Heft) in Table 3.

Table 3: Cox Regression of Times to First Lung Cancer Events

```
No. of subjects =        80915                     Number of obs    =     80915
No. of failures =          763
Time at risk    =    3526808.2                     LR chi2(5)       =    606.00
Log likelihood  =   -8097.0742                     Prob > chi2      =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         ARB |   1.256748   .0938048     3.06   0.002      1.08571    1.454731
         age |    1.06357   .0049333    13.29   0.000     1.053944    1.073283
        male |   1.332871   .1221992     3.13   0.002     1.113651    1.595245
   ex-smoker |   4.404436    .540857    12.07   0.000     3.462297    5.602945
curr. smoker |   10.59602   1.362723    18.35   0.000     8.235168    13.63369
------------------------------------------------------------------------------
                                                        Stratified by study
```

ARB use, age, male sex, and ex- or current smoking status are all associated with higher risks of lung cancer. Whether male sex is an independent risk factor is unclear because men in the trials had much higher rates of smoking than women (71% vs. 32% for any smoking). Cox regressions including interaction terms between ARB use and age, sex, and smoking status produced no statistically significant interactions (all $p > 0.4$). However, the global test for failure of the proportional hazards assumption is significant ($p = 0.003$) with age and ex-smoking status significantly contributing to the failure.

Lung cancer event rates were high for current smokers as shown in Figure 5. At five years the cumulative rate of lung cancer events in baseline current smokers in the ARB arms approaches 4%. The absolute risk difference in smokers at five years was about 1.1% and appears to be accelerating.

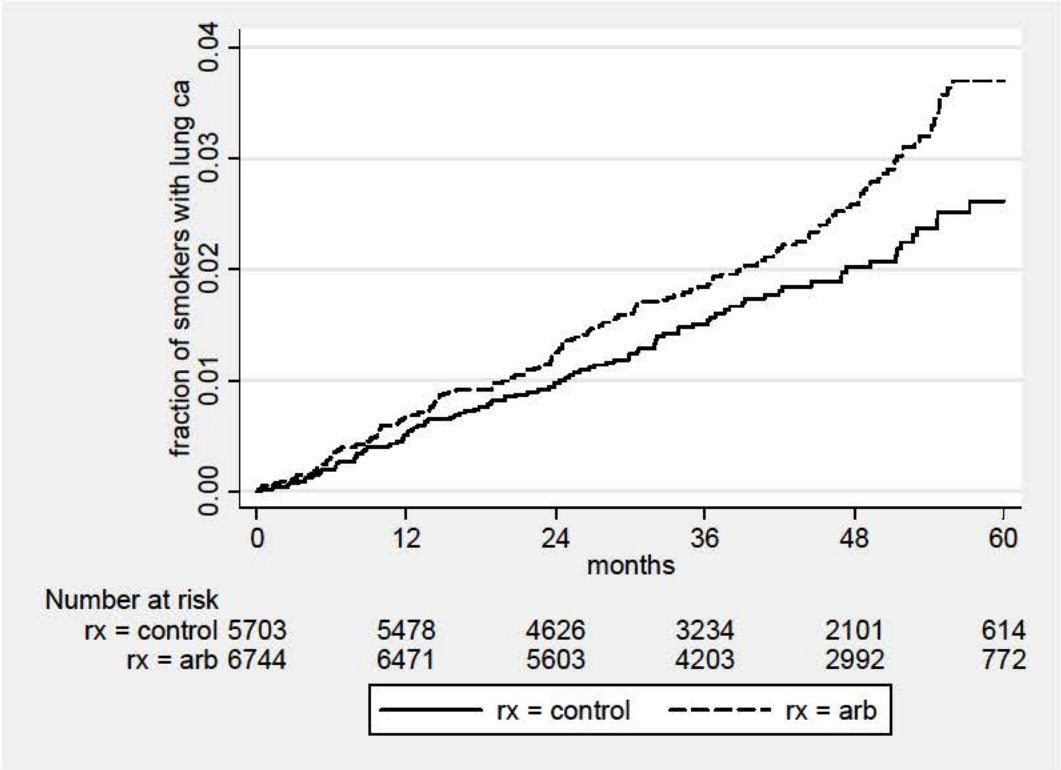


Figure 5: Times to First Lung Cancer Events for Current Smokers at Baseline

To explore age effects I analyzed separately age groups split at the median age of 65. While patients older than 65 at baseline showed proportional hazards for the treatment effect, patients aged 65 or younger showed the pattern depicted in Figure 6. There appears to be an accelerating risk for patients aged 65 or younger. In patients aged 65 or younger most lung cancer events (about 52%) occurred in current smokers while about 20% of these patients were current

smokers. However, late divergences of the curves are seen for both ex-smokers and non-smokers.

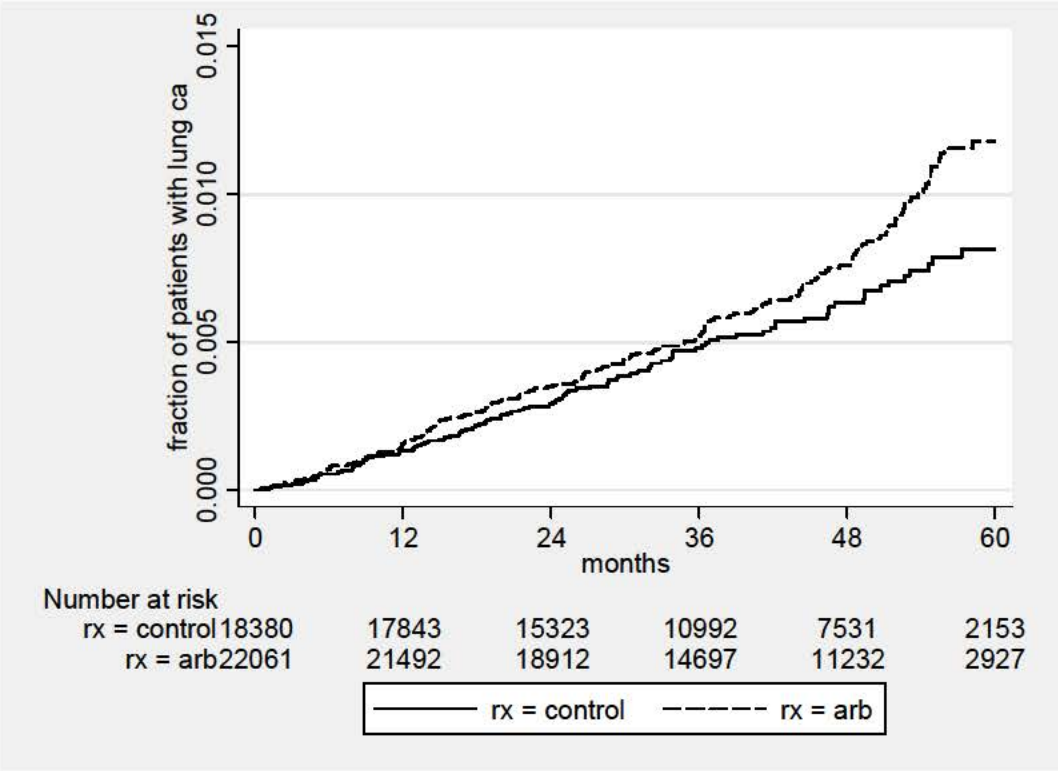


Figure 6: Times to First Lung Cancer Events for Patients 65 or Younger at Baseline

Prostate Cancer

I identified new or recurrent prostate cancer events during the censoring periods in 221 of the 11,087 men in the five trials excluding most ACEI use. The pooled RR comparing the ARB arms to the control arms is 1.23 (95% CI 0.95-1.6, p = 0.13). I show the forest plot of RRs by trial in Figure 7. The pooled RR excluding LIFE (the index study) is 1.36 (95% CI 0.88-2.1, p = 0.15). About 10% of the patients with prostate cancer events had a history of prostate cancer. The pooled RR for new prostate cancers, 1.25, is similar to that for new and recurrent prostate cancers and is also not statistically significant (p = 0.13). The pooled RR for new or recurrent prostate cancers in all 11 trials, including the ones with substantial ACEI use, is 1.04 (p > 0.6).

I show the Kaplan-Meier plot of times to first prostate cancer events (new or recurrent) in Figure 8. There is a suggestion of a slightly higher prostate cancer rate in the ARB arms beginning several months after randomization but some convergence of the curves later.

