

Cross-Discipline Team Leader Review Memo

Date	December 8, 2014
From	Thomas A. Marciniak, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 206-143
Supp #	000
Proprietary / Established (USAN) names	Corlanor/ ivabradine
Dosage forms / strength	oral tablets / 5 mg, 7.5 mg
Proposed Indication(s)	to reduce the risk of (b) (4) hospitalizations for worsening heart failure in patients with chronic heart failure (b) (4) in sinus rhythm with heart rate ≥ 70 beats per minute (bpm), (b) (4) maximally tolerated doses of beta blockers or when beta blocker therapy is contraindicated (b) (4)
Recommended:	approval to reduce the risk of cardiovascular mortality and hospitalizations for worsening heart failure in patients with chronic heart failure (b) (4) and in sinus rhythm with either non-ischemic etiology and a heart rate ≥ 70 beats per minute (bpm) or with ischemic etiology and a heart rate ≥ 75 bpm and taking a loop diuretic, (b) (4) including maximally tolerated doses of beta blockers or when beta blocker therapy is contraindicated (b) (4)

1. Introduction to Review

Ivabradine is an inhibitor of the cardiac pacemaker I_f current that the applicant claims is a (b) (4) heart rate lowering agent". Ivabradine is approved in Europe for the treatment of angina and for the treatment of heart failure (HF) in patients in sinus rhythm and whose heart rate is ≥ 75 bpm in combination with standard therapy including beta blockers (BBs) or when beta blockers are not tolerated. This application is for the HF indication

One outcome study, SHIFT (Swedberg, Komajda et al. 2010), primarily supports the HF indication, but there are three placebo-controlled outcome studies that are relevant. I list them in Table 1.

Table 1: Placebo-Controlled Outcome Trials of Ivabradine in HF and IHD

Trial	Population	N	Results
SHIFT	HF + LVEF \leq 35 + HR \geq 70	6,558	\downarrow HF hospitalization; \downarrow CV death?
BEAUTIFUL	Stable IHD + LVEF $<$ 40 + HR \geq 60	10,917	neutral for CV death & HF hospitalization; \downarrow MI ?
SIGNIFY	Stable IHD + LVEF $>$ 40 + HR \geq 70	19,102	\uparrow CV death & MI in symptomatic angina

CV = cardiovascular; HF = heart failure; HR = heart rate; IHD = ischemic heart disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction

The results of these three outcome trials are complex, inconsistent, and difficult to interpret. On the one hand SHIFT appears to demonstrate a highly significant benefit for HF hospitalizations in HF patients with higher heart rates and intolerant of, or inadequately dosed with, BBs. Mortality in SHIFT leans favorable. On the other hand BEAUTIFUL (Fox, Ford et al. 2008) failed to show any HF hospitalization or mortality benefit in IHD patients with reduced systolic function. While BEAUTIFUL suggested an MI benefit not seen in SHIFT, the large confirmatory trial SIGNIFY (Fox, Ford et al. 2014) failed to confirm this benefit and even suggests a detrimental impact in patients with symptomatic angina. Furthermore, SHIFT was performed entirely outside the U.S. with practice patterns, e.g., little intracardiac defibrillator (ICD) and cardiac resynchronization therapy (CRT) use, differing from U.S. guidelines and raising the issue of relevance to U.S. practice. Additionally, analyses of SHIFT suggest several significant drug interactions and subgroup variations. In this review I present the data addressing all of these issues. Finally, I propose and justify a modified indication for ivabradine use in HF patients.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

All studies were not conducted under U.S. IND. Ivabradine was approved in Europe for the treatment of angina in 2005 and in 2012 for the treatment of heart failure (HF) in patients in sinus rhythm and whose heart rate is ≥ 75 bpm in combination with standard therapy including beta blockers (BBs) or when beta blockers are not tolerated. Recently the EMA added restrictions to the European label based on the unfavorable subgroup analysis of the SIGNIFY study.

3. CMC/Microbiology/Device

The CMC reviews are pending. The reports from the CMC reviewers to date indicate that there are not any issues that justify disapproval that will not be resolved by the PDUFA date.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer, Dr. Jean Wu, states that there is no approvability issue from the pharmacology/toxicology perspective. Her findings most relevant to clinical use are the following:

- Ivabradine is the first for the class of HCN (hyperpolarization activated cyclic nucleotide gated) channel blockers. It inhibits I_f in pacemaker cells of rabbit sinoatrial node and I_h in mouse retina rods with comparable potency, IC_{50} of $\sim 3 \mu M$.
- Rats in the 52-week studies at exposures 2 to 3 fold higher than the human exposures at maximum recommended human dose (MHRD) showed myocardial lesions including necrosis and fibrosis. These findings are similar to those reported with beta blockers and were not seen in dogs.

- While electroretinographic studies in dogs showed some abnormalities that normalized after a 1 week recovery period, no changes were detected on ophthalmoscopic and transmission electron microscopic exams.
- In pregnant rats treated during organogenesis, external abnormal shape of the heart (dysplasia) with or without simple anomalies of the major proximal arteries was observed at exposure close to human AUC_{24h} at MRHD and above. Teratogenic effects include interventricular septal defect and complex anomalies of the major proximal arteries observed at exposure 3 times human AUC_{24h} at MRHD.

COMMENT: The pharmtox review critiques studies performed by the applicant and submitted. However, other studies published in the literature are also highly relevant. HCN channels are upregulated in animal models of HF. (Fernandez-Velasco, Goren et al. 2003; Herrmann, Hofmann et al. 2012; Hofmann, Fabritz et al. 2012) Overexpression of I_f has also been reported in ventricular myocytes from failing human hearts. (Stillitano, Lonardo et al. 2008) In a mouse HF model with HCN channel overexpression HCN channel blockade by ivabradine reduced lethal arrhythmias. (Kuwabara, Kuwahara et al. 2013) In a rat MI model with HCN channel upregulation spironolactone reduced HCN upregulation and ventricular premature beats (VPBs) and ivabradine reduced VPBs in both spironolactone and untreated rats. (Song, Yang et al. 2011) Finally, HCN channel remodeling in atria was demonstrating in a dog HF model (Zicha, Fernandez-Velasco et al. 2005) and could be responsible for the increased incidence of atrial fibrillation with ivabradine.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology reviewers, Drs. Martina Sahre and Sreedharan Sabarinath find, from a clinical pharmacology perspective, the information in general support approval and sufficient to provide appropriate dosing instructions for safe and effective use. Some noteworthy findings are the following:

- Ivabradine is extensively metabolized, with CYP3A4 being the main responsible enzyme for the metabolism of the drug, including the main metabolite S18982.
- (b) (4) at levels similar to human exposures. However, an interaction study with metformin did not show an effect upon metformin exposure.
- They report an association between baseline and on-treatment heart rate reduction and incidence rate for cardiovascular death or hospitalization for worsening of heart failure for both ivabradine and placebo treatments.

COMMENT: Missing from the clinical pharmacology review is any discussion of the possible drug interactions observed in the clinical trials, i.e., the strong interaction between ivabradine and loop diuretics for CV mortality and the possible one with statins for CV mortality. The review also does not discuss the clinical evidence for OCT2 inhibition effects. While the metformin interaction study was negative, post-baseline creatinine values were slightly higher

with ivabradine than with placebo and renal insufficiency adverse events were more frequent with ivabradine, both possibly related to OCT2 inhibition.

6. Clinical Microbiology

Ivabradine an oral non-antimicrobial drug for which there are no clinical microbiology concerns.

7. Clinical/Statistical

7.1. Efficacy

7.1.1. Dose identification/selection and limitations

The applicant based dose selection on the heart rate (HR) reduction, limited by the occurrence of high rates of visual symptoms at dosages of 10 mg BID and higher. The starting dosage in the pivotal SHIFT study was 5 mg BID that the investigators could up-titrate to 7.5 mg BID or down-titrate to 2.5 mg BID to achieve a target HR of 50-60 bpm without symptomatic bradycardia. Whether this HR target is optimal, and what starting HR is advisable, are review issues.

7.1.2. Studies essential for approval

One reportedly successful study in HF patients (SHIFT) supports the proposed indication. See Section 1 above.

7.1.3. Other studies

Two unsuccessful studies (BEAUTIFUL in ischemic heart disease (IHD) patients with systolic dysfunction and SIGNIFY in IHD patients without systolic dysfunction) are relevant because about 68% of SHIFT patients had an ischemic etiology for their HF. See Section 1 above.

7.1.4. Primary clinical and statistical reviewers' findings and conclusions

The primary clinical reviewers, Drs. Preston Dunnmon (efficacy) and Nhi Beasley (safety), recommend approval for what they describe as a "two-tiered" indication. Both tiers restrict the indication to (b) (4) with ejection fraction $\leq 35\%$ and (b) (4) HR \geq (b) (4) bpm. One tier, in patients on a maximally tolerated dose of a beta blocker, restricts the benefit of the indication to HF hospitalizations. The other tier, in patients (b) (4) .

COMMENT: Regardless of whether the CV mortality benefit is reduced or absent in patients on maximum labeled dosages of beta blockers (an observation I support), I don't see the advantage of specifying a split indication. The critical parts of the indication are the restrictions on eligible patients. Furthermore, the binary split does

not convey the real situation because the data suggest that patients on lower dosages of beta blockers do appear to enjoy some beneficial effects upon CV mortality. I favor a single, non-tiered indication as I justify below.

The primary statistical reviewer, Dr. Steve Bai, does not make a recommendation regarding approval. He concludes that the primary objective of the SHIFT study was reached but finishes by stating that the issue of inconsistent findings among the three large outcome trials of ivabradine needs to be addressed.

In the primary clinical review many of the summary statements and conclusions regarding efficacy are not supported or are contradicted by the data. The first discussion in the opening Section 1.1 Recommendation on Regulatory Action is the following:

“It should be noted that the benefit for reduction of hospitalization for WHF is progressively attenuated as beta-blocker dosing approaches guideline-directed target doses of beta blockers. For CV mortality, a nominally significant improvement with ivabradine therapy is seen only in the sub-population taking no beta-blockers at all. This benefit disappears when any background beta-blocker therapy is present.”

These statements are not supported by the data:

- The first sentence in the quote above is completely wrong. In the proposed indicated population (see Section 7.1.6.4) the HF hospitalization benefit is independent of beta blocker dosage—see Figure 18.
- The second and third sentences in the quote misrepresent the relationship between beta blocker dosage and CV mortality. The CV mortality benefit is more than “nominally significant” “only in the sub-population taking no beta-blockers at all.” It is highly statistically significant ($p = 0.001$) in my entire proposed indicated subgroup (within the limitation that the indicated subgroup is a *post hoc* subgroup)—see also Figure 15. It is true that the CV mortality benefit does appear to vary by baseline beta blocker dosage—see Figure 17. The benefit appears to be attenuated with increasing beta blocker dosages but still present at the lower dosages.

The primary efficacy review frequently hypothesizes mechanisms and draws conclusions based on them not supported by the data. An example of this illogic is the following:

“Ivabradine demonstrates rate dependence of I_f blockade. Accordingly, concomitant therapy with other negative chronotropes appears to blunt the clinical effect of ivabradine (no significant benefit in patients taking at least 50% of target doses of guideline-directed beta-blockers or digoxin, section 6.1.7). SHIFT is

essentially a trial of combination negative chronotropes (ivabradine ± beta-blockers ± digoxin ± Amiodarone).”

Digitalis (dig) preparations were taken by about 22% of patients at baseline but amiodarone only in about 3%. Because their use was uncommon and not randomly assigned, I would hardly call SHIFT a trial of combination chronotropes. Regardless, there are no statistically significant interactions between ivabradine, dig, and amiodarone for any endpoint. The efficacy reviewer apparently bases his conclusion that dig and ivabradine together are ineffective based on an insignificant hazard ratio of 0.92 for the subgroup of patients taking dig at baseline as shown in his Table 49. However for my proposed indicated subgroup there are again no statistically significant interactions between ivabradine and dig or amiodarone while the ivabradine benefit for HF hospitalizations is nominally statistically significant (RR 0.76, $p = 0.039$) in the patients on baseline dig in the indicated subgroup. There is a statistically significant favorable interaction between dig and MRA use and a statistically significant unfavorable interaction between dig and loop diuretic use in the whole study as shown in Table 11. I believe that these latter interactions, consistent with what we understand about the effects of hypokalemia upon digitoxicity, are more contributory to the effects of dig in SHIFT than ivabradine’s rate dependence of I_f blockade.