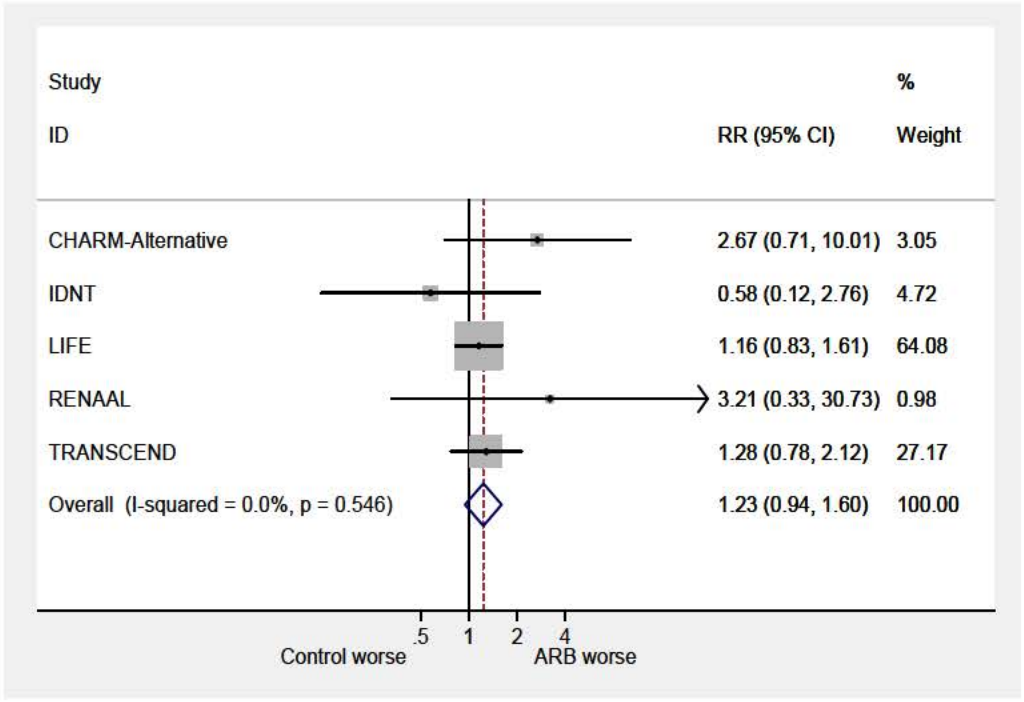
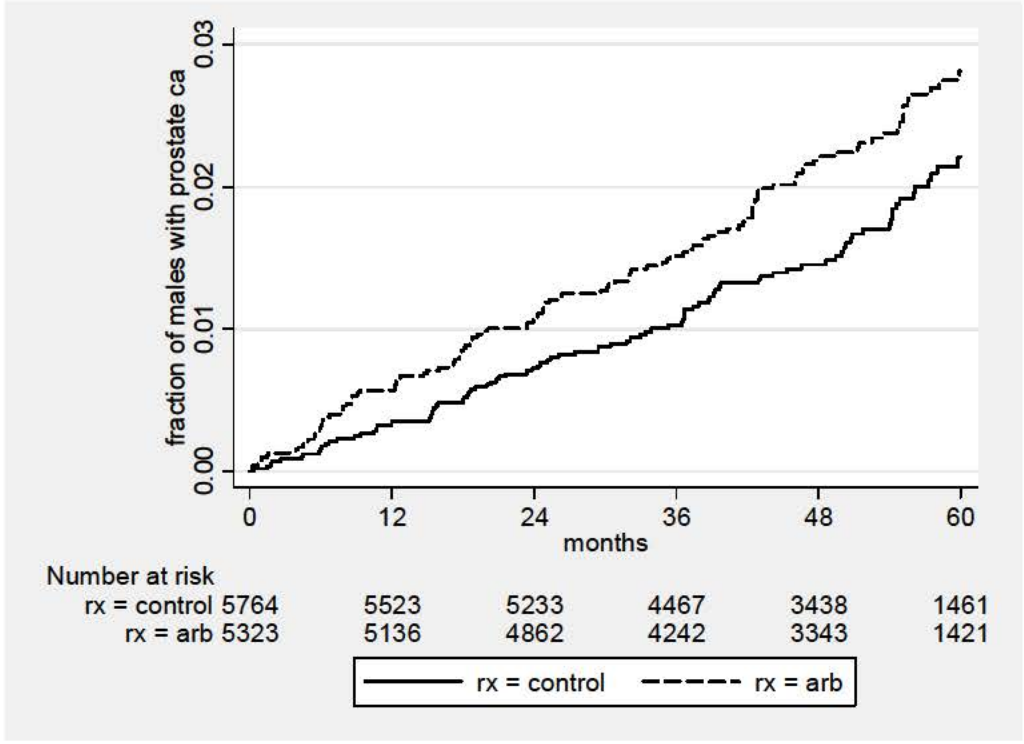


Figure 7: Risk Ratios of Patients with Prostate Cancer Events by Trial



p = 0.12 by log rank stratified by study

Figure 8: Times to First Prostate Cancer Events in Men

Survival after a prostate cancer event, about 81% at two years, was similar in the ARB and control arms. Survival from randomization was not significantly different at two years in men regardless of prostate cancer events or ARB use (about 93%).

Hematologic Malignancies

I identified new or recurrent hematologic malignancy events during the censoring periods in 98 of the 20,376 patients in the five trials excluding most ACEI use. The pooled RR comparing the ARB arms to the control arms is 0.69 (95% CI 0.46-1.03, p = 0.07). I show the forest plot of RRs by trial in Figure 9. The pooled RR excluding LIFE (the index study) is 0.83 (95% CI 0.45-1.53, p >0.5). About 6% of the patients with hematologic malignancy events had a history of hematologic malignancy. The pooled RR for new hematologic malignancies is 0.74 and less significant (p = 0.17). The pooled risk ratio for new or recurrent hematologic malignancies in all 11 trials, including the ones with substantial ACEI use, is 0.97 (p > 0.7).

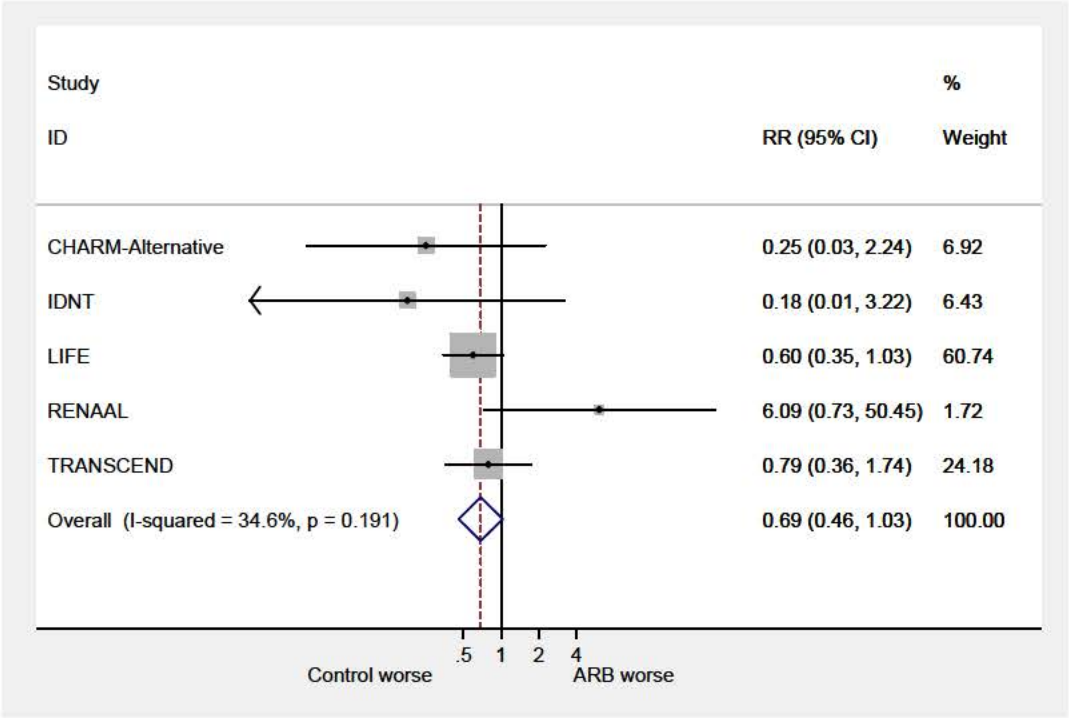
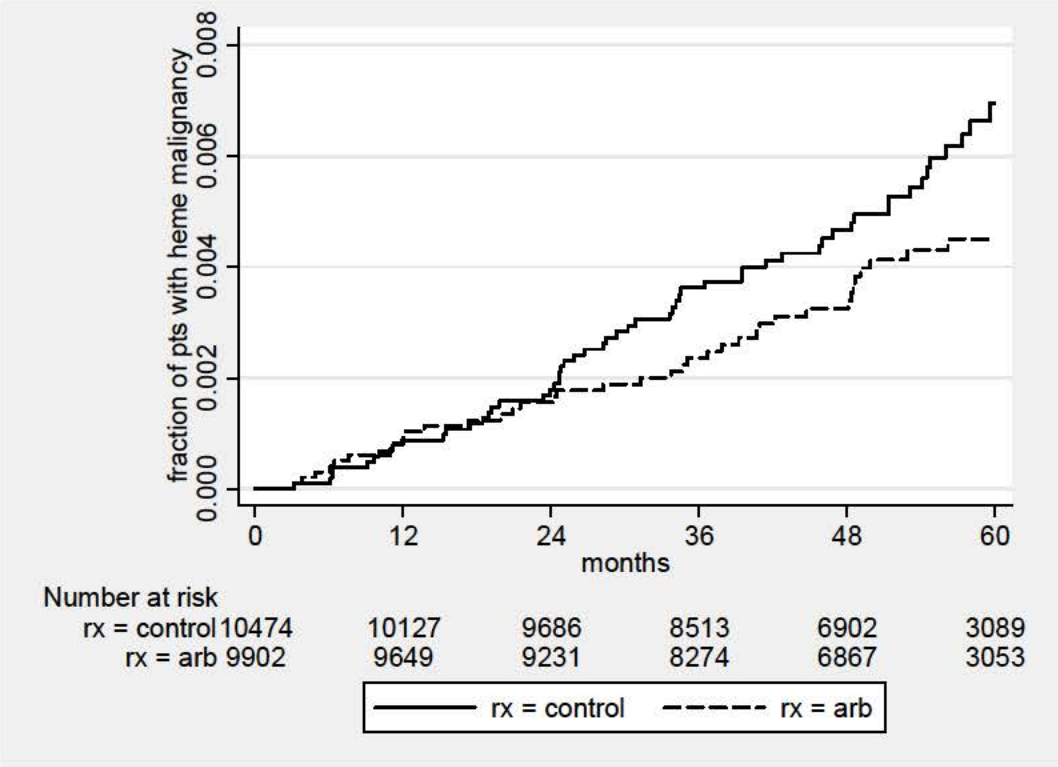


Figure 9: Risk Ratios of Patients with Hematologic Malignancy Events by Trial

I show the Kaplan-Meier plot of times to first hematologic malignancy events (new or recurrent) in Figure 10. The curves diverge after 24 months and remain apart thereafter.



p = 0.06 by log rank stratified by study

Figure 10: Times to First Hematologic Malignancy Events

Survival after a hematologic malignancy event was poor, about 48% at two years, and similar in the ARB and control arms.

Solid Cancers

I identified new or recurrent solid cancer events (excluding non-melanoma skin cancers and brain tumors) during the censoring periods in 4,459 of the 89,925 patients in the eleven trials. The pooled RR comparing the ARB arms to the control arms is 1.05 (95% CI 0.99-1.11, p = 0.10). I show the forest plot of RRs by trial in Figure 11. The pooled RR for all fifteen trials is also about 1.05 (95% CI 0.99-1.11, p = 0.093).

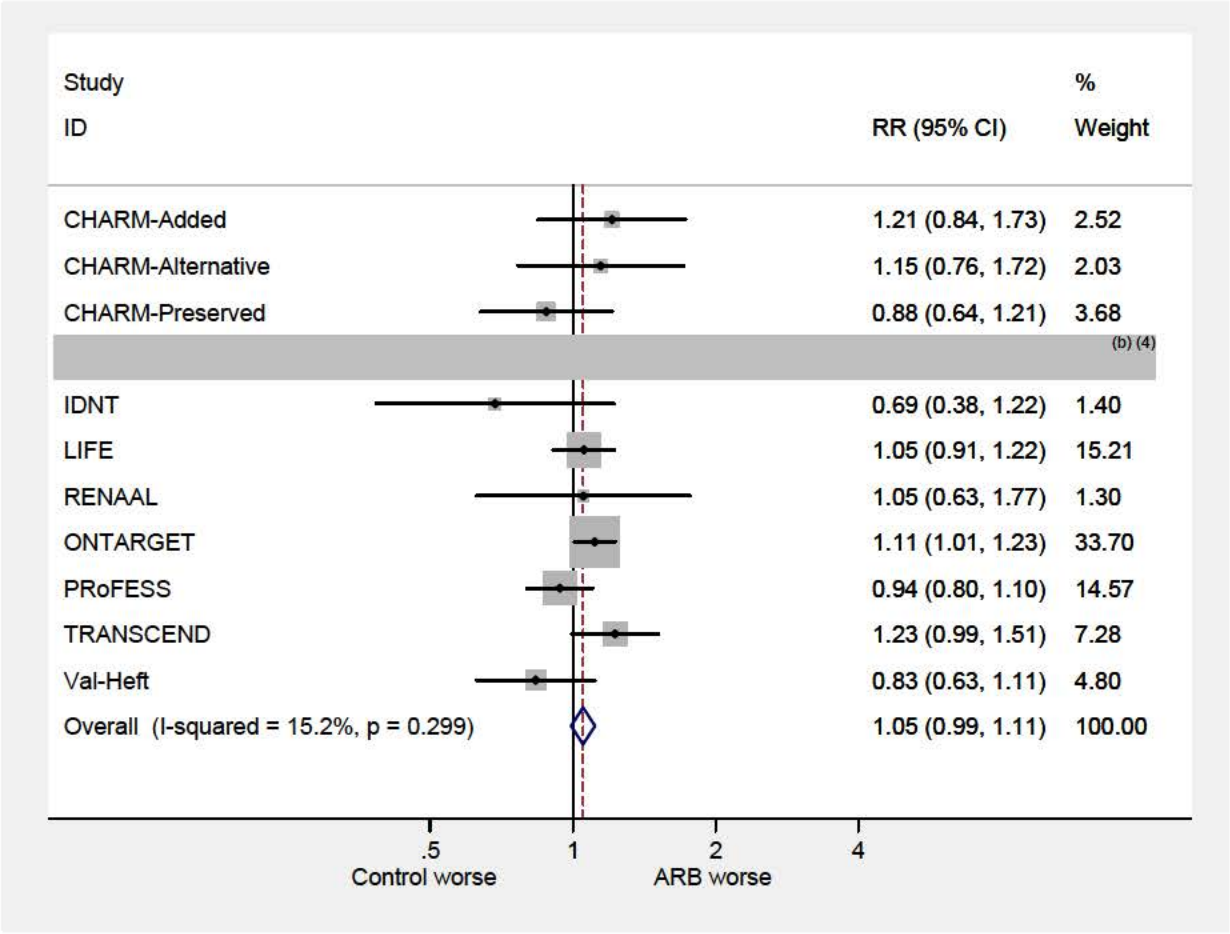
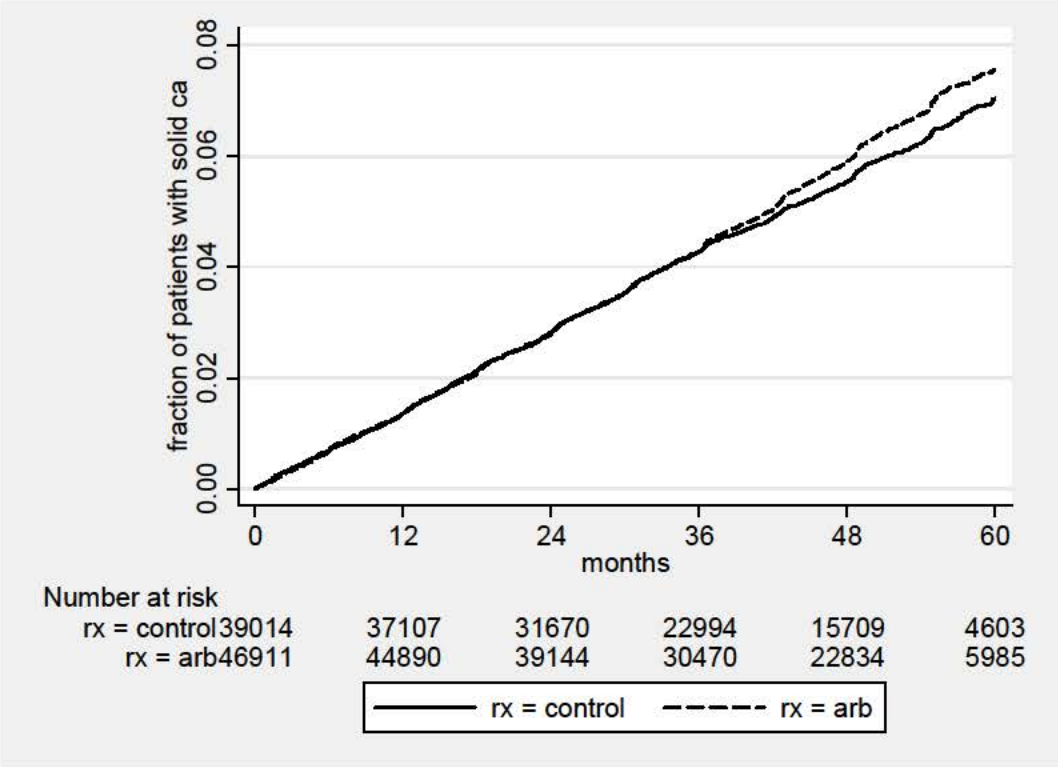


Figure 11: Risk Ratios of Patients with Solid Cancer Events by Trial

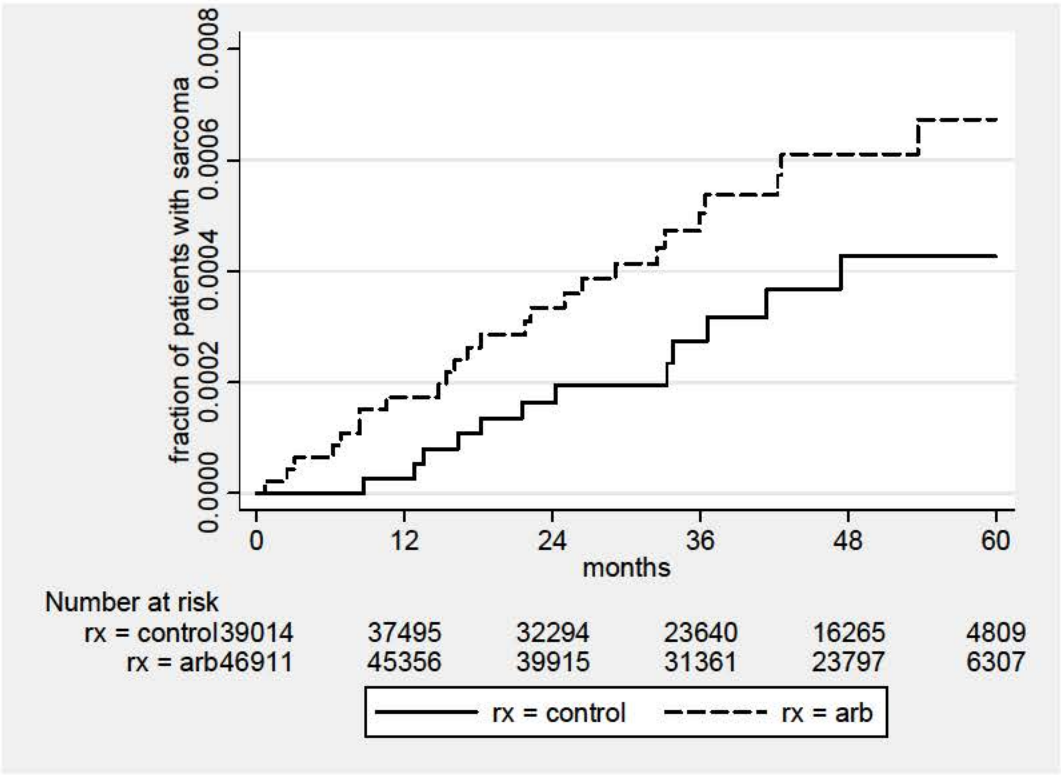
I show the Kaplan-Meier plot of times to first solid cancer events (new or recurrent) in Figure 12. There appears to be slight late divergence of the curves, but the divergence is not statistically significant. The survival curves after a solid cancer event are virtually identical regardless of ARB use (HR 0.99, $p > 0.8$).



p = 0.12 by log rank stratified by study

Figure 12: Times to First Solid Cancer Events

I examined cross-tabulations of the sites of the first solid cancer events by ARB use as exploratory analyses of whether any other specific solid cancer events are imbalanced by ARB use. In addition to lung and prostate cancers sarcomas were imbalanced, with a pooled RR of about 1.8 and p value of 0.081 for eight of the 11 trials having sarcomas and 0.043 for 10 trials having sarcomas. I show the Kaplan-Meier plot of times to first sarcoma events in Figure 12. The incidence curves diverge immediately.



p = 0.037 by log rank stratified by study

Figure 13: Times to First Sarcoma Events

Discussion

ARB use appears to be associated with an increased incidence of lung cancer. The p value for the primary meta-analysis of RR is low ($p = 0.003$) and consistent with a time-to-first-event analysis by a log rank test stratified by study ($p = 0.0033$). The identical meta-analysis except excluding the index LIFE study produces the same estimate for the RR and a similar, highly statistically significant p value ($p = 0.005$). The increased risk of lung cancer with ARBs is robust to sensitivity analyses including a meta-analysis of all 15 large ARB outcome trials that collected cancer sites. The shapes of the incidence curves are consistent with a cancer promoter effect, i.e., delayed initial divergence of the rates in ARB and control arms followed by continuing divergence throughout the duration of follow-up.