The efficacy review provides the following comments on my proposed indication:

“The Cross Disciplinary Leader, Dr. Marciniak, has performed some post hoc logistic regression analyses of the PCE and its components. He has found a strong association between the use of loop diuretics and CV mortality. The safety reviewer has confirmed his analysis and agrees that there is a strong association; however the nominal p-values are descriptive without adjustment of multiplicity. The association is that the treatment effect in the ivabradine group + loop diuretic is different from the treatment effect in the placebo+ loop diuretic group. It does not confirm that loop diuretics and ivabradine are more effective than loop diuretics and placebo. In addition, there is not a plausible biologic mechanism for this interaction. Most subjects taking loop diuretic were taking furosemide. Furosemide is an OAT3 substrate. There is no evidence that ivabradine or its major metabolite is affected by OAT3. The reviewer believes that subjects taking loop diuretics identifies a more advanced symptomatic heart failure and have higher risk for cardiovascular events, and so these patients are likely to derive more benefit from treatments.”

I have the following responses to the primary reviewers’ critique:

- The valid criticism is that my analyses are *post hoc* (and hence also subject to multiplicity issues.) I believe this—again!—will be one of the major topics for discussion at the advisory committee meeting. We have incorporated such *post hoc* restrictions in indications into many of our recent approvals, e.g., exclusion of patients with a history of stroke in the vorapaxar indication. The primary

efficacy reviewer also fails to note that these *post hoc* and multiplicity criticisms apply equally to his complex, two-tiered indication.

- I have done more than “some post hoc logistic regression analyses of the PCE and its components.” I have provided a comprehensive set of analyses exploring and documenting the importance of the loop diuretic interaction, including supporting logistic regressions from all three trials, demonstration of a dose response by categorical analyses in the two trials randomizing HF patients (SHIFT and BEAUTIFUL), and establishing with logistic regressions of all endpoints that including loop diuretic use in the indication (for ischemic patients) provides better discrimination between patients who benefit from ivabradine and those who do not than the reviewer’s tiered indication (for SHIFT having the same eligibility criteria as the EMA indication)—compare Figure 15 and Figure 16.
- The two sentences in the quote above regarding the interaction is “different” but does not confirm “more effective” are garbled. The interaction is not just “different”, it is directional, i.e., the combination of ivabradine with a loop diuretic has a favorable effect upon CV death risk. What the reviewer may have meant is that, because it is not a randomized comparison, the association does not prove causality. While I believe that there is a causal interaction, causality is not necessary for the association to be valuable for labeling: To be useful all we need is that the association, causal or not, is the best way of discriminating between patients who will benefit and those who will not.
- The assertion and explanation that “there is not a plausible biologic mechanism” is both wrong and inconsistent. It is wrong because it is plausible that a drug that, in preclinical studies, has anti-arrhythmic effects upon ventricular receptors may interact favorably with drugs that are pro-arrhythmic. It is inconsistent that it discusses only a non-existent PK mechanism while ignoring the possible PD interactions, regarding which the primary review includes many speculative interactions not supported by the data. Finally, knowing the mechanism is never a requirement for either efficacy or safety findings and, in this case for which predictive power is the critical criterion, completely unnecessary.
- That loop diuretic dose is correlated somewhat with severity of HF is true, but there is no evidence that ivabradine effectiveness is related to severity of HF. The interaction analyses for SHIFT consistently show that loop diuretics, not HF severity measures such as LVEF and NYHA class, interact favorably with ivabradine—see Table 11, Table 12, Table 13, and Table 14. Furthermore, in BEAUTIFUL ivabradine appeared to work better in the patients with less severe HF (see Section 7.1.6.4) while still showing a loop diuretic dose-response for CV death (see Table 9.)

COMMENT: I would not blindly accept any of the conclusions or comments regarding efficacy in the primary clinical review. The data tabulations and analyses are more useful but I would cross compare to this review any sequences of analyses that do not address all the major factors that appear to influence ivabradine efficacy, i.e., beta blockers, loop diuretics, heart rate, and ischemic etiology. The primary clinical review also addresses some important efficacy topics that I did not include in this summary review, e.g., all cause and CV hospitalizations compared to the endpoint HF hospitalizations. It also covers the multitude of peripheral topics that a complete review should address, such as financial disclosures and effects in different regions. Finally, it contains the comprehensive listings and subcategories of adverse events that I did not include in this summary review, in particular the non-fatal bradycardia events.

7.1.5. Pediatric use

Dilated cardiomyopathy with HF, not of an ischemic etiology, is a rare pediatric disorder. [REDACTED] (b) (4)

COMMENT: [REDACTED] (b) (4)

I believe that the FDA should be more aggressive in enforcing PREA and ensuring that we do understand how drugs that should benefit children do benefit children.

7.1.6. Discussion of notable efficacy issues

COMMENT: The ivabradine development program is one that forces us to consider subgroups and a subgroup approval. With only one study in three successful and a common element, i.e., ischemic heart disease (IHD), shared by all three, I think we need to understand why the results differ so greatly and for which patients the negative results are minimized and the benefits optimized. I discuss the inconsistencies among the studies and my interpretation of them below.

7.1.6.1. Inconsistencies and concerns among the studies

SHIFT overall was successful because of a substantial reduction in HF hospitalizations in the ivabradine arm, about 30%, $p < 0.001$. However, SHIFT was conducted outside the U.S. in regions, e.g., Eastern Europe, with hospitalization practices different than in the U.S. SHIFT was double-blind but most patients could be unblinded because of the substantial HR reduction produced by ivabradine. Regardless, BEAUTIFUL was neutral for HF hospitalizations while SIGNIFY approached a detrimental effect. Similarly, CV mortality ranged from

slightly favorable in SHIFT to neutral in BEAUTIFUL to slightly detrimental for ivabradine in SIGNIFY. MI results did not follow this pattern but appear random relative to fractions of HF or IHD patients, i.e., neutral in SHIFT, favorable in BEAUTIFUL, and unfavorable in SIGNIFY. I show in Table 2 the statistics on which I base these qualitative comments.

Table 2: Inconsistencies among SHIFT, BEAUTIFUL, and SIGNIFY

Trial	Population	CVD		HF hospital		MI	
		RR	p*	RR	p*	RR	p*
SHIFT	HF + LVEF≤35	0.9	0.1	0.7	<0.001	1.0	0.2
	IHD (68%)	0.9	0.2	0.8	0.003	1.0	0.8
BEAUTIFUL	IHD + LVEF<40	1.0	0.8	1.0	0.9	0.9	0.1
	HR≥70 (49%)	1.0	0.8	1.0	0.8	0.6	0.001
SIGNIFY	IHD + LVEF>40	1.1	0.3	1.2	0.08	1.1	0.4
	symptomatic (63%)	1.2	0.1	1.2	0.2	1.2	0.04

CVD = cardiovascular death; HF = heart failure; HR = heart rate; IHD = ischemic heart disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; RR = risk ratio ivabradine/placebo; *p value from logistic regressions

I’ve also included in Table 2 the SHIFT IHD subgroup and the two “pre-specified” subgroups that have generated recommendations by the sponsor or the EMA:

- The SHIFT subgroup with IHD behaved like the study as a whole, at least for these unadjusted analyses.
- The BEAUTIFUL subgroup with HR ≥ 70 (the HR inclusion criterion for SHIFT and SIGNIFY) has an apparent large benefit for MIs that inspired SIGNIFY.
- The pre-specified symptomatic angina subgroup of SIGNIFY (large at >12,000 patients and pre-specified because ivabradine’s original indication was for symptomatic angina) showed a significant detriment for MIs and an unfavorable lean for CV death.

COMMENT: The favorable MI subgroup results in BEAUTIFUL look random. The trend from neutral to unfavorable CV mortality from SHIFT to SIGNIFY could reflect differential effects by heart failure severity—but at best ivabradine produced neutral results. However, because the majority of HF patients also have IHD, the negative results for CV mortality in the largest study remains concerning. Finally, the differences in HF hospitalizations are difficult to explain because there is no difference by IHD etiology in SHIFT and so the neutral results in the BEAUTIFUL systolic dysfunction population and the negative results in SIGNIFY are hard to understand. I argue that we need to understand the basis for some of these inconsistencies in order to be confident that ivabradine has a favorable benefit-risk.

I have been unable to identify factors that explain the inconsistencies in effects upon HF hospitalizations. I have identified a factor that appears to explain the differing effects upon CV mortality. I discuss it next. However, because the discussion involves examining interactions between ivabradine and other drugs, I list in Table 3 the rates of use of some common cardiac medications in all three trials.

Table 3: Common Cardiac Medications at Randomization in SHIFT, BEAUTIFUL, and SIGNIFY

	SHIFT	BEAUTIFUL	SIGNIFY
BB-any	90%	87%	83%
BB-at target	23%	12%	
MRA	60%	27%	5%
loop diuretic	73%	43%	8%
ACEI	79%	80%	59%
ARB	14%	11%	23%
digitalis	22%	9%	0.5%
statin	57%	74%	92%

ACEI = ACE inhibitor; ARB = angiotensin receptor blocker; BB = beta blocker; MRA = mineralocorticoid receptor antagonist

7.1.6.2. Ivabradine-loop diuretic interaction

Loop diuretic use was common in both SHIFT and BEAUTIFUL but more frequent in SHIFT and infrequent in SIGNIFY at randomization as shown in Table 4.

Table 4: Loop Diuretic Usage in SHIFT, BEAUTIFUL, and SIGNIFY

		SHIFT	BEAUTIFUL	SIGNIFY
At randomization	%	73%	43%	8%
	Mean dosage*	43	47	31
Post randomization	%	79%	50%	16%
	Mean max dosage*	87	65	47

*total daily dosage equivalent to furosemide (see text); dosage sparsely recorded in BEAUTIFUL

Furosemide was the most commonly used loop diuretic in all studies (about 83-86%) with torsemide second (9 to 15%), bumetanide third (2 to 4%), and infrequent ethacrynic acid (<1%). Dosages appeared to be recorded regularly in SHIFT and SIGNIFY but not in BEAUTIFUL (26%). I converted dosages to furosemide equivalents using the following equivalences: furosemide 40 mg = bumetanide 1 = ethacrynic acid 50 = torsemide 20. The median dosages at randomization for SHIFT and BEAUTIFUL were 40 mg and for SIGNIFY 24 mg with mean dosages as shown in Table 4.

COMMENT: Note that not only was the baseline loop diuretic use in SIGNIFY low but also the dosage was lower. Much of the baseline use in SIGNIFY was for

hypertension. Loop diuretic use about doubled during the course of the study and the average dosage increased as well, likely because later use reflected the development of heart failure.

Because I have observed consistent relationships between baseline potassium levels and CV deaths in the MRA HF trials (see below) and hence I believe that CV death is the best endpoint for evaluating serious arrhythmia risk, I focused my analyses on CV death. However, there are problems with the adjudications of CV deaths in the three trials: While the SHIFT adjudications classified the vast majority of deaths as CV or non-CV, leaving only about 7% of deaths as unknown, both the BEAUTIFUL and the SIGNIFY adjudications left about 40% of the deaths as unknown or unclassifiable. The convention followed was to count the unknown deaths as CV deaths in analyses of CV mortality. The approach of using only definite CV deaths has less power because of the fewer numbers of CV deaths while the approach counting unknown deaths as CV deaths has more noise because of the uncertainty regarding the true causes of death. I examined both approaches and comment on both results when the results are differentiated, e.g., for SIGNIFY.

I show the simplest logistic regression of CV mortality for ivabradine and loop diuretic use at randomization for SHIFT in Table 5, for BEAUTIFUL in Table 6, and for SIGNIFY in Table 7.