The estimate of overall effect size is modest, about a 24% increase in lung cancer incidence. However, some analyses suggest an increasing effect size with increasing duration of therapy. Because ARBs are indicated for life-long treatment (e.g., hypertension, diabetic nephropathy) any consistent or increasing effect upon cancer rates is concerning. The absolute risk difference during the first five years of treatment in the trial populations as a whole is small, i.e., about 0.8 excess lung cancer cases per year per 1,000 patients treated. However, in subgroups at risk for lung cancer, i.e., smokers, the absolute risk increase exceeds 1% at five years. Furthermore, survival following a lung cancer event is dismal, about 34% at one year, and significantly more ARB patients died with lung cancer.

While these absolute risks may not outweigh the cardiovascular benefits of blood pressure reduction in hypertensive patients, there are many other alternative antihypertensives. I believe that these effects of ARBs upon lung cancer should not be ignored and that patients and providers should be fully informed about the risk.

The results regarding prostate cancer are inconclusive. None of the analyses are statistically significant or close to statistically significant. However, because the number of prostate cancer events in the trials excluding most ACEI use and submitted to the FDA is not large and hence the power of these analyses is low and because the results in the non-index trials are supportive, we can not reject definitively an effect of ARBs upon prostate cancer. Additional investigation of this hypothesis is justified. For prostate cancers there is some reassurance: The analyses suggest that, regardless of whether there is some effect of ARBs upon prostate cancer incidence, the effect is not greatly concerning because the data do not suggest a statistically or clinically significant effect upon mortality. Lung cancer, not prostate cancer, appears to be the significant concern for ARBs.

The results regarding hematologic malignancies are also inconclusive. The pre-specified meta-analysis is not statistically significant ($p = 0.07$) but the Kaplan-Meier plot in Figure 10 of times to first hematologic malignancy events is somewhat consistent with a tumor suppressor effect.

For both prostate cancers and hematologic malignancies the inconsistent trial is one of the diabetic nephropathy trials, IDNT or RENAAL. The hematologic malignancy hypothesis, like the one for prostate cancer, needs additional investigation.

The results regarding all solid cancers (excluding non-melanoma skin and brain tumors) are inconclusive but not inconsistent with the lung cancer results. There is a trend towards more solid cancers with ARB use but this may reflect the increased incidence of lung cancers (and possibly prostate cancers.) The sarcoma differences may be chance variations because the incidence curves diverge immediately before we would expect to detect a cancer promotion effect. However, following-up on this possible association is also appropriate.

I did not hypothesize regarding possible effects of dosage because most trials tested the maximum approved dosages and the dosage ranges tested in a few trials were limited to two-fold. In fact, all eleven of the trials included in the primary meta-analyses tested the maximum approved dosages. Of the other trials IRMA 2 tested both maximum and half maximum dosages (b) (4). IRMA 2 is too small, and confounded by poor follow-up, to provide any insight into effects of dosage. (b) (4)

For the prostate cancer and hematologic malignancy hypotheses I postulated that the effects, if real, would be shared with ACEIs. The data appear to support this belief because the analyses including the trials with substantial ACEI use produce RRs very close to 1.0 for both prostate and hematologic malignancies. The picture is less clear for lung cancers. The RR is higher and more significant in the five trials excluding most ACEI use than in the six trials having substantial ACEI use. Whether this is a real difference or a chance effect or related to the differing trial designs and conduct is unclear. For lung cancer we might also speculate that there could be a detection bias with ACEIs resulting from ACEI-induced cough. Other studies have usually not associated ACEI use with a higher risk of cancer. (Grossman, Messerli et al. 2002; Sipahi, Chou et al. 2011) However, we can make a similar statement for ARB use and cancer.

The strengths of this study are that I pre-specified well-defined hypotheses to test and an analytical plan providing details on cancer ascertainment and censoring, I had access to and utilized fully the raw trial data to resolve ambiguities in cancer ascertainment, and I performed patient-level meta-analyses and time-to-event and survival analyses with baseline cofactor explorations. The use of raw trial data is also a limitation because I analyzed only trials submitted to the FDA with such data. While there could be a "submission bias" analogous to a "publication bias", my expectation is that a submission bias would decrease the likelihood of finding an association between ARB use and cancer: If a drug company observed that a clinical trial of an ARB had a suspicious association between an ARB and cancer, the company should

be less likely rather than more likely to submit such a study for FDA review. In fact I believe that the drug companies did not consider cancer events in determining whether or not to submit a trial to the FDA but based their decisions to submit on the targeted efficacy indications and their business goals.

One internal FDA criticism of all of the ARB and cancer meta-analyses is that they are "fishing expeditions" (see email reproduced in Appendix 2) with severe multiplicity issues. However, as I described in the Introduction, I had identified lung cancer as a potential problem for losartan based on my review in 2002 of the LIFE trial. I formulated the lung cancer hypothesis based on the LIFE trial results; I provide documentation of the lung cancer hypothesis in Appendix 2. The one valid criticism is that the most appropriate meta-analysis may be the one excluding the LIFE trial. Because the results for that analysis are highly supportive of a lung cancer risk with ARB use, I argue that multiplicity is not an issue for the principal finding of an increased risk of lung cancer with ARB use.

Another potentially controversial aspect of the analytical plan is the decision to exclude trials because of data quality issues. I believe that the justifications of the exclusion of the five trials are valid and I provide documentation of them as Appendix 1 to this review. However, regardless of whether one considers the exclusions to be appropriate or not, they do not affect the conclusion that some ARBs appear to be associated with a higher incidence of lung cancer; they only affect the conclusion that ARBs as a class have this association. Adding to the meta-analyses the one small irbesartan trial excluded (IRMA 2) changes the results minimally. Hence for the four ARBs contributing the bulk of the data to the primary meta-analyses (candesartan, irbesartan, losartan, and telmisartan) we should have confidence that their use is associated with an increased incidence of lung cancer. Furthermore, the meta-analysis of all 15 trials that collected cancer sites for malignancies (i.e., all trials with data submitted to the FDA except VALIANT) produces a pooled RR of 1.16 and a p value of 0.027. The cancer site data submitted to the FDA are consistent with a class effect on lung cancers.

That missing trials should not negate the association between ARB use and lung cancer is illustrated strikingly by the missing losartan trials. In response to an FDA request Merck initially submitted trial-level data from five losartan clinical outcome studies conducted by Merck: LIFE and RENAAL (with raw data from prior submissions and included in these meta-analyses) (b) (4) I commented in the Introduction that the ARB Trialists Collaboration analyzed only LIFE and, while Bangalore *et al.* analyzed LIFE and RENAAL, they mis-referenced and mis-counted incident cancer cases in RENAAL: Bangalore *et al.* counted only seven cancer cases (actually drug withdrawals for cancer) while I verified from the raw data 55 solid cancers excluding brain and non-melanoma skin cancers. The lung cancer RRs (b) (4) (b) (4) to 3.0 for RENAAL ((b) (4)

(b) (4) The pattern of lung cancer trial RRs, i.e., 10 of 11 trials with RRs exceeding 1 in the primary meta-analysis and (b) (4) supports that ARB use, in particular losartan, is associated with an increased risk of lung cancer.

While we lack good data definitively confirming or refuting an association with lung cancer for four FDA-approved ARBs (azilsartan, eprosartan, olmesartan, and valsartan), the one study with valid data for valsartan (Val-Heft) has a RR estimate for lung cancer nearly identical to the primary meta-analysis. (b) (4) The association of ARBs with lung cancer remains significant in a meta-analysis of all 15 trials collecting cancer sites and having complete data submitted to the FDA. I conclude that the increased incidence of lung cancers with ARB use is likely a class effect of ARBs and that it would be inappropriate to classify azilsartan, eprosartan, olmesartan, and valsartan as safe because of their lack of adequate studies.

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(b) (6)

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Appendix 1: Justifications for the Exclusions of Five Studies from the Angiotensin Receptor Blockers and Cancer Meta-analysis

IRMA-2 (The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes.)

The NEJM publication reports the completeness of follow-up ambiguously: "A total of 30 patients in the placebo group, 27 in the group assigned to receive 150 mg of irbesartan per day, and 20 in the group assigned to receive 300 mg of irbesartan per day withdrew from the study for various reasons (Fig. 1)." In Figure 1 an additional 18 patients had no measurement of albuminuria and 3 received no drug treatment. The numbers "Completed study" are 171, 168, and 174 in Figure 1. By these numbers (171+168+174)/611 = 84% completed the study. However, four of the incomplete follow-ups were deaths, so 85% represents better the percentage with complete follow-up.

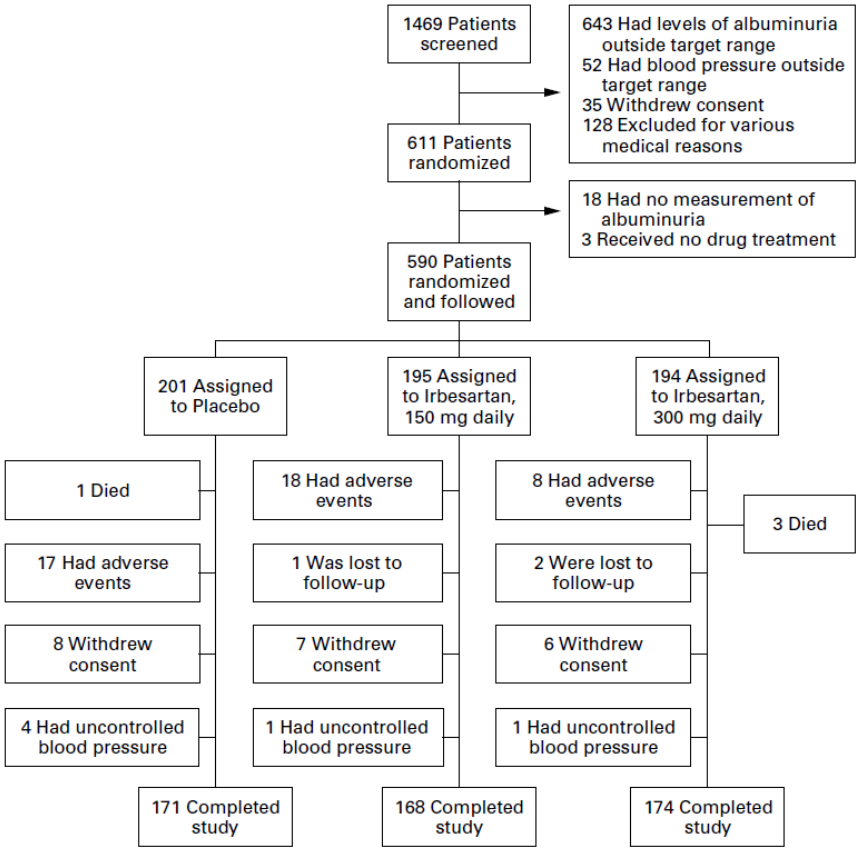


Figure 1. Profile of the Trial.
All 590 patients who underwent randomization and follow-up were included in the intention-to-treat analyses.

The ambiguity is that neither the study report nor the publication defines explicitly what "withdrew from the study" or not "completed study" represents. It is obvious that these patients didn't complete treatment, but did they have follow-up adequate for determining cancer events? The study report states the following:

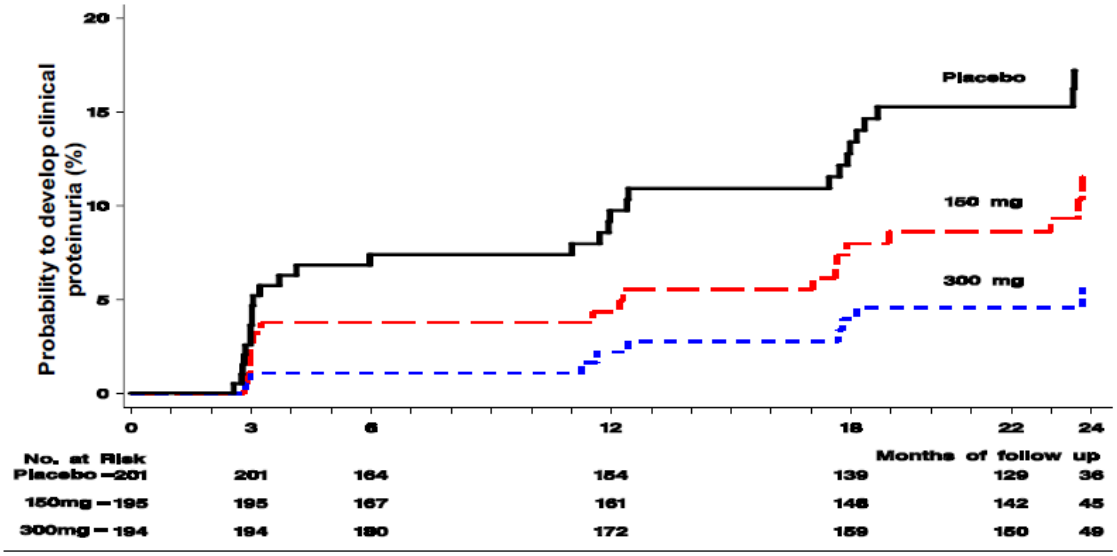
> "In the main study and GFR sub-study, AEs occurring within 10 days after study drug discontinuation were reported to the Sponsor. In the GFR extension study, AEs occurring within 4 weeks of study drug discontinuation were reported to the Sponsor."

It also states:

> "Additionally, all subjects prematurely withdrawn from the study were assessed for survival and nephrology status 2 years after the date of randomization with the exception of those who were lost-to-follow-up or deceased (added by Amendment No. 9)."

The study report has the following figure:

Figure 10.1.1.2 Estimates of Probability to Develop Clinical Proteinuria: Intent-to-Treat Subjects