Table 5: Logistic Regression of CV Mortality for Ivabradine and Loop Diuretic Use at Randomization in SHIFT

Logistic regression	Number of obs	=	6558
	LR chi2(3)	=	63.12
	Prob > chi2	=	0.0000
Log likelihood = -2677.8716	Pseudo R2	=	0.0116

cvd	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]
1.ivabradine	1.346517	.2197495	1.82	0.068	.9779057 1.854072
1.loopdiur0	2.403064	.3188253	6.61	0.000	1.852817 3.116722
ivabradine# loopdiur0					
1 1	.6124058	.110904	-2.71	0.007	.4294282 .8733496
_cons	.0891568	.0108164	-19.93	0.000	.070289 .1130892

Table 6: Logistic Regression of CV Mortality for Ivabradine and Loop Diuretic Use at Randomization in BEAUTIFUL

Logistic regression	Number of obs	=	10917
	LR chi2(3)	=	130.29
	Prob > chi2	=	0.0000
Log likelihood = -3187.5888	Pseudo R2	=	0.0200

cvd	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]
1.ivabradine	1.232758	.1302186	1.98	0.048	1.002222 1.516324
1.loopdiur0	2.463344	.2463212	9.02	0.000	2.024928 2.996682
ivabradine# loopdiur0					
1 1	.765917	.1058008	-1.93	0.054	.5842518 1.004069
_cons	.0588631	.0045787	-36.41	0.000	.0505395 .0685574

Table 7: Logistic Regression of Definite CV Mortality for Ivabradine and Loop Diuretic Use at Randomization in SIGNIFY

Logistic regression	Number of obs	=	19102
	LR chi2(3)	=	25.37
	Prob > chi2	=	0.0000
Log likelihood = -1170.2575	Pseudo R2	=	0.0107

cvd	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]
1.ivabradine	1.3014	.198299	1.73	0.084	.9654068 1.754331
1.loopdiur0	3.353724	.806807	5.03	0.000	2.092924 5.374045
ivabradine# loopdiur0					
1 1	.5345416	.1940491	-1.73	0.084	.262409 1.088891
_cons	.008872	.0010155	-41.28	0.000	.0070891 .0111033

For SIGNIFY I used definite CV mortality (not including unknowns) for Table 7—the interaction for CV mortality including unknowns is remote from statistical significance. (See below.) With the variation of using definite CV mortality for SIGNIFY the CV mortality results are consistent among the three trials: Ivabradine in the absence of loop diuretic use has a detrimental effect upon CV mortality, loop diuretic use is a highly significant predictor of increased CV mortality, and the concomitant use of both ivabradine and a loop diuretic has a favorable effect upon CV mortality. For SIGNIFY, there was nearly double the use of loop diuretics, with higher average dosage, post-randomization than at randomization. (See Table 4.) Using post-randomization loop diuretic use the odds ratio for the interaction term remains about 0.5 while the interaction becomes nominally statistically significant (p = 0.021).

Another confirmation of an interaction between ivabradine and loop diuretics would be demonstration of a dose-response. Hence I calculated a “furosemide-equivalent” dosage for all loop diuretics as I described above and I cross-tabulated CV death rates by furosemide-equivalent dosages and ivabradine use. I show the cross-tabulations for SHIFT in Table 8, for BEAUTIFUL in Table 9, and for SIGNIFY in Table 10.

Table 8: CV Death Rates by Maximum Furosemide-Equivalent Dose at Randomization in SHIFT

Dose category	Mean dose	N	CV death		
			placebo	ivabradine	RR*
0	0	1,781	8%	11%	1.3
2.5 - 20	18	1,088	13%	13%	1.0
25 - 40	40	2,027	17%	15%	0.9
45 - 80	76	1,051	19%	16%	0.8
85 - 320	146	571	25%	16%	0.7
> 320	496	40	22%	41%	1.9

*RR = risk ratio ivabradine/placebo

Table 9: CV Death Rates by Available Maximum Furosemide-Equivalent Dose at Randomization in BEAUTIFUL (About 26% Available)

Dose category	Mean dose	N	CV death		
			placebo	ivabradine	RR*
0	0	6,252	6%	7%	1.2
2.5 - 20	18	217	4%	6%	1.3
25 - 40	39	459	11%	10%	0.8
45 - 80	69	129	17%	11%	0.6
85 - 320	165	44	39%	19%	0.5
> 320	563	4	0%	0%	

*RR = risk ratio ivabradine/placebo

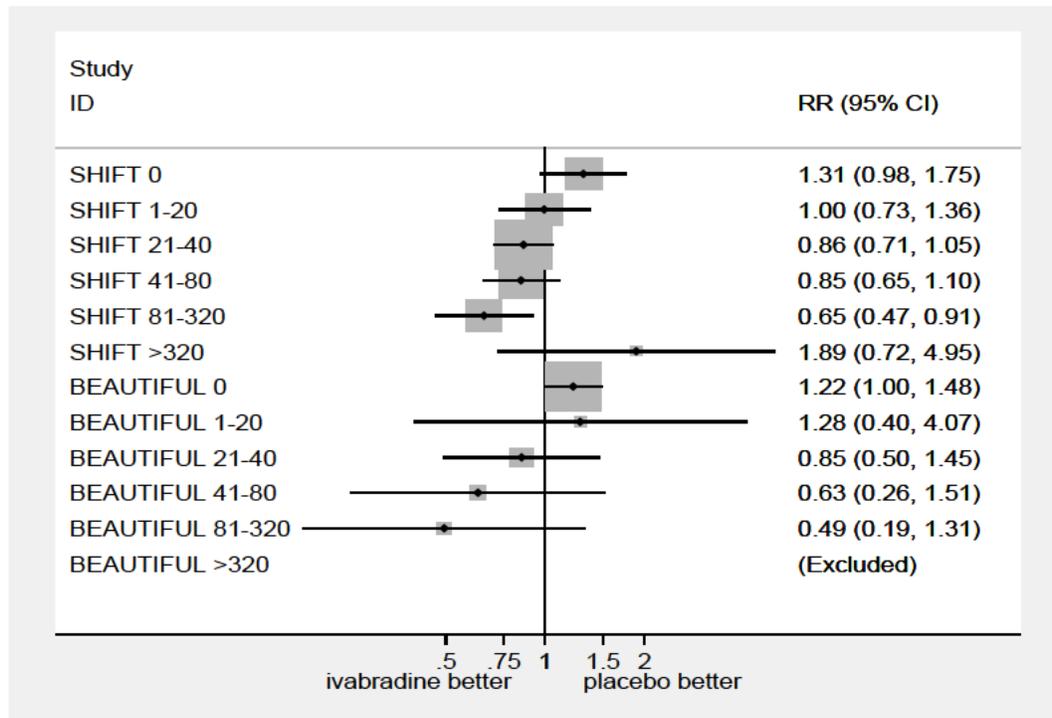
Table 10: CV Death Rates by Maximum Furosemide-Equivalent Dose at Randomization in SIGNIFY

Dose category	Mean dose	N	CV death		
			placebo	ivabradine	RR*
0	0	17,517	1%	1%	1.3
2.5 - 20	15	786	4%	2%	0.5
25 - 40	38	644	2%	2%	1.4
45 - 80	69	126	4%	1%	0.4
85 - 320	140	27	0%	10%	
> 320	450	2		0%	

*RR = risk ratio ivabradine/placebo

The patients with dosages > 320 mg are few in number and likely represent patients with more severe or unstable HF. Their course may be dictated more by their underlying disease than by a drug interaction. Excluding the > 320 mg category there is a clear dose-response for the ivabradine-loop diuretic interaction in SHIFT, the trial with highest loop diuretic use and dosages consistently recorded. The data from BEAUTIFUL also support a dose-response despite the sparse availability of dosages. The SIGNIFY loop diuretic data are too sparse to suggest or confirm or refute a dose-response. I show a graphic presentation of the dose-response in SHIFT and BEAUTIFUL in Figure 1.

Figure 1: CV Mortality Risk Ratios by Loop Diuretic Dose at Randomization in SHIFT and BEAUTIFUL

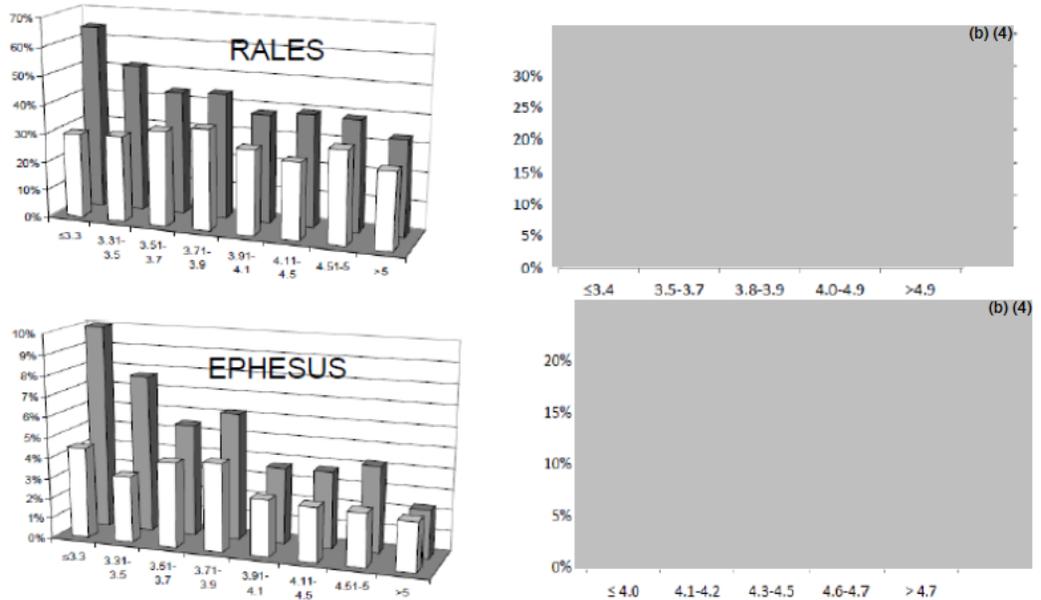


COMMENT: Considering the strong, highly statistically significant interaction in SHIFT between ivabradine and loop diuretics for CV mortality, the supportive evidence for an interaction in both BEAUTIFUL and SIGNIFY, and the dose-responses for loop diuretic dose in SHIFT and BEAUTIFUL, the evidence is compelling that ivabradine and loop diuretics interact. There are some ancillary considerations regarding the interaction that I address below, e.g., whether the interaction is operative for HF hospitalizations, the relationship to heart reductions, etc., but the existence of an interaction is undeniable. Some observers have dismissed the interaction as loop diuretic use indicating severity of HF, but (as I show below) other markers of HF severity do not interact with ivabradine use. Furthermore, the dose-response for loop diuretics is impressive—loop diuretic use would have to be a superb indicator of HF severity and ivabradine efficacy would have to correlate highly with HF severity in order to produce the results seen in Table 8 and Table 9. Finally, regardless of whether the interaction is mechanistic or simply associative, loop diuretic use predicts a beneficial effect of ivabradine upon CV mortality while absence of use predicts a detrimental effect of ivabradine upon CV mortality (at least in ischemic patients as I document below), so the loop diuretic interaction belongs in labeling.

There is strong prior evidence that loop diuretic use affects CV mortality. In ^(b)₍₄₎ the major mineralocorticoid receptor antagonist (MRA—i.e., spironolactone and eplerenone) trials ^(b)₍₄₎ EPHESUS, RALES, ^(b)₍₄₎ low baseline serum potassium levels are associated with much higher CV mortality in the placebo arms but not in the MRA arms. The intervention responsible for low serum potassiums is loop diuretic use and, in fact, the strongest association between low serum potassiums and CV mortality and the beneficial impact of MRA use is found in RALES, the trial of spironolactone in class 3-4 heart failure that required loop diuretic use as an entry criterion. Because the association between potassium levels and CV mortality has not been widely published or appreciated, I have included my review of the ^(b)₍₄₎ MRA trials as Attachment 1 and I illustrate the relationships between baseline potassium levels and CV mortality below.

I show CV mortality rates by baseline serum potassium levels for the MRA trials in Figure 2 and for SHIFT in Figure 3. I show the corresponding CV mortality risk ratios for SHIFT in Figure 4.

Figure 2: CV Mortality Rates by Baseline Serum Potassium Levels in the MRA Trials



white bars = MRA (eplerenone or spironolactone); black bars = placebo (see Attachment 1 for more legible graphs)

Figure 3: CV Mortality by Baseline Serum Potassium Levels in SHIFT

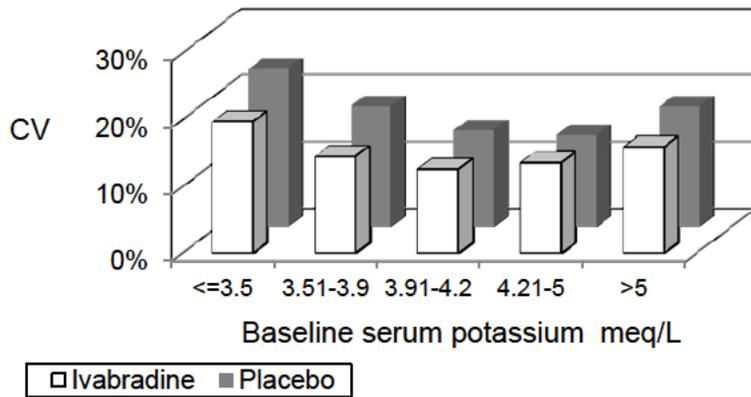
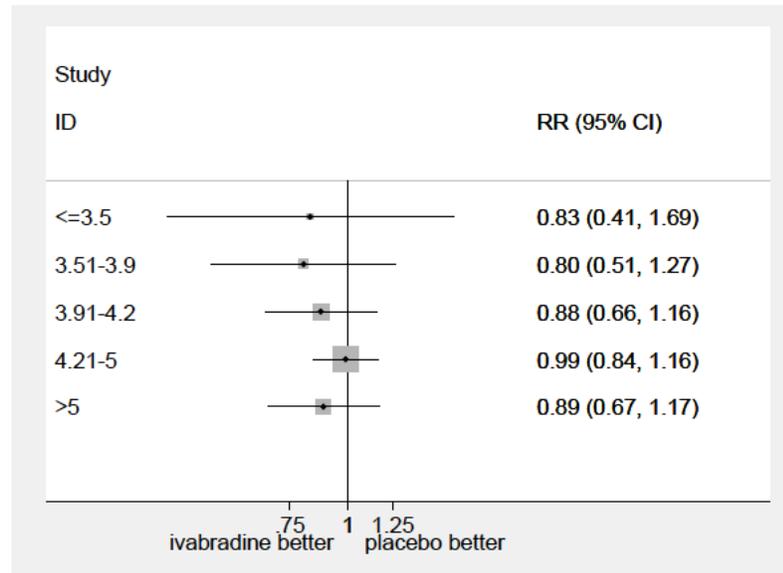


Figure 4: CV Mortality Risk Ratios by Baseline Serum Potassium Levels in SHIFT



COMMENT: While at least some of the interaction between MRAs and loop diuretics likely involves their opposite effects upon potassium levels, ivabradine's effects are more independent of potassium levels. I discuss below the lack of an effect and the lack of an interaction for ivabradine with potassium levels further below.