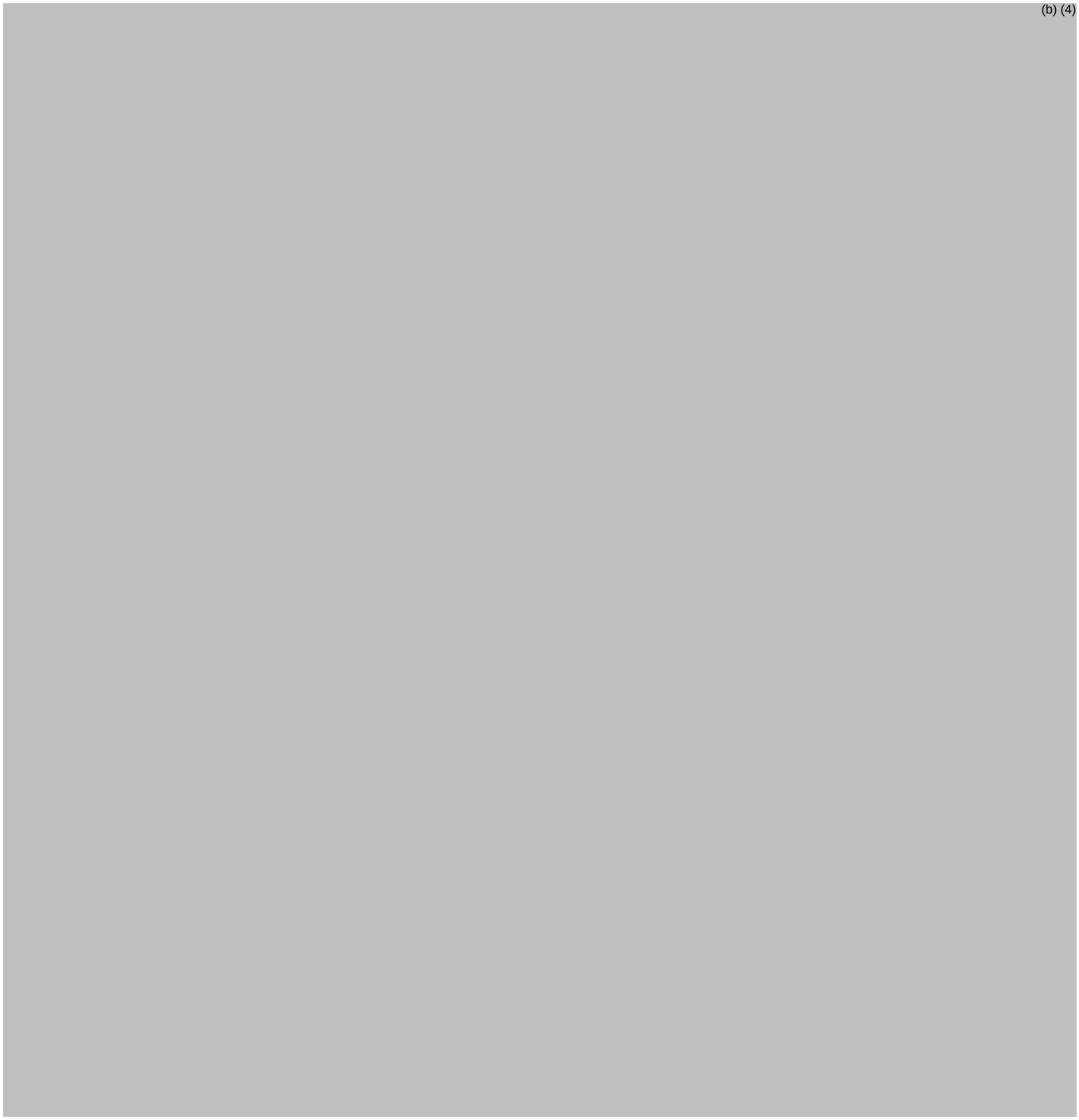


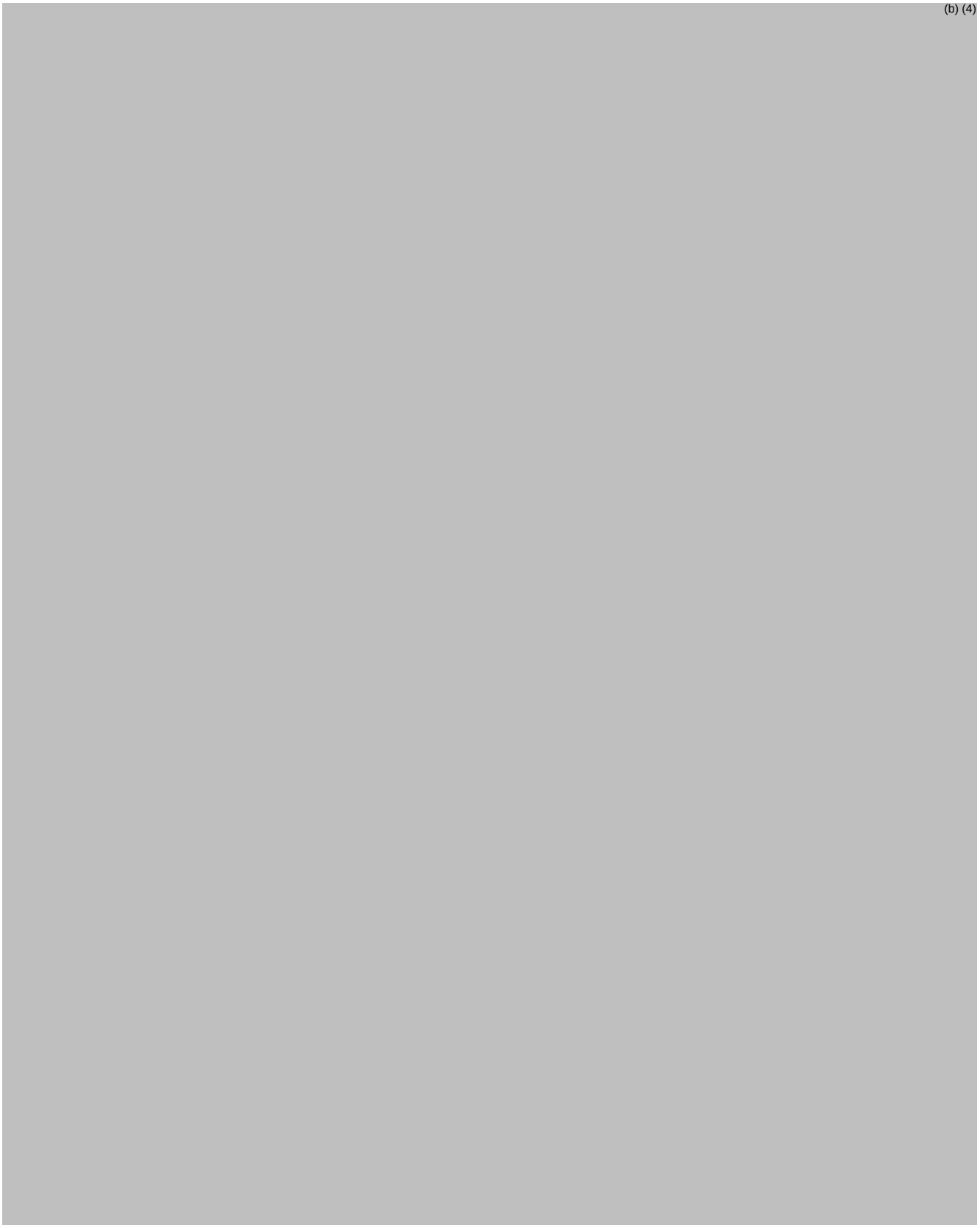
EFC2481
Dataset: Intent-to-Treat Subjects
Source: Appendix 10.1.11.3
Note: The sample size at Month 24 declines because most subjects completed Visit 9 at Month 22. Thus, this decline in sample does not indicate premature discontinuation of these subjects from the study.

Note the low numbers at risk at month 24 (IRMA 2 was reported as a 2-year study) and the explanation in the footnote in the figure.

I interpret the above as that IRMA 2 did not collect AE information 10 days to 4 weeks after treatment discontinuation. Follow-up was early even in those counted as completing the two year study. The 85% complete (about 15% incomplete) likely represents an optimistic estimate of the completeness of follow-up. IRMA 2 fails the pre-specified criterion that incompleteness of follow-up not exceeds 10%.

(b) (4)




(b) (4)

VALIANT (Multinational, multicenter, double-blind, randomized, active controlled, parallel group study comparing the efficacy and safety of long-term treatment with valsartan, captopril and their combination in high-risk patients after myocardial infarction.)

VALIANT has incomplete cancer ascertainment. The reasons for the incomplete cancer ascertainment are complicated and dependent upon the trial design, particularly how adverse event data were collected—or not collected. The most relevant section from the sponsor's "Response to FDA information request: cancer data for valsartan" dated 06-Oct-2010 is the following:

4 Ascertainment scheme for cancer

FDA request

"Comment on the ascertainment scheme for cancer."

Novartis response

Val-HeFT, VALIANT, (b) (4)

For the above-mentioned studies, all coding of investigator reported terms was re-mapped to the Medical Dictionary for Regulatory Activities (MedDRA) version 13.0, which is the latest version of MedDRA available at Novartis. Adverse events consistent with solid organ tumors were identified by the use of the Maintenance and Support Services Organization (MSSO) Standardized MedDRA Query (SMQ) "Malignant or unspecified tumors" (Narrow Search MedDRA version 13.0). Per FDA's request, all MedDRA Preferred Terms, considered to be related to hematologic/ liquid tumors, were deleted from the SMQ. Preferred terms consistent with hematologic tumors (e.g. leukemia, lymphomas and myelomas) were identified as hematological malignancies using the most recent International Classification of Diseases for Oncology and are presented in Appendix 1. As a result, 365 of the 1814 preferred terms for malignant or unspecified tumors, in the Narrow Standardized MedDRA version 13, were excluded.

Information on the most frequent MedDRA preferred terms is included for each study to provide additional data on cancer type. In addition, we have included information, using the Narrow Search MedDRA version 13 SMQ, on the incidence of breast neoplasms, malignant and unspecified SMQ, prostate neoplasms, malignant and unspecified SMQ, and lung cancer for these specific cancer types. This information was previously provided in the June 24, 2010 letter sent to FDA. As there is no specific SMQ for lung cancer in MedDRA 13, preferred terms selected by Novartis medical reviewers are used (Appendix 2).

Protocols [redacted] (b) (4) were not mapped to the narrow MedDRA terms as noted above. The cancer adverse events were taken directly from the post-text adverse event tables, as an electronic MedDRA coded dataset was unavailable.

The sponsor's response completely neglects how the cancer events were captured in the valsartan trials. For VALIANT event capture was complicated and ambiguously specified. The protocol specified the following regarding collection of adverse events:

Adverse events

Adverse events will be recorded in the CRF or the Serious Adverse Event (SAE) form if they meet the following criteria:

- Primary and secondary efficacy parameters (as described in Section 3.5.2)
- Pre-specified safety and tolerability parameters (known side effects of either captopril and/or valsartan) as described in the previous section
- Serious adverse events (as described in the following section).

Other non-serious adverse events will not be collected in the CRF. However, information

Appears This Way On Original

The criteria for SAEs were the usual regulatory ones with the criteria most applicable to malignancies being fatal or requiring or prolonging hospitalization. However, note that the first method for recording AEs above is "Primary and secondary efficacy parameters". The relevant ones from Section 3.5.2 are the following:

Primary efficacy parameters

The primary efficacy parameter is all-cause mortality (time to death).

Secondary efficacy parameters

Secondary efficacy parameters are as follows:

- All-cause (unplanned and elective) hospitalization

Death and all-cause hospitalizations were the first primary and first secondary efficacy parameters. However, where investigators should have recorded malignancies (on the efficacy and death CRFs or some other CRF) is ambiguous per the following directions reiterated for each visit:

- For adverse events occurring since the last visit:
  - ◊ Complete the Serious Adverse Event CRF for any serious adverse events that are **suspected to be related** to the administration of study medication. (See Section 3.5.3: Safety assessments, for the definitions to be used in evaluating the seriousness of an adverse event and for determining the relationship of an adverse event to study medication.)
  - ◊ Record serious events **not suspected to be related** to study medication in the CRF and/or endpoint documentation.

Potentially an investigator should never have recorded a malignancy event as an AE or SAE but only as a death event or hospitalization event. However, the hospitalization CRF captured only the primary admission diagnosis (e.g., which could be "hemoptysis" or "chest pain" for an eventual lung cancer diagnosis, with the latter never captured on the CRFs):

And the death form did not capture a text cause for a malignancy death but only a checkbox:

Hence for patients with new malignancies who didn't die during the study we might not know that they had a new malignancy; for those who died we might only know that they died from a malignancy but not know the cancer site (including not knowing hematologic vs. solid cancer.) Similarly, history of cancer at baseline was recorded as a checkbox for "History of Cancer within 5 years." Determining whether cancers are incident (new) or recurrent in VALIANT is impossible for many cases.

The unfortunate ambiguities in the protocol and CRFs are reflected in the data. I analyzed all relevant VALIANT AE, hospitalization, and death datasets for cancer diagnoses. The numbers of neoplasms used for the FDA M-A were 143 valsartan, 83 control. (RR 0.86.) (VALIANT had three arms with 1:1:1 randomization: valsartan alone, valsartan+captopril, and captopril alone. For the FDA M-A and these analyses "ARB" or "valsartan" references the combined valsartan alone and valsartan+captopril arms and "control" references the captopril alone arm.) The counts of patients with neoplasms in the AE datasets are virtually identical (143 valsartan, 82 control, RR 0.87) to the FDA M-A counts. The hospitalization data set identifies another 103

patients with neoplasms not included in these numbers and the death dataset identifies another 79 (55 valsartan, 24 control, RR 1.15) who died of a malignancy excluding patients with reported hematologic malignancies. Combining the AE and death neoplasms yields 198 valsartan and 106 control neoplasms, RR 0.94. Combining the AE, hospitalization, and death neoplasms (all sources) yields 248 valsartan and 134 control neoplasms, RR 0.93. Note that, while the VALIANT FDA M-A results are favorable for valsartan, the unreported cases are unfavorable.

The NDA documents neoplasms for an additional 156 patients, 70% more than those counted in the FDA M-A. All of these numbers are likely still underreporting because, as documented above, the event reporting in VALIANT did not guarantee that all malignancies were reported. The death rate was high in patients with reported neoplasms, i.e., about 44% during the study in neoplasms reported other than death only. There were 46 cases reported only as malignancy deaths. If we assume that the death rate in unreported cases is the same as the death rate in reported neoplasms, then we would expect 46/0.44 = 105 cases either reported as a malignancy death only or not reported at all such that we do not have cancer site data.

The cancer data collected in VALIANT, both regarding completeness of ascertainment and the reporting of cancer sites, are too incomplete to be valid for any cancer M-As.

Appendix 2: Documentation of the ARB and Lung Cancer Hypothesis

One internal FDA criticism of all of the ARB and cancer meta-analyses is that they are "fishing expeditions" with severe multiplicity issues as expressed in the following email message:

From: Unger, Ellis
Sent: Wednesday, September 05, 2012 2:25 PM
To: Soukup, Mat; Jagadeesh, Gowra G; Gordon, Maryann; Stockbridge, Norman L; Nguyen, Quynh M; McCloskey, Carolyn A; Andraca-Carrera, Eugenio; Zornberg, Gwen; Ton, Phuong Nina; Marciniak, Thomas; Wachter, Lori; Southworth, Mary Ross
Cc: Temple, Robert
Subject: RE: Finalized - SAFETY-935 General Review (REV-CLINICAL-03)

I attempted to attach the following comments to Norman's memo without success. (DARRTS would not accept them, presumably because there were too many characters.) I plan to place this into DARRTS in the next day or two:

I agree with Dr. Stockbridge. I also note that no analysis, or group of analyses, no matter how carefully conducted, can circumvent the multiplicity problem here.

When considering adverse events, one can always perform a meta-analysis on a group of randomized controlled studies (RCTs) with a total sample size in the tens of thousands and find statistically significant differences, so-called "signals," especially at p-values that are only barely statistically significant (i.e., p-values just less than 0.05). One has no way of knowing how many other drugs or drug groups were assessed, or how many potential safety issues were considered (e.g., cancer [and many types of cancer], myocardial infarction, stroke, diabetes, dementia, etc.). Moreover, one has no way of knowing how criteria were established to make decisions about which studies to include or exclude in the meta-analysis.

Thus, such analyses amount to post hoc "fishing expeditions;" useful for hypothesis generation, but by no means conclusive. One must be cognizant of the inherent multiplicity and inflation of Type-I error, with the potential, or even the likelihood, of finding false positives. For example, if Sipahi et al had reported ALL safety signals of interest in the 61,590 subjects, it would not have been surprising if they had found some with RR <= 0.93, the reciprocal of 1.08, i.e., suggesting that ARBs prevent some adverse event.

Finally and importantly, it is critical to recognize that performance of additional, related, analyses on the same group of RCTs, no matter how comprehensive and refined those analyses might be, does not circumvent the original multiplicity issue. They amount to "fishing" in the same "waters." Similar findings are expected; they do not "confirm" the original finding

By Dr. Unger's arguments, we could rarely have safety concerns because most safety concerns arise from *post hoc* findings, e.g., *torsades de pointes* with terfenadine, cardiac events with rofecoxib. Dr. Unger in particular should be a supporter of *post hoc* analyses rather than an opponent because[redacted] (b) (4)

However, while Dr. Unger's "fishing expedition" analogy does not even apply to most safety analyses, it is completely inapplicable to the Sipahi *et al.* meta-analysis and to this review. While Sipahi *et al.* initiated their meta-analysis based on *post hoc* findings in the candesartan CHARM trials, they tested their hypothesis prospectively in the other ARB studies. My concerns with losartan and lung cancer predated Sipahi *et al.*'s observations: I noted an imbalance in lung cancers in the LIFE trial in 2002. Because it was not statistically significant and an isolated finding I did not specifically comment upon it in my review. I did include the following table in my review for future reference—and Sipahi *et al.* used the data in the table for their meta-analysis:

Table 82: Sponsor's Serious Adverse Events with Frequencies ≥ 0.5% of Patients

	Losartan (N=4605)		Atenolol (N=4588)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	1715	(37.2)	1660	(36.2)
Patients with no adverse experience	2890	(62.8)	2928	(63.8)
Body as a Whole/Site Unspecified	**414**	**(9.0)**	**398**	**(8.7)**
Abdominal pain	24	(0.5)	31	(0.7)
Chest pain	21	(0.5)	26	(0.6)
Drug overdose	88	(1.9)	65	(1.4)
Inguinal hernia	29	(0.6)	28	(0.6)
Syncope	59	(1.3)	49	(1.1)
Cardiovascular System	**357**	**(7.8)**	**396**	**(8.6)**
Atrial fibrillation	96	(2.1)	93	(2.0)
Bradycardia	9	(0.2)	43	(0.9)
Deep venous thrombosis	30	(0.7)	21	(0.5)
Pulmonary embolism	18	(0.4)	25	(0.5)
Transient ischemic attack	35	(0.8)	49	(1.1)
Digestive System	**287**	**(6.2)**	**261**	**(5.7)**
Colonic malignant neoplasm	26	(0.6)	21	(0.5)
Endocrine System	**39**	**(0.8)**	**39**	**(0.9)**
Eyes, Ears, Nose, and Throat	**92**	**(2.0)**	**93**	**(2.0)**
Cataract	27	(0.6)	22	(0.5)
Hemic and Lymphatic System	**53**	**(1.2)**	**50**	**(1.1)**
Anemia	31	(0.7)	16	(0.3)
Hepatobiliary System	**107**	**(2.3)**	**79**	**(1.7)**
Cholecystitis	29	(0.6)	24	(0.5)
Cholelithiasis	51	(1.1)	46	(1.0)
Metabolism and Nutrition	**26**	**(0.6)**	**28**	**(0.6)**
Musculoskeletal System	**385**	**(8.4)**	**367**	**(8.0)**
Hip osteoarthritis	35	(0.8)	33	(0.7)
Knee osteoarthritis	33	(0.7)	16	(0.3)
Musculoskeletal chest pain	26	(0.6)	24	(0.5)
Nervous System	**122**	**(2.6)**	**124**	**(2.7)**
Vertigo	41	(0.9)	39	(0.9)
Psychiatric Disorder	**57**	**(1.2)**	**37**	**(0.8)**
Respiratory System	**189**	**(4.1)**	**193**	**(4.2)**
Lung malignant neoplasm	29	(0.6)	12	(0.3)
Pneumonia	75	(1.6)	96	(2.1)
Skin and Skin Appendages	**127**	**(2.8)**	**129**	**(2.8)**
Basal cell carcinoma	66	(1.4)	58	(1.3)
Urogenital System	**318**	**(6.9)**	**274**	**(6.0)**
Breast malignant neoplasm	37	(0.8)	36	(0.8)
Prostatic disorder	28	(0.6)	22	(0.5)
Prostatic malignant neoplasm	58	(1.3)	42	(0.9)
Although a patient may have had 2 or more serious adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.				

Note that lung malignant neoplasm SAEs as reported by the sponsor are 29:12 losartan:control , a significant imbalance. Both the Sipahi *et al.* and FDA meta-analyses used these numbers. However, not all lung cancers are reported as "lung malignant neoplasm" or as SAEs. The counts of lung cancers in LIFE in the datasets are 45:36, not statistically significant for the LIFE study alone. (Note that the differing LIFE lung cancer counts illustrate well the problems of depending upon published statistics—even from FDA reviews—for meta-analyses. One has to understand completely how the numbers were generated and their limitations in order to perform a definitive meta-analysis. Sipahi *et al.* were correct when they concluded that their findings warranted further investigation—but the FDA meta-analysis did not recognize its limitations. The differing LIFE lung cancer counts also illustrate that the counts used in this review are not always less favorable for ARBs than those used in other meta-analyses.)

When the publication of the Sipahi *et al.* meta-analysis stimulated interest in this topic and a formal response from the FDA, I communicated my observations from the LIFE study to the FDA staff responsible for the formal response in the following email messages:

From: Marciniak, Thomas
Sent: Friday, June 11, 2010 12:43 PM
To: Southworth, Mary Ross
Cc: Stockbridge, Norman L
Subject: RE: ARBs and risk of cancer

Attachments: LIFE cancers.doc

You're right, I didn't include it in my review because the signal is weak so I did not want to create a stir. I've attached what analysis logs regarding cancer stats in LIFE I have.

Tom

_____

From: Southworth, Mary Ross
Sent: Friday, June 11, 2010 12:29 PM
To: Marciniak, Thomas
Subject: RE: ARBs and risk of cancer

Was there a review of the cancer finding in the LIFE study? I have looked through the NDA and IND and am having trouble locating anything pertinent.

_____

From: Marciniak, Thomas
Sent: Friday, June 11, 2010 10:48 AM
To: Southworth, Mary Ross; U, Khin M; Karkowsky, Abraham M
Cc: Pease-Fye, Meg; Stockbridge, Norman L; U, Khin M
Subject: RE: ARBs and risk of cancer

Losartan in the LIFE study (lung cancer if I remember correctly), although weak and there is also a weak signal for HCTZ and renal cell carcinoma. Khin knows about telmisartan.

Tom

_____

From: Southworth, Mary Ross
Sent: Friday, June 11, 2010 10:03 AM
To: Marciniak, Thomas; U, Khin M; Karkowsky, Abraham M
Cc: Pease-Fye, Meg; Stockbridge, Norman L
Subject: ARBs and risk of cancer

We were recently informed about the impending publication of a meta-analysis about the association b/w ARBs and cancer (see below).

In investigating the background of this issue, I see that there was a cancer signal (fatal cancers) in the CHARM program and it looks like some of the more recent large ARB trials (TRANSCEND, ONTARGET) did target collection of cancer events. I imagine this was in an attempt to further investigate this signal. Do any of you have info on this--or point me to a review in which you discussed it? Thanks!

<< OLE Object: Picture (Metafile) >>
THE LANCET ONCOLOGY: PRESS RELEASE
EMBARGO: 1830H (New York time) Sunday 13 June 2010
WIDELY USED CLASS OF BLOOD PRESSURE MEDICATIONS LINKED TO INCREASED CANCER RISK

Note that I reaffirmed at the start of the FDA formal response that the signal in LIFE for losartan was an increased rate of lung cancer.

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

/s/

THOMAS A MARCINIAK
03/07/2013

Angiotensin Receptor Blockers (ARBs) and Cancer
Overview of Key FDA Documents

The issue of ARBs and cancer—and the unmitigated risk to public health—has now been outstanding since 2010. Because there have been many reviews, documents, and communications produced on this topic, this document provides an overview and brief descriptions of the key FDA documents.