I hypothesize that ivabradine's protective mechanism is based on its inhibition of HCN channels in ventricular myocytes. Note that ivabradine's interaction with loop diuretics is a qualitative one: With concomitant loop diuretic use ivabradine's effect upon CV mortality is beneficial; without loop diuretic use its effect is detrimental. I hypothesize that there are two ivabradine mechanisms in play: Ivabradine has a pro-arrhythmic effect in patients with ischemia, such as the symptomatic angina patients of SIGNIFY. This detrimental mechanism may be bradycardia-associated re-entrant tachyarrhythmia escape, but I do not have evidence to confirm this mechanism. In SHIFT, at least in the patients with HF of ischemic etiology, this harmful mechanism is still active. However, ivabradine also opposes the detrimental effects of loop diuretics, perhaps through inhibition of increased automaticity in ventricular myocardium. This latter beneficial mechanism appears to be quantitatively greater than the detrimental mechanism such that there is a net benefit of ivabradine for CV mortality in SHIFT (particularly with some other subgroup restrictions that I discuss below.)

These mechanistic proposals are speculative. We should not a priori reject other possibilities, such as a detrimental effect upon MIs seen in SIGNIFY and possibly in the proposed indicated subgroup of SHIFT. We have not had adequate time to explore the support for various mechanisms and the available data may ultimately prove to be inadequate. Regardless, the usefulness of loop diuretics as a predictor

of benefit does not depend upon knowing the mechanism—or even that the interaction is causal.

I have referenced many other factors that do not appear to affect the ivabradine-loop diuretic interaction. To demonstrate the lack of effects and to explore other factors I show a comprehensive logistic regression model for SHIFT in Table 11 and the corresponding Cox regression model in Table 12.

The results of the logistic and Cox regressions are similar (as they are for most clinical trials that I have analyzed.) Hence I present mainly the logistic regression results in this review. I have included in these regressions all of the baseline factors that are significant or that illustrate lack of interaction with ivabradine. Note that the loop diuretic interaction remains highly statistically significant in these comprehensive multiple variable models while NYHA class 3 to 4 (the `nyha3to4` variable—basically class 3 vs. class 2 because SHIFT had few (11) class 4 patients) is a significant predictor of worse CV mortality but does not interact with ivabradine. Similarly, LVEF at baseline (`lv_ef0`) is a significant predictor but also does not interact with ivabradine. I show an interaction analysis (using the Stata `mfpigen` command) between ivabradine, loop diuretic use, and HF severity (baseline LVEF and NYHA class) for CV mortality in SHIFT in Table 13.

Table 11: Logistic Regression of CV Mortality for Multiple Baseline Factors in SHIFT

Logistic regression		Number of obs = 6558	
Log likelihood = -2464.7082		LR chi2(35) = 489.45	Prob > chi2 = 0.0000
		Pseudo R2 = 0.0903	
cvd	Odds Ratio	Std. Err.	z P> z [95% Conf. Interval]
1.ivabradine	.9733132	.3425768	-0.08 0.939 .4882648 1.940215
1.loopdiur0	1.990226	.3666921	3.74 0.000 1.386984 2.855836
ivabradine#loopdiur0			
1 1	.6216669	.1183225	-2.50 0.013 .4281025 .9027506
age	1.016807	.0045621	3.71 0.000 1.007905 1.025788
1.agege75	1.1826	.1982362	1.00 0.317 .8514386 1.642565
agege75#ivabradine			
1 1	.6959321	.151272	-1.67 0.095 .4545111 1.065588
male	1.354837	.1344622	3.06 0.002 1.115344 1.645756
1.nyha3to4	1.338139	.144574	2.70 0.007 1.082771 1.653735
nyha3to4#ivabradine			
1 1	1.066212	.163107	0.42 0.675 .7900029 1.438993
lvef0	.9637947	.0067157	-5.29 0.000 .9507217 .9770476
hr0	1.017878	.0047828	3.77 0.000 1.008546 1.027295
1.hrgt75	1.271416	.1627386	1.88 0.061 .9893174 1.633954
hrgt75#ivabradine			
1 1	.7626729	.1167783	-1.77 0.077 .5649432 1.029608
sbp0	.9890537	.0026835	-4.06 0.000 .9838081 .9943273
weight	.9930221	.002529	-2.75 0.006 .9880778 .9979911
hxmi	1.382987	.1558568	2.88 0.004 1.108898 1.724825
1.ischemic	1.373898	.2101602	2.08 0.038 1.018003 1.854213
ischemic#ivabradine			
1 1	.8840288	.1572153	-0.69 0.488 .6238628 1.25269
creatinine0	1.991669	.2477995	5.54 0.000 1.560675 2.541687
k0imp	.789886	.0787719	-2.37 0.018 .6496476 .9603976
k0gt5	1.370837	.1875345	2.31 0.021 1.048429 1.79239
1.mra0	1.947043	.3778919	3.43 0.001 1.330975 2.848269
mra0#ivabradine			
1 1	.9018048	.1452085	-0.64 0.521 .6577368 1.23644
mra0#loopdiur0			
1 1	.7205463	.1395521	-1.69 0.091 .4929525 1.053219
1.bbtgimp	.7830168	.1098988	-1.74 0.081 .5947061 1.030955
bbtgimp#ivabradine			
1 1	1.051137	.2043006	0.26 0.797 .7181552 1.538509
1.arb0	.6955238	.1379446	-1.83 0.067 .4715107 1.025965
arb0#ivabradine			
1 1	1.401427	.414002	1.14 0.253 .78544 2.500505
1.acei0	.8848387	.1367951	-0.79 0.429 .6535357 1.198006
acei0#ivabradine			
1 1	1.69106	.4023905	2.21 0.027 1.060753 2.6959
1.statin0	.5470328	.0611224	-5.40 0.000 .4394453 .6809605
statin0#ivabradine			
1 1	1.436874	.2285973	2.28 0.023 1.051957 1.962634
1.dig0	1.341114	.3525058	1.12 0.264 .8011821 2.244917
dig0#mra0			
1 1	.6444696	.122003	-2.32 0.020 .4446962 .9339882
dig0#loopdiur0			
1 1	1.705313	.421699	2.16 0.031 1.050302 2.768814
_cons	.0910309	.0672919	-3.24 0.001 .0213778 .3876275

Table 13: Interaction Analysis of CV Mortality for Loop Diuretic Use and HF Severity in SHIFT

MFPIGEN - interaction analysis for dependent variable cvd (6558 observations)

variable 1	function 1	variable 2	function 2	dev. diff.	d.f.	P	Sel
ivabradine	Linear	loopdiur0	Linear	7.3027	1	0.0069	2
	Linear	lvef0	Linear	1.1606	1	0.2813	2
	Linear	nyha3to4	Linear	0.2043	1	0.6513	2
loopdiur0	Linear	lvef0	Linear	0.0076	1	0.9304	2
	Linear	nyha3to4	Linear	0.0055	1	0.9409	2
lvef0	Linear	nyha3to4	Linear	0.3095	1	0.5780	2

Sel = number of variables selected in MFP adjustment model
 Smallest P-value (.0068853) is for ivabradine # loopdiur0

The interaction analysis confirms that loop diuretic use, and not HF severity, interacts with ivabradine use.

COMMENT: I conclude that the above analyses strongly support that there is a statistically and clinically significant interaction between ivabradine and loop diuretic use and that HF severity is not the explanation for this interaction. I have other comments about the regression analyses in Table 11 and Table 12:

- *The baseline risk factors, such as age, male, history of MI (hxmi), behave as one would expect. While there is no interaction with sex (not shown), there is a suggestion that the elderly (agege75 = age ≥ 75 years) have an enhanced benefit with ivabradine. While this possible interaction is not seen in BEAUTIFUL and SHIFT and may represent a chance variation, the trial results in the elderly mitigate the concern that the average age in SHIFT (mean and median about 61) is younger than the typical U.S. HF patients.*
- *While higher baseline heart rate (hr0) is associated with worse CV mortality, the favorable interaction between ivabradine and for HR > 75 approaches nominal statistical significance. I discuss the relationship between ivabradine and HR further below.*
- *CV mortality has a U-shaped relationship to baseline serum potassium (k0imp, k0gt5, i.e., K > 5 mm/L), shown better by Figure 3, Although not shown there is no interaction between baseline potassium and ivabradine. Also not shown is that the change from baseline to month 4 (the first visit with repeat lab values) in serum potassium was -0.036 in the ivabradine arm and -0.033 in the placebo arm. The favorable interaction between ivabradine and loop diuretics does not appear to be mediated through serum potassium levels.*

- *There is no interaction with MRAs. The investigators have also published regarding the lack of interaction with MRAs. There is a marginally statistically significant interaction between MRAs and loop diuretics.*
- *The variable `bbtgimp` is beta blocker at target dose. There does not appear to be an interaction with ivabradine.*
- *ACE inhibitor use (`acei0`) has a nominally significant detrimental interaction with ivabradine. The pattern for angiotensin receptor blockers (ARBs) is similar, although the interaction is not significant. Neither BEAUTIFUL nor SIGNIFY show this interaction so it may be a chance finding. However, see the discussion of OCT inhibition below.*
- *There appears to be a nominally significant detrimental interaction with statin use at baseline (`statin0`). I discuss this possible interaction below.*
- *Digitalis drugs (`dig0`) show a significant beneficial interaction with MRAs and a significant (logistic regression only) detrimental interaction with loop diuretics. Hypokalemia is a recognized risk factor for digitalis toxicity and arrhythmias. I believe these interactions confirm the critical role of loop diuretics in contributing to arrhythmias and CV death in HF.*

I propose that there are several important concepts demonstrated by the multiple variable analyses of ivabradine and of MRAs:

- *Ivabradine has a beneficial interaction with loop diuretics that we must characterize for labeling.*
- *While loop diuretics are necessary to control congestion in HF, they convey a risk of CV death. (Song, Yang et al. 2011) Some of that risk is mediated through their effects on potassium levels and MRAs mitigate some (much?) of that risk. Whether other methods of maintaining potassium levels are effective or additive to MRA use should be investigated. In addition, ivabradine—and likely beta blockers—also reduce the risk of CV death. This message regarding the risks of loop diuretics may be the most valuable outcome of the ivabradine trials.*
- *We may be missing other drug interactions because we depend upon targeted pharmacokinetic studies and fail to analyze interactions using the events captured in outcome trials. Besides the significant ivabradine-loop diuretic interaction, the CV death analyses in SHIFT suggest other clinically relevant interactions: ivabradine-statins, digitalis-loop diuretic, digitalis-MRA, and MRA-loop diuretic.*
- *Multiple variable analyses are critical for understanding the subgroup variations and drug interactions in large clinical outcome trials.*

The other component of the pre-specified primary endpoint is HF hospitalization. HF hospitalization is the component responsible for success in SHIFT as a whole. Hence I show the same comprehensive logistic regression model I used for CV death for HF hospitalization in Table 14. There is no ivabradine-loop diuretic interaction for HF hospitalization.

COMMENT: Besides the lack of an ivabradine-loop diuretic interaction the results for HF hospitalizations have substantial differences from those for CV death:

- *The elderly may fare slightly worse with ivabradine but the interaction is not statistically significant.*
- *There is no interaction between ivabradine and HF severity, either by NYHA class or LVEF (the latter not shown.)*
- *A favorable interaction with higher HR is not well supported.*
- *There is a marginal unfavorable interaction with ischemic etiology.*
- *There is a marginal unfavorable interaction with MRAs. However, this interaction is not significant in simpler models, e.g., in a model with ivabradine and MRA use and their interaction, the interaction term OR is 1.2, $p = 0.18$.*
- *There are no significant interactions between ivabradine and beta blockers at target dose, ACE inhibitors, ARBs, or statins.*
- *There is a significant, favorable interaction between MRAs and loop diuretic use but there are no significant interactions with digitalis drugs.*

Table 14: Logistic Regression of HF Hospitalizations for Multiple Baseline Factors in SHIFT

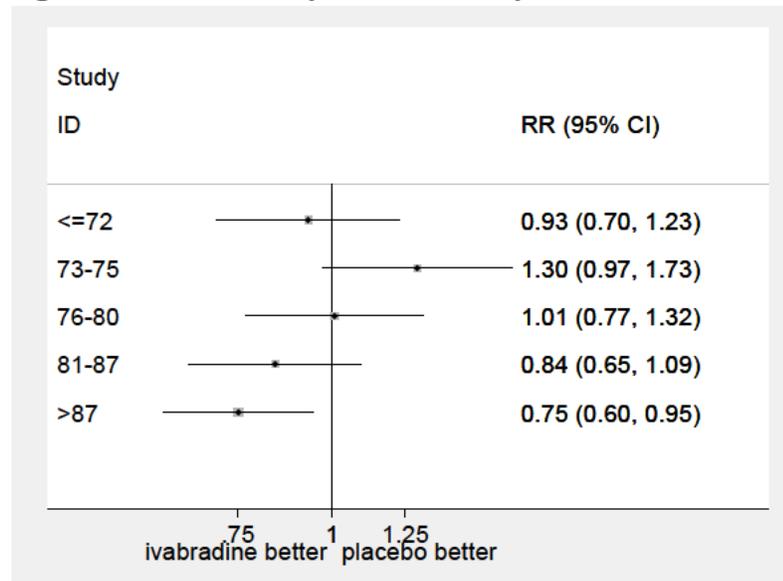
Logistic regression		Number of obs	=	6558		
		LR chi2(35)	=	557.53		
		Prob > chi2	=	0.0000		
Log likelihood = -2842.0959		Pseudo R2	=	0.0893		
hfhosp	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
1.ivabradine	.5173017	.1685545	-2.02	0.043	.2731452	.9797028
1.loopdiur0	2.515188	.4106811	5.65	0.000	1.826358	3.463817
loopdiur0##ivab						
1 1	1.100602	.2028126	0.52	0.603	.7669652	1.579373
age	1.019964	.0041811	4.82	0.000	1.011802	1.028192
1.agege75	.9365662	.144594	-0.42	0.671	.6920281	1.267515
agege75#ivabradine						
1 1	1.32946	.2614574	1.45	0.148	.9042202	1.954682
male	.9095991	.0780511	-1.10	0.269	.7687938	1.076193
1.nyha3to4	1.324726	.1246712	2.99	0.003	1.101586	1.593064
nyha3to4#ivab						
1 1	1.050442	.1465671	0.35	0.724	.799107	1.380828
lvef0	.9566334	.0061142	-6.94	0.000	.9447246	.9686924
hr0	1.025905	.0044435	5.90	0.000	1.017232	1.034651
1.hrgt75	1.09571	.12385	0.81	0.419	.8779767	1.367441
hrgt75#ivabradine						
1 1	.8538772	.1194565	-1.13	0.259	.6491024	1.123253
sbp0	.9919823	.002435	-3.28	0.001	.9872213	.9967663
weight	1.004212	.0022435	1.88	0.060	.9998239	1.008618
hxmi	1.146831	.1155954	1.36	0.174	.9412436	1.397323
1.ischemic	1.039926	.1371762	0.30	0.767	.8030098	1.346741
ischemic#ivab						
1 1	1.321414	.2112378	1.74	0.081	.9659795	1.807631
creatinine0	1.770407	.2016502	5.01	0.000	1.416188	2.213224
k0imp	.8333144	.0760046	-2.00	0.046	.6969039	.9964257
k0gt5	1.340088	.1675275	2.34	0.019	1.048872	1.712159
1.mra0	1.66761	.3050894	2.80	0.005	1.165111	2.386833
mra0#ivabradine						
1 1	1.281086	.1885179	1.68	0.092	.9601073	1.709372
mra0#loopdiur0						
1 1	.6068518	.1135937	-2.67	0.008	.4204848	.8758203
1.bbtgimp	.7045341	.0848666	-2.91	0.004	.5563758	.8921457
bbtgimp#ivabradine						
1 1	1.168465	.2053625	0.89	0.376	.8279683	1.64899
1.arb0	1.143502	.1928122	0.80	0.426	.8216956	1.591339
arb0#ivabradine						
1 1	.9287948	.2350179	-0.29	0.770	.5656342	1.52512
1.acei0	1.107611	.1580859	0.72	0.474	.837332	1.465131
acei0#ivabradine						
1 1	.8140968	.174204	-0.96	0.336	.5352198	1.238283
1.statin0	.7798802	.0767814	-2.53	0.012	.6430203	.9458693
statin0#ivabradine						
1 1	1.102148	.1609	0.67	0.505	.8278943	1.467252
1.dig0	1.885902	.4427561	2.70	0.007	1.190368	2.987838
dig0#mra0						
1 1	1.052901	.1852062	0.29	0.769	.745865	1.486327
dig0#loopdiur0						
1 1	.8051268	.1735426	-1.01	0.315	.527704	1.228395
_cons	.0269427	.018207	-5.35	0.000	.0071651	.1013109

COMMENT: The HF hospitalization endpoint in SHIFT does not appear to be encumbered with the interactions observed for the CV death endpoint. However, the HF endpoint is not supported by BEAUTIFUL and SIGNIFY as I outlined in Section 7.1.6.1 above and discuss further below.

7.1.6.3. Heart rate effects

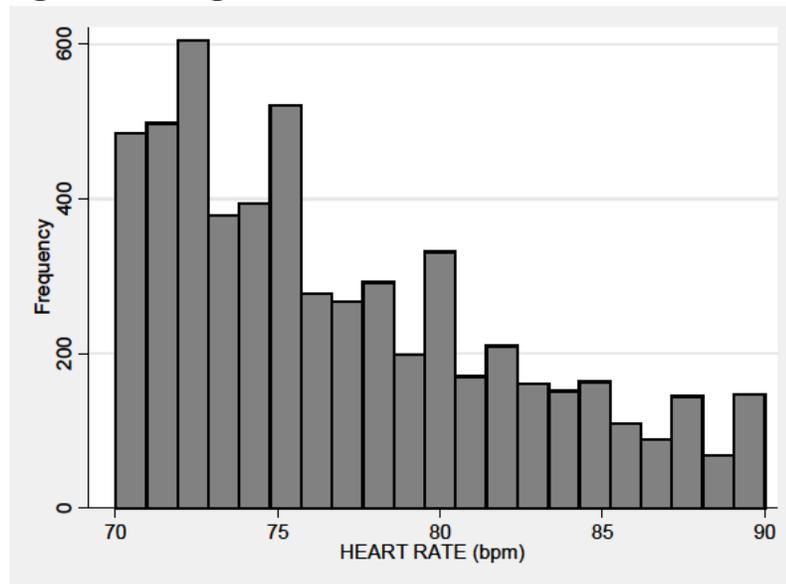
The sponsor has proposed reducing heart rate (HR) as ^{(b) (4)} mechanism for ivabradine efficacy. The logistic regressions above do suggest that there is an interaction between ivabradine and HR. Hence it should be informative to analyze the relationships between HR and changes in HR and outcomes. I show in Figure 5 the CV mortality risk ratios by baseline HR quintile for SHIFT.

Figure 5: CV Mortality Risk Ratios by Baseline Heart Rate Quintile in SHIFT



For the four higher quintiles there is a gradient from higher risk with ivabradine in the 73-75 quintile to greatest benefit in the highest quintile >87. The lowest quintile is somewhat inconsistent in Figure 5 with the other quintiles. It or the second quintile is similarly inconsistent in some of the forest plots of subgroups that I show below. I show a histogram of baseline HR for the range 70 to 90 in Figure 6.

Figure 6: Histogram of Baseline HRs 70-90 in SHIFT



While the baseline HRs should have been taken from baseline ECGs and should be free of biases, there appear to be digit preferences for 72, 75, and 80.

COMMENT: The digit preferences suggest that the baseline HRs are not completely reliable.

The relationship between HR and outcome is more complex than Figure 5 depicts. There are several effect modifiers. While the relationship between HR and CV mortality for ischemic patients on a loop diuretic is similar to that shown in Figure 5 (see Figure 7), those for other subgroups are not. I show in Figure 8 the relationship for ischemic patients not on a loop diuretic at baseline in SHIFT and for non-ischemic patients in Figure 9.

Figure 7: CV Mortality Risk Ratios by Baseline Heart Rate Quintile for Ischemic Patients on a Loop Diuretic at Baseline in SHIFT

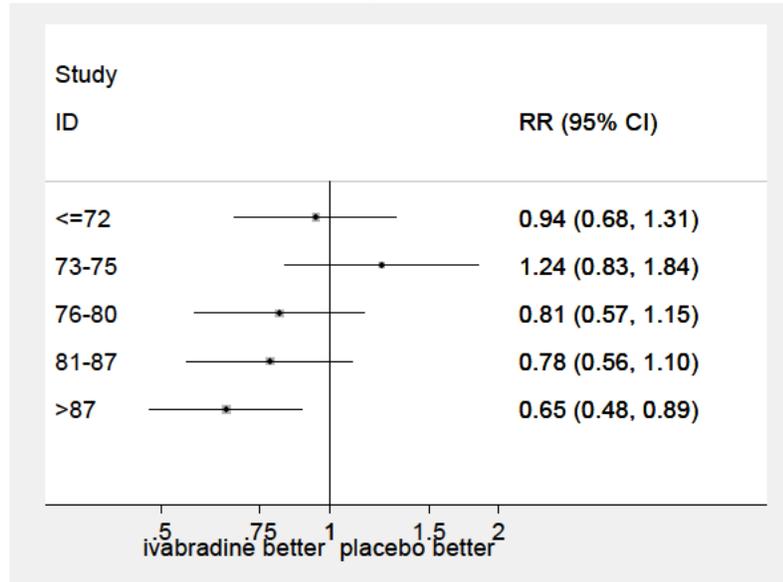


Figure 8: CV Mortality Risk Ratios by Baseline Heart Rate Quintile for Ischemic Patients Not on a Loop Diuretic at Baseline in SHIFT

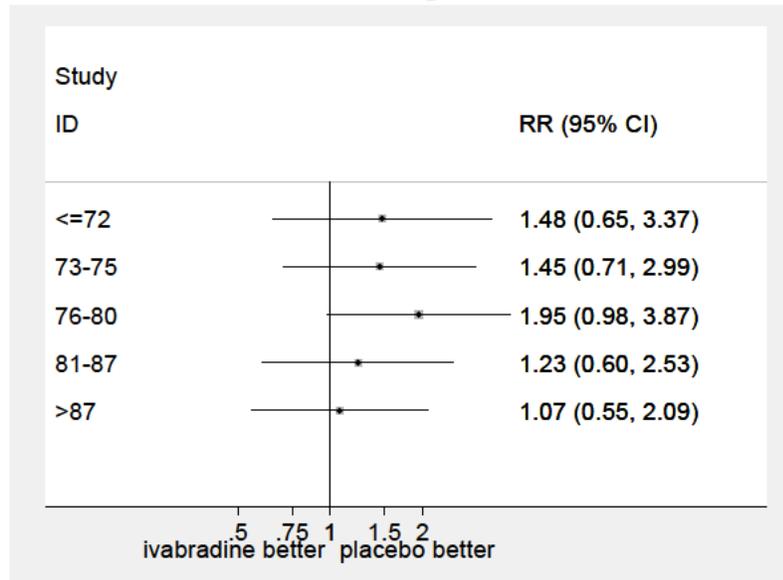
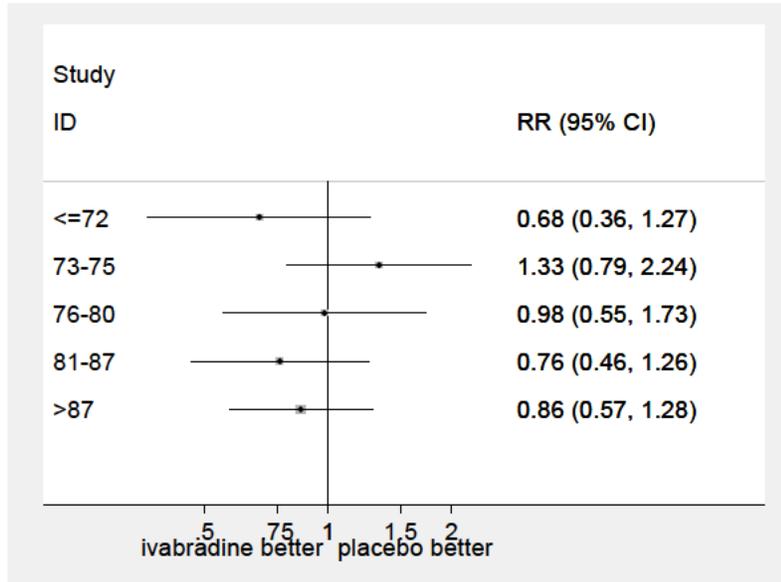


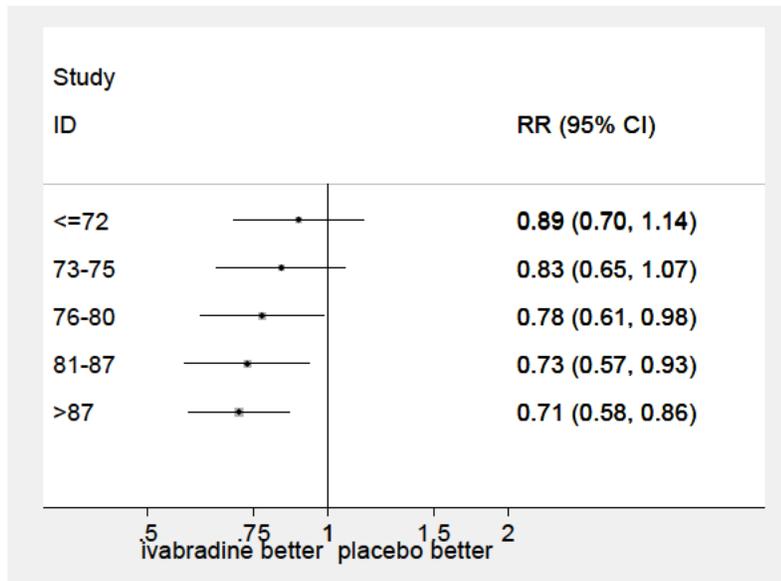
Figure 9: CV Mortality Risk Ratios by Baseline Heart Rate Quintile for Non-Ischemic Patients in SHIFT



For ischemic patients not on a loop diuretic CV mortality is worse with ivabradine at the lower HRs, approaching neutral only at the highest HRs. For non-ischemic patients CV mortality is favorable to neutral overall with no clear pattern by baseline HR.

The pattern for HF hospitalizations is somewhat different. I show in Figure 10 the HF hospitalization risk ratios by baseline HR quintile in SHIFT.

Figure 10: HF Hospitalization Risk Ratios by Baseline Heart Rate Quintile in SHIFT



For entire SHIFT ivabradine has a clear gradient of lower HF hospitalization rates than placebo with greater benefit at higher baseline HR. However, the pattern is again different for ischemic and non-ischemic patients. I show the pattern for ischemic patients in Figure 11 and for non-ischemic patients in Figure 12.

Figure 11: HF Hospitalization Risk Ratios by Baseline Heart Rate Quintile in Ischemic Patients in SHIFT

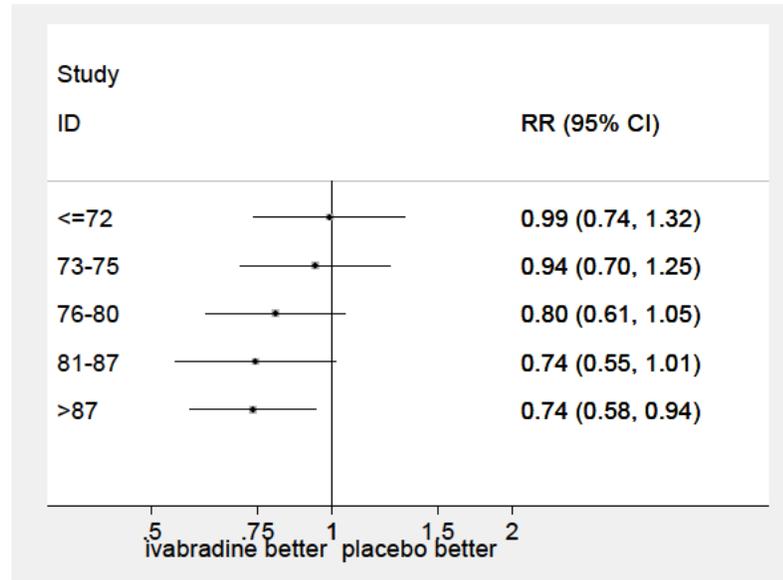
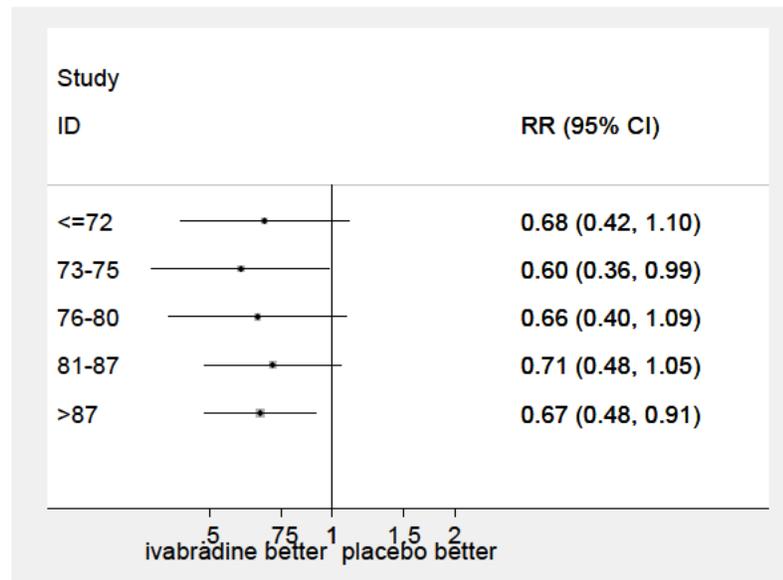


Figure 12: HF Hospitalization Risk Ratios by Baseline Heart Rate Quintile in Non-Ischemic Patients in SHIFT



Ischemic patients show the gradient of risk by baseline HR but starting at no benefit for the lower baseline HR. Non-ischemic patients show a similar benefit regardless of baseline HR. The pattern may also vary for ischemic patients based

on loop diuretic use. I show the pattern for ischemic patients on a loop diuretic in Figure 13 and for ischemic patients not on a loop diuretic in Figure 14.

Figure 13: HF Hospitalization Risk Ratios by Baseline Heart Rate Quintile in Ischemic Patients on a Loop Diuretic at Baseline in SHIFT

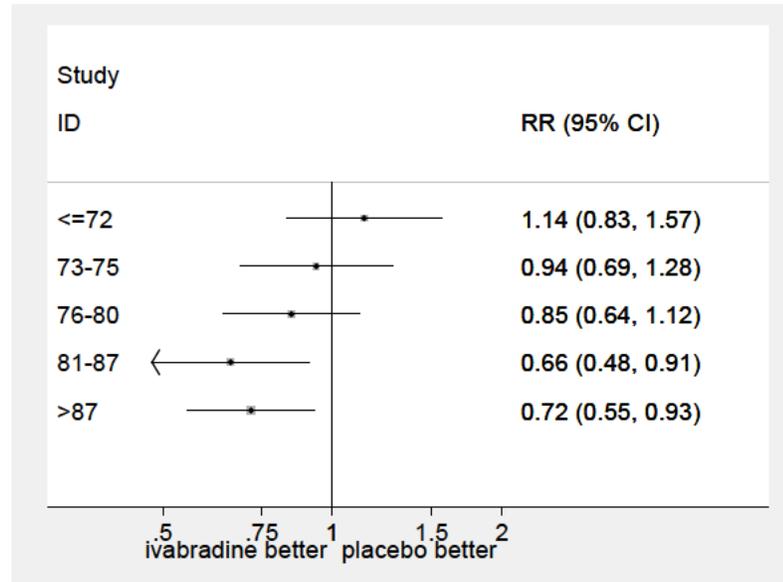
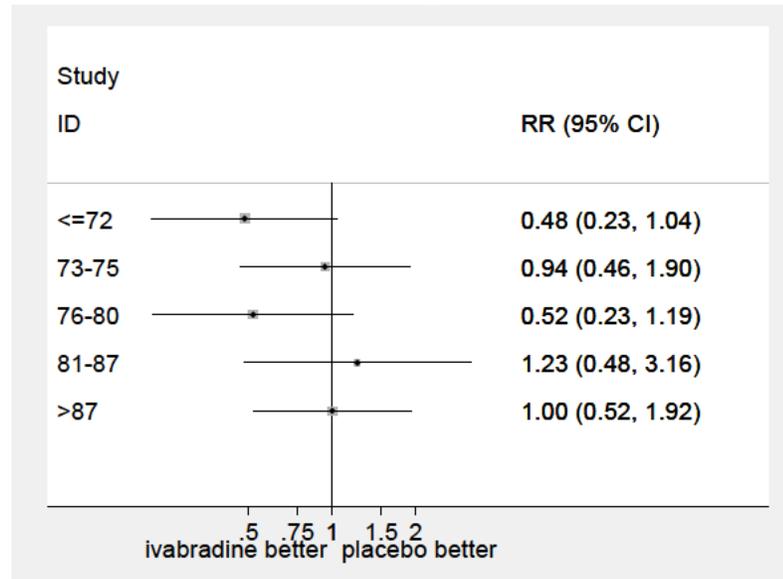


Figure 14: HF Hospitalization Risk Ratios by Baseline Heart Rate Quintile in Ischemic Patients Not on a Loop Diuretic at Baseline in SHIFT



Ischemic patients not on a loop diuretic at baseline show almost the opposite relationship between HF hospitalization and baseline HR than those on a loop diuretic. While the pattern in ischemic patients not on a loop diuretic could be a chance variation in a smaller subgroup, the size of the subgroup is not exceptionally small (1,381).

In SHIFT ivabradine was started at 5 mg BID and could be titrated to 7.5 mg BID at day 14 and adjusted thereafter in the dose range 2.5 to 7.5 mg BID to achieve a HR of 50 to 60 bpm. Examining post-randomization HRs should be informative particularly regarding whether the titration approach and target HR range used in SHIFT were reasonable. However, besides the post-randomization limitations for assessing causality there is also the usual limitation of missing data: By day 28 20 placebo and 18 ivabradine patients had died. An additional 115 patients (62 ivabradine, 53 placebo) lacked day 28 HR data. These latter patients were not similar to the ones with day 28 data, e.g., of them 18 patients in each arm (about 31%) died before the end of study. Within these two limitations I show in Table 15 the rates of CV death and HF hospitalization by HR at day 28.

Table 15: CV Deaths and HF Hospitalizations by Heart Rate at Day 28 in SHIFT

HR at 28d	placebo			ivabradine		
	n	CVD	HF hosp	n	CVD	HF hosp
<50	9	0%	0%	146	10%	10%
50-54	68	4%	13%	414	12%	9%
55-59	161	8%	11%	645	11%	10%
60-69	854	12%	13%	1075	13%	16%
≥70	2123	15%	25%	907	15%	24%

CVD = CV death; HF hosp = heart failure hospitalization; HR = heart rate

The median HR at day 28 was 62 bpm in the ivabradine arm and 74 bpm in the placebo arm at day 28. Note that, while I have included the statistics for the placebo and ivabradine arms for the same heart rate category in the same row in Table 15, the comparison in the same row of placebo to ivabradine is not a randomized or even a quasi-randomized one. Achieving a HR at day 28 < 60 bpm was favorable for both CV death and HF hospitalizations for both arms. For the ivabradine arm, with greater numbers of patients with HR < 60 bpm, there does not appear to be much difference in outcomes for any of the HR categories < 60 bpm including <50 bpm.

Another approach is to examine outcomes by the drop in HR at day 28. The median drop in HR by day 28 was 16 bpm in the ivabradine arm and 4 bpm in the placebo arm. I show in Table 16 the rates of CV death and HF hospitalization by HR drop at day 28.

Table 16: CV Deaths and HF Hospitalizations by Heart Rate Drop at Day 28 in SHIFT

HR drop d28	placebo			ivabradine		
	n	CVD	HF hosp	n	CVD	HF hosp
>30	42	17%	10%	205	17%	18%
30-21	139	15%	19%	710	11%	13%
20-11	690	11%	15%	1343	13%	14%
10-1	1220	14%	19%	653	13%	19%
no drop	1110	16%	26%	258	16%	24%

CVD = CV death; HF hosp = heart failure hospitalization; HR = heart rate

The patients in both arms with the most extreme drops in HR (> 30 bpm) fared poorly for CV death, but the ivabradine arm had about 5-fold more patients in this category. For these patients the distributions of baseline HRs was similar for the two arms, with medians of 94 and 96 and 10th percentiles of 81 and 84.

COMMENT: The situation for ivabradine is complex, with many factors apparently modifying its efficacy. I will start with the easiest question to answer, i.e., the last question of whether the target heart rate range was reasonable. The statistics in Table 15 and Table 16 suggest that targeting a heart rate of <60 bpm is reasonable with the additional restriction that extreme drops in HR (>30 bpm) should be avoided.

Both the loop diuretic analyses and logistic regressions in Section 7.1.6.2 and the HR relationship in this section document that several factors are important for ivabradine efficacy and safety. The important factors I've discussed so far are ischemic etiology, loop diuretic use, and baseline HR. (I discuss beta blocker dose in Section 7.1.6.4.3 below.) I interpret the impact of the three factors as follow:

- *For patients with HF of an ischemic etiology, ivabradine's benefit-risk is favorable only in patients on a loop diuretic. In such patients not on a loop diuretic CV mortality is unfavorable—see Figure 1 and Figure 8. HF hospitalizations show a different relationship to baseline HR than CV mortality does—compare Figure 14 to Figure 8—such that one cannot carve out a subgroup of these patients with a favorable benefit-risk.*
- *For patient with HF of an ischemic etiology on a loop diuretic ivabradine's benefit-risk is favorable for patients with higher baseline HR—see Figure 7 and Figure 13. Based on these figures the cutpoint at which the ivabradine benefit-risk becomes favorable is about a HR of 75 bpm. In fact, the EMA labeling uses the cutpoint of ≥ 75 bpm.*
- *For patients with HF of non-ischemic etiology neither loop diuretic use nor baseline HR appears critical—see Figure 9 and Figure 12 for relation to HR. Regarding HR, it is not clear whether the SHIFT entry criterion of \geq*

70 bpm is optimal—would non-ischemic patients with HR \geq 65 benefit? Regarding loop diuretic use and non-ischemic etiology, for analyses of the study as a whole the interaction terms between ivabradine and ischemic and loop diuretic use are all nonsignificant. For the non-ischemic etiology subgroup analyzed separately the OR for the ivabradine-loop diuretic interaction term is 1.0, $p > 0.9$.

Based on these analyses I propose a restricted indicated population of patients with (b) (4) and having a non-ischemic etiology with HR > 70 bpm or an ischemic etiology with HR ≥ 75 bpm and on a loop diuretic. I suggest that the additional restrictions for the patient with HF of ischemic etiology are necessary to achieve efficacy in that subpopulation and to avoid the detrimental effects upon CV mortality seen in SIGNIFY. I show below how this indicated population behaves in SHIFT and, as possible, in BEAUTIFUL.

7.1.6.4. Proposed indicated population results

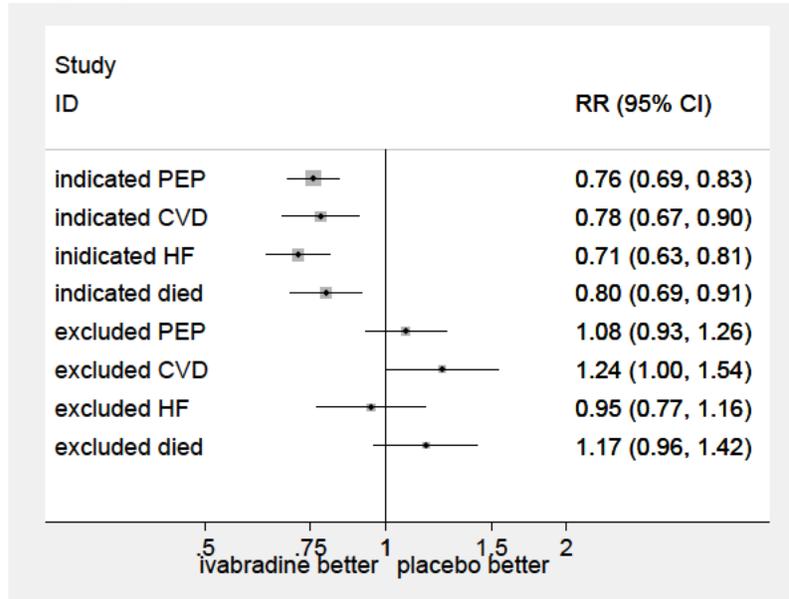
My proposed indicated population is justified immediately above and fully stated as “to reduce the risk of cardiovascular mortality and hospitalizations for worsening heart failure in patients with chronic heart failure (b) (4) (b) (4) in sinus rhythm with either non-ischemic etiology and a heart rate ≥ 70 beats per minute (bpm) or with ischemic etiology and a heart rate ≥ 75 bpm and taking a loop diuretic, (b) (4) maximally tolerated doses of beta blockers or when beta blocker therapy is contraindicated (b) (4).” The subgroup of SHIFT corresponding to the proposed indicated population constitutes about 61% of SHIFT.

7.1.6.4.1. Discriminatory power of the proposed indicated population

An appropriate test of whether the eligibility restrictions are good is whether they discriminate well between patients who benefit and those who do not. I show in Figure 15 the risk ratios for the outcomes of interest for both the indicated subgroup and the excluded subgroup of SHIFT. For comparison I show in Figure 16 the same risk ratios for the EMA labeled and excluded subgroups of SHIFT. With reference to SHIFT the EMA restriction (and the primary clinical reviewer’s restriction) is solely for HR ≥ 75 bpm, constituting about 64% of SHIFT.

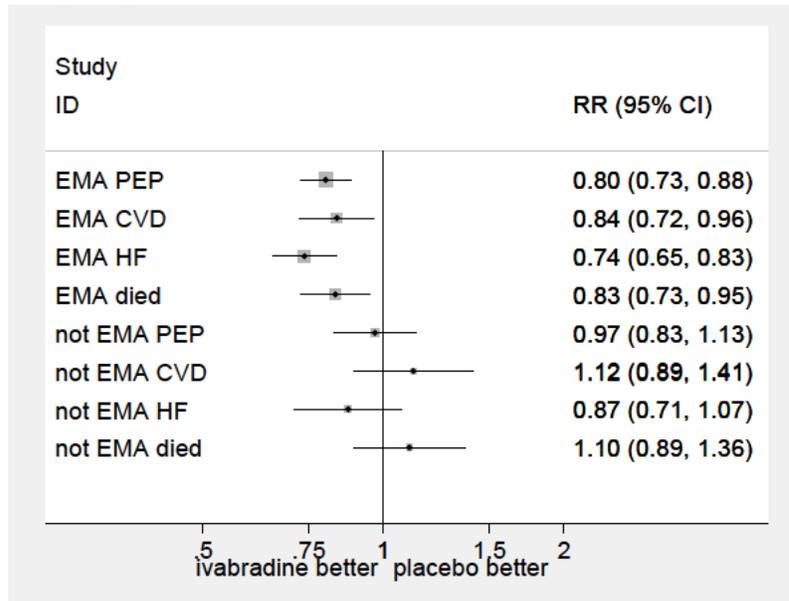
The patterns in Figure 15 and Figure 16 look similar, but note the following: Every RR for the proposed indicated subgroup is better than the corresponding RR for the EMA labeled subgroup and every RR for the excluded (non-indicated) subgroup is worse than the corresponding RR for the EMA non-indicated subgroup.

Figure 15: Endpoint Risk Ratios in the Proposed Indicated and Excluded Subgroups of SHIFT



CVD = CV death; died = all cause mortality; HF = heart failure hospitalization; PEP = primary endpoint (CVD+HF); RR = risk ratio ivabradine/placebo

Figure 16: Endpoint Risk Ratios in the EMA Labeled and Excluded Subgroups of SHIFT



CVD = CV death; died = all cause mortality; HF = heart failure hospitalization; PEP = primary endpoint (CVD+HF); RR = risk ratio ivabradine/placebo

COMMENT: The proposed indication discriminates better than the EMA indication between patients who benefit from ivabradine and those who do not. In addition, note the following:

- The EMA indication excludes my proposed loop diuretic restriction in ischemic patients so the comparison supports including it.*
- One could argue that all my proposed indication proves is that one can post hoc select a subgroup that looks good. However, I argue that the lack of benefit in BEAUTIFUL and the concerning findings in SIGNIFY mandate that we consider approval for a justified subgroup. I also argue that I have provided strong justifications (from SHIFT data, from other studies, and from mechanisms) for the proposed restrictions based on ischemic etiology, loop diuretic use, and heart rate.*
- The risk reductions in the proposed indicated subgroup in Figure 15 are impressive: a 29% reduction in HF hospitalizations and a 20% reduction in all cause mortality. These statistics are better than those reported for LCZ696, the ARB/nepriylsin inhibitor combination hailed as a breakthrough in HF therapy—ignoring the fact that the LCZ696 benefits are likely inflated because its trial PARADIGM-HF was stopped early.*

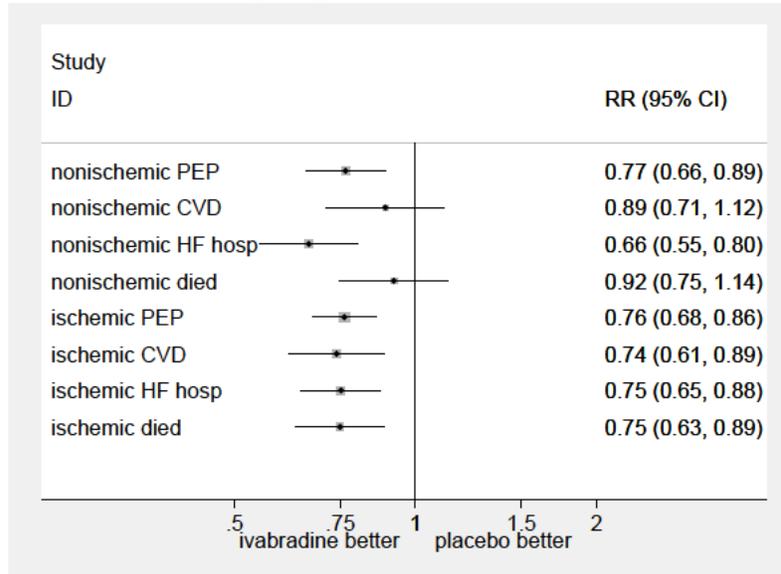
7.1.6.4.2. Endpoint results in the proposed indicated subgroups in SHIFT

For the indicated population I am proposing different eligibility criteria by etiology: For HF patients with non-ischemic etiology I propose only a restriction for a starting HR ≥ 70 ; for HF patients with ischemic etiology I propose a higher starting HR, ≥ 70 , and the use of a loop diuretic. Be

In SHIFT the subgroups corresponding to the two indicated subpopulations are similar in size, i.e., 2,107 for the non-ischemic subgroup and 1,913 for the ischemic subgroup. I show in Figure 17 the endpoint risk ratios in the ischemic and non-ischemic subgroups of SHIFT corresponding to the proposed indicated population.

The non-ischemic patients show a greater HF hospitalization benefit but a smaller or neutral mortality benefit than the ischemic patients. While not shown, the EP results in the non-ischemic patients are similar regardless of a HR < 75 or ≥ 75 bpm.

Figure 17: Endpoint Risk Ratios in the Proposed Indicated Ischemic and Non-Ischemic Subgroups of SHIFT



COMMENT: Both ischemic and non-ischemic patients in the proposed indicated population benefit greatly, although the benefit for non-ischemic patients is predominantly for HF hospitalizations.

7.1.6.4.3. CV death causes in SHIFT

Because there is an apparent death benefit for ivabradine, it is informative to examine causes of death. I show the CV death causes in the indicated and not indicated subgroups of SHIFT in Table 17.

Table 17: CV Death Causes in the Indicated and Not Indicated Subgroups of SHIFT

CV death cause	indicated			not indicated		
	placebo	ivab	Δ	placebo	ivab	Δ
arrhythmia	157	141	-16	62	85	23
hf	120	68	-52	29	36	7
hf vs. arrhythmia	0	1	1	1	0	-1
mi	11	12	1	9	15	6
other CV	30	22	-8	17	21	4
total	318	244	-74	118	157	39

hf = heart failure; mi = myocardial infarction

The CV death cause contributing most to the ivabradine death benefit in the indicated subgroup is HF, followed by arrhythmia and then other CV (the latter including stroke). The causes contributing most to the ivabradine death detriment in the non-indicated subgroup is arrhythmia, with HF, MI, and other CV also contributing.

COMMENT: Both HF and arrhythmia deaths were lower in the ivabradine arm of the indicated subgroup in SHIFT. To confirm whether both contribute and to understand better the ivabradine benefit it would be worthwhile to analyze in greater detail the SHIFT (and BEAUTIFUL and SIGNIFY) deaths. I did not have time to do so for this CDTL review given the reduced review time for a priority review with an advisory committee meeting.

7.1.6.4.4. Relationship of ivabradine benefit to beta blocker dose in SHIFT

There is another question that I can answer for the indicated subgroup: How does beta blocker dosing affect ivabradine efficacy? I show in Figure 17 the CV mortality risk ratios by beta blocker dose fraction and in Figure 18 the HF hospitalization risk ratios.

Figure 18: CV Mortality Risk Ratios by Beta Blocker Dose Fraction in the Indicated Subgroup of SHIFT

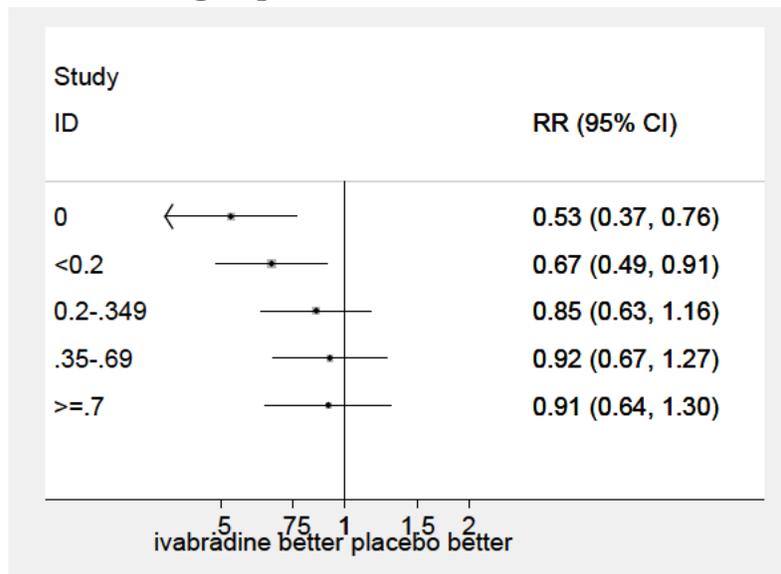
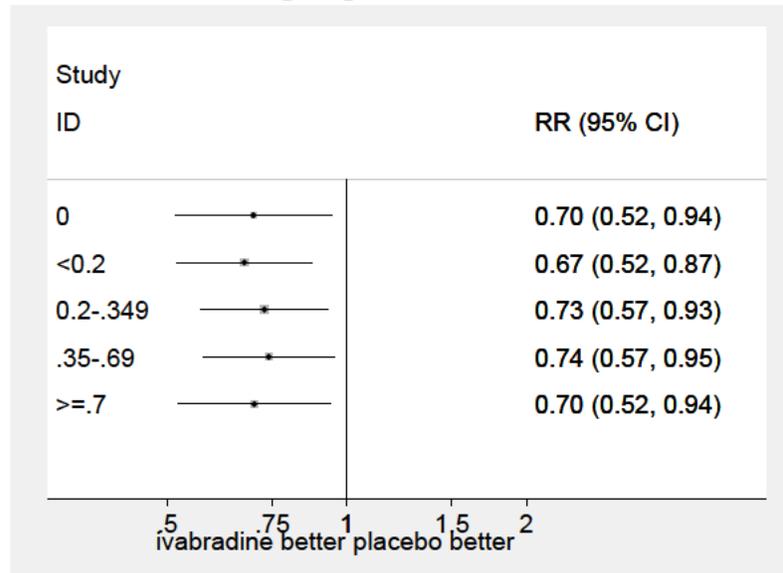


Figure 19: HF Hospitalization Risk Ratios by Beta Blocker Dose Fraction in the Indicated Subgroup of SHIFT



The beta blocker (BB) fraction is the fraction of the recommended dose for HF in the U.S. or, for BBs not approved for HF in the U.S., the EMA label. I generated the categories prior to examining effects upon outcomes by examining the BB dose distributions and specifying cutpoints that separate the modal dose fractions (about 0.125, .25., .5, and 1) such that the cutpoints are at the least frequent dosages separating the modal peaks, e.g., most dosages in the 0.2-.349 category were about 0.25 with few or no dosages at 0.2 or 0.349. The CV mortality benefit of ivabradine is much greater for patients not taking a BB or taking a low BB dose at baseline. Whether there is any mortality benefit at the higher dosages is unclear, but there is insufficient power for the analyses to resolve this question definitively. For HF hospitalizations there is no difference in the ivabradine benefit regardless of BB dosage.

COMMENT: Ivabradine appears to add benefit on top of a BB. A good question is whether a BB adds benefit on top of ivabradine. The available ivabradine trials and data cannot answer this latter question.

7.1.6.4.5. MIs and strokes in SHIFT

Finally, while myocardial infarctions (MIs) and strokes were not components of the primary endpoint, it is informative to examine their rates in these cardiac patients. MIs, counting both MI hospitalizations and MI deaths, were virtually dead even in the two arms of the indicated subgroup (OR 0.99, $p > 0.9$). Strokes, counting both adjudicated strokes and strokes reported as adverse events, were significantly fewer in the ivabradine arm of the indicated subgroup (88 vs. 112, OR 0.63, 95% CI 0.43 to 0.91, $p = 0.015$).

COMMENT: The lower stroke rate in the ivabradine arm is unexpected, particularly considering that ivabradine is associated with a higher rate of atrial fibrillation (afib) as discussed in the primary clinical review and as I summarize in Section 7.2.7.1 below. I also address strokes below regarding BEAUTIFUL and SIGNIFY.

7.1.6.4.6. Proposed indicated population, BEAUTIFUL, and SIGNIFY

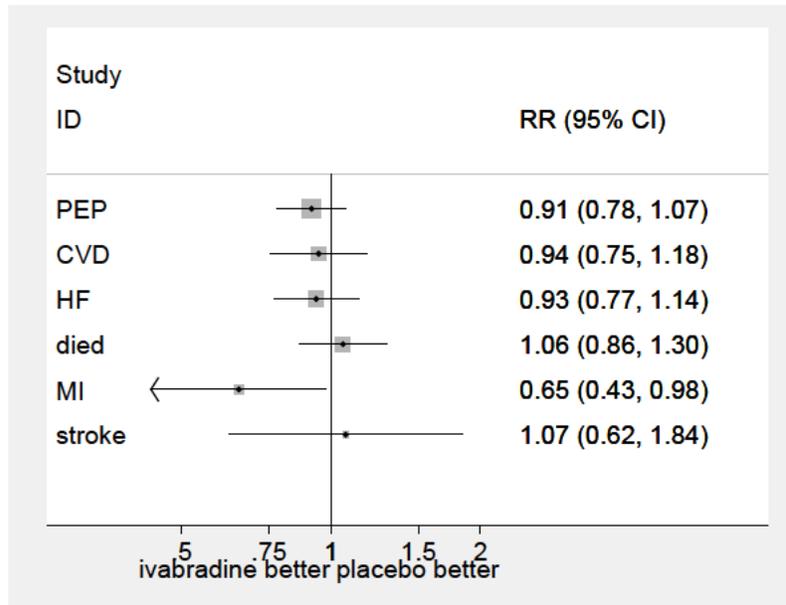
The BEAUTIFUL study as a whole is not supportive of the SHIFT findings—see Table 2. There is another unexpected variation: In SHIFT ivabradine appears to be highly successful in patients with more severe HF, i.e., LVEF \leq 35. However, in BEAUTIFUL ivabradine appears to be more beneficial in patients with LVEF $>$ 35 (e.g., RR for the primary SHIFT endpoint in the indicated population 0.71) than in patients with LVEF \leq 35 (RR 0). By NYHA class the results are mixed, with ivabradine only showing a benefit for CV death in class 1 patients and for HF hospitalizations in class 3 patients. All of these “benefits” are point estimates, not statistically significant differences.

COMMENT: These BEAUTIFUL “benefits” appear to be random variations. Given that HF severity did not appear to be a predictive factor in SHIFT, I do not include it in my BEAUTIFUL analyses. The lack of significance of HF severity raises the question of what HF severity measures, if any, should be included in the indication. NYHA class? LVEF? ^{(b) (4)}

I show in Figure 19 the endpoint risk ratios for patients with baseline HR \geq 75 and on a loop diuretic in BEAUTIFUL (1,716 patients or about 16% of the entire study.)

The BEAUTIFUL results in this subgroup are weakly supportive of benefits for CV death and HF. Stroke results are neutral. There appears to be a significant benefit for MIs that SIGNIFY did not confirm.

Figure 20: Endpoint Risk Ratios for Patients with HR \geq 75 and on a Loop Diuretic in BEAUTIFUL



CVD = CV death; died = all cause mortality; HF = heart failure hospitalization; PEP = SHIFT primary endpoint (CVD+HF); RR = risk ratio ivabradine/placebo

COMMENT: I have tried many variations of matching a BEAUTIFUL subgroup to the SHIFT entry criteria (e.g., including LVEF or NYHA class, omitting loop diuretic use, exploring other HR criteria) but none produce more favorable results for ivabradine than those in Figure 19, the original one proposed based on the SHIFT entry criteria excluding the HF severity criteria. BEAUTIFUL seems only weakly supportive of SHIFT, with the possible explanation being chance variation due to the small size of the BEAUTIFUL subgroup similar to SHIFT.

The sponsor has constructed, using a published methodology (Deville and Tille 2004), a “calibrated” subgroup of BEAUTIFUL ^{(b) (4)}

. Please see the description of the calibrated subgroup results in the primary clinical review. The sponsor claims that this subgroup was ^{(b) (4)}

” However, I did not find that the baseline characteristics of the calibrated subgroup matched SHIFT, e.g., 20% HR < 70 bpm vs 0%; 17% LVEF > 35 vs. 0%; 8% NYHA class 1 vs. 0%; 83% male vs. 76%; and 14% beta blocker dose \geq 70% of recommended vs. 25%. Some factors were imbalanced in the subgroup, e.g., MRAs at baseline (a matching variable for the calibration) ivabradine 56% vs. placebo 65%, $p = 0.003$. The latter imbalance favors ivabradine because MRA use at baseline was a strong, highly significant predictor of subsequent HF hospitalizations (RR 2.4) and CV death (RR 1.9). Hence I do not trust the calibrated subgroup results.

SIGNIFY excluded patients with reduced systolic function so its results are not useful for analyzing the proposed indicated population. Stroke rates in SIGNIFY were similar in the two arms (RR 1.1, $p > 0.5$).

COMMENT: Neither BEAUTIFUL nor SIGNIFY support an ivabradine benefit for stroke.

7.2. Safety

7.2.1. General safety considerations

The major safety concern for ivabradine is bradycardia, as well as other adverse cardiac events (e.g., tachyarrhythmias) related to bradycardia. We suspect, but have not proved, that the excess cardiac deaths in the ivabradine arm of the symptomatic angina subgroup of SIGNIFY are related to bradycardia events. The bradycardia adverse events (AEs) are covered in detail in the primary clinical review. Because their most clinically significant impact, CV death, is an efficacy endpoint that I reviewed extensively regarding efficacy, I do not discuss them further in this safety section.

Among other ivabradine AEs the nuisance safety concern for ivabradine is phosphene, a luminous visual disturbance. The manageable AE for ivabradine is atrial fibrillation (afib) but, of course, management of afib has its complications. The poorly understood safety concerns of ivabradine are its potential interactions with statins and interactions (b) (4) If ivabradine conveys a real benefit for HF hospitalizations and for CV death as it appears to do from the efficacy review above, then its benefit-risk is favorable despite these safety concerns.

7.2.2. Safety findings

Please see the primary clinical review for the detailed safety findings. I discuss the major findings in Section 7.2.5 below.

7.2.3. Safety update

The major data provided with the 120-day safety update were the SIGNIFY data. I have incorporated the SIGNIFY data into the analyses of safety and efficacy in this review.

7.2.4. Immunogenicity

Immunogenicity is not a significant concern for this small molecule.

7.2.5. Special safety concerns

One special safety concern of ivabradine is a visual phenomenon called phosphene. Patients and their physicians describe the phosphenes with words like “light flashes”,

“bright spots”, “light glare”, and “halos”. In SHIFT they were reported by 2.8% of the ivabradine patients and 0.5% of placebo patients. Most were reported within the first six months. None were serious. They led to discontinuation in 0.2% of ivabradine patients.

COMMENT: The mechanism for phosphenes with ivabradine is inhibition of the retinal I_h current, another HCN receptor-mediated current similar to I_f . They should be of short duration and appear to be in the clinical trials and in the post-marketing use in Europe. The phosphene AEs seem tolerable given the CV outcome benefits.

The other special safety concern is that ivabradine is a teratogen in preclinical studies, causing heart malformations. The primary clinical review summarizes the post-marketing experience from Europe with 16 pregnancies. Of the 9 live births two neonates had growth