List of Key FDA documents

1007 FDA safety comm.pdf
1007 Southworth plan.pdf
1008 FDA pharmtox review.pdf
1103 DB7 ARBs SAP v15.pdf
1105 DB7 M-A.pdf
1105 Southworth memo.pdf
1106 FDA safety comm.pdf
1106 Southworth press release.pdf
1205 Marciniak losartan & ca review.pdf
1207 DB7 M-A addendum.pdf
1208 Marciniak ARB ca review plan v1p2.pdf
1208 Marciniak M-A addendum review.pdf
1209 Stockbridge-Unger decision memo.pdf
1303 Marciniak ARBs & ca review.pdf
1303 Marciniak ARBs & ca-addendum.pdf
1304 Stockbridge et al decision memo.pdf
1304 Unger decision memo.pdf
1305 FDA ARBs preclin.pdf
1305 Marciniak ARBs & ca decision response.pdf
1307 FDA rodent carc studies.pdf
1311 Marciniak preclin comments.pdf
1311 Marciniak pub hlth impact.pdf
1407 Marciniak MRA trial results.pdf
1412 Marciniak LCZ696 & ca review.pdf

Note the following document naming conventions:

- The four digits starting each document name are the document's year and month to facilitate reading in chronological order.

- The last name of the principal author follows the year and month with the following variations:
    - The FDA public safety communications do not have named authors.
    - DB7 references the FDA Division of Biometrics 7.

- The rest of the document name is an abbreviated description of the contents. More details are provided below under Document Descriptions.

Overview

The issue of ARBs and cancer—and the unmitigated risk to public health—has now been outstanding for over three years. It was the topic of a 2011 FDA public safety communication that falsely reassured the public about the safety of ARBs based on an admittedly flawed meta-analysis—a fact that would be extremely embarrassing to FDA management if scrutinized. Because drug safety communications are cleared at least as high as the level of the Director of the Center for Drug Evaluation and Research and because the FDA management at the Division and Office levels have affirmed and reaffirmed their refusal to make public the analyses supporting and refuting the association of ARBs with cancer making it impossible for the medical community and patients to form their own judgments based on the best data available, this issue must be reviewed outside of the FDA.

The document that describes best the available data and documents the association of ARBs with cancer is *1303 Marciniak ARBs & ca review.pdf*. This document provides the results of a rigorous, patient-level meta-analysis of all major ARB trials with adequate cancer data submitted to the FDA. The meta-analysis estimates that ARB use is associated with increased risks of lung cancer and of lung cancer deaths. The last document *1311 Marciniak pub hlth impact.pdf* uses the results of the meta-analysis to estimate the public health impacts of the association. These two documents are the most valuable ones for understanding the issue of ARBs and cancer. Read them first to judge whether this issue is worth scrutinizing.

The original FDA meta-analysis, upon which the June 2011 safety communication (*1106 FDA safety comm.pdf*) clearing ARBs is based, is *1105 DB7 M-A.pdf*. That meta-analysis has many flaws including not counting "lung carcinoma" as lung cancer, an error that the authors have admitted. The flaws are described in *1205 Marciniak losartan & ca review.pdf*. The original FDA meta-analysis was revised in *1207 DB7 M-A addendum.pdf* but still with flaws documented in *1208 Marciniak M-A addendum review.pdf*.

The first decision memo not to reopen the tracked safety issue (TSI) was *1209 Stockbridge-Unger decision memo.pdf* and is superseded by *1303 Marciniak ARBs & ca review.pdf* and *1303 Marciniak ARBs & ca-addendum.pdf*. The additional decision memos *1304 Stockbridge et al decision memo.pdf* and *1304 Unger decision memo.pdf* reaffirming the refusal to reopen the issue have many flaws addressed in *1305 Marciniak ARBs & ca decision response.pdf*.

The last documents filed by FDA reviewers are partial reviews of preclinical data, *1305 FDA ARBs preclin.pdf* and *1307 FDA rodent carc studies.pdf*. The problems with them are addressed in *1311 Marciniak preclin comments.pdf*.

Document Descriptions

1007 FDA safety comm.pdf

The first ARBs and cancer safety communication announced that the FDA was evaluating the issue because of a published meta-analysis. (Sipahi I, Debanne SM, Rowland DY, Simon DI, Fang JC. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. The Lancet Oncolology 2010;11(7), 627-36) The Sipahi *et al.* paper is worth reading but is not included with the FDA documents because of copyright restrictions.

1007 Southworth plan.pdf

The FDA high-level analysis plan proposed doing a study-level meta-analysis. The plan recognizes the superiority of a patient-level analysis: "At this time, our analysis will focus on study-level data since the finding of increased cancer risk in the published meta-analysis has uncertain validity. Should the signal be confirmed with our new analysis, we may consider doing a patient level analysis to further assess the risk."

1008 FDA pharmtox review.pdf

A review of the pre-clinical evidence by Division pharmacology and toxicology staff presented both the pre-clinical evidence supporting tumor promotion and that supporting tumor suppression.

1103 DB7 ARBs SAP v15.pdf

The FDA meta-analysis statistical analysis plan (SAP) does not define incident cancer or the censoring period. The data to be analyzed are sponsor submitted trial-level data specifically for this meta-analysis. Compare this plan to *1208 Marciniak ARB ca review plan v1p2.pdf*.

1105 DB7 M-A.pdf

The original FDA meta-analysis has many flaws, e.g., not counting lung carcinomas as lung cancers. The flaws are described in *1205 Marciniak losartan & ca review.pdf*.

1105 Southworth memo.pdf

This memo reiterates the findings of the original FDA meta-analysis, *1105 DB7 M-A.pdf*.

1106 FDA safety comm.pdf

This FDA safety communication states that "FDA has concluded that treatment with an ARB medication does not increase a patient's risk of developing cancer." Such a drug safety communication is cleared at the Center director level.

1106 Southworth press release.pdf

This news release states that "The FDA has determined that any concern about a relationship between ARB use and development of cancer has been resolved by this analysis" (the original FDA meta-analysis *1105 DB7 M-A.pdf*).

1205 Marciniak losartan & ca review.pdf

This review identifies problems with *1105 DB7 M-A.pdf* including failure to count lung carcinoma as lung cancer and failure to define incident cancer and the censoring period. It recommended performing a patient-level meta-analysis expeditiously.

1207 DB7 M-A addendum.pdf

This addendum to *1105 DB7 M-A.pdf* counted lung carcinoma as lung cancer but not metastatic lung carcinoma. Because some study-level cancer summaries reported the same patient by more than one MedDRA term, e.g., lung carcinoma and malignant lung neoplasm, the authors calculated alleged "minimum and maximum possible OR" (odds ratio) rather than requesting sponsors to submit unambiguous statistics on cancers by patient. The flaws in this addendum are described in *1208 Marciniak M-A addendum review.pdf*.

1208 Marciniak ARB ca review plan v1p2.pdf

This plan for a patient-level analysis of the raw data for all large ARB outcome trials submitted to the FDA was reviewed by the Division and Office directors. It corrected all of the flaws in the FDA meta-analyses *1105 DB7 M-A.pdf*" and *1207 DB7 M-A addendum.pdf*. The Division Director's comment was ""For my part, I think you did well in anticipating my major concerns--blinding, multiplicity, what studies to include, what to lump or split, and how the results might influence regulatory decision-making. We aren't likely to agree about how exactly those issues are handled, but I think you did well by addressing each."

1208 Marciniak M-A addendum review.pdf

This review identifies the flaws in the FDA meta-analysis addendum, *1207 DB7 M-A addendum.pdf*.

1209 Stockbridge-Unger decision memo.pdf

This decision memo by the Division and Office directors closed the safety issue without further action despite the identified flaws in the FDA meta-analyses.

1303 Marciniak ARBs & ca review.pdf

This review reports the results of a rigorous, patient-level meta-analysis of all major ARB trials with adequate cancer data submitted to the FDA. The meta-analysis results suggest an association between ARB use and lung cancer.

1303 Marciniak ARBs & ca-addendum.pdf

This addendum to *1303 Marciniak ARBs & ca review.pdf* adds analyses of all-cause mortality and recommendations for regulatory action. Its recommendations include holding an advisory committee meeting addressing the issue and expanding the meta-analysis to all large ARB trials including the ones for which raw data were not previously submitted.

1304 Stockbridge et al decision memo.pdf

This decision memo by the Division Deputy Director for Safety, the Division Director, and the Office Director left the safety issue closed without further action. The flaws in it are addressed in *1305 Marciniak ARBs & ca decision response.pdf*. While this memo was authored at the Division and Office level, because the issue was one already addressed in a FDA public safety communications, the action should have been cleared at least as high as the Center level.

1304 Unger decision memo.pdf

This memo provides the Office Director perspective on the issue. The flaws in it are also addressed in *1305 Marciniak ARBs & ca decision response.pdf*.

1305 FDA ARBs preclin.pdf

This memo describes preclinical *in vivo* studies that it claims were not adequately addressed in the earlier preclinical review, *1008 FDA pharmtox review.pdf*.

1305 Marciniak ARBs & ca decision response.pdf

This review identifies the flaws in the April 2013 decision memos, *1304 Stockbridge et al decision memo.pdf* and *1304 Unger decision memo.pdf*.

1307 FDA rodent carc studies.pdf

This "overview" of the ARB rodent carcinogenicity studies is a flawed, non-standard meta-analysis of some of those studies. Its flaws are addressed in *1311 Marciniak preclin comments.doc*. Among other errors it, like the FDA clinical trials meta-analysis, does not count lung cancers correctly in some of the rodent studies.

1311 Marciniak preclin comments.pdf

This review summarizes the suggestive evidence from the ARB rodent carcinogenicity studies and identifies the flaws in *1307 FDA rodent carc studies.pdf*.

1311 Marciniak pub hlth impact.pdf

This review estimates the public health impact of the association of ARBs and lung cancer.

1407 Marciniak MRA trial results.pdf

This review includes the cancer findings in the (b) (4) outcome trials of mineralocorticoid receptor antagonists (MRAs): RALES and (b) (4) for spironolactone and EPHESUS and (b) (4) for eplerenone. The results are suggestive that lung cancer is more frequent with MRA use.

1412 Marciniak LCZ696 & ca review.pdf

This review evaluates cancer findings in the PARADIGM trial of the combination ARB-neprilysin inhibitor LCZ696. It also expands on the results of ARB trials with ACE inhibitor controls.

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/s/

THOMAS A MARCINIAK
12/28/2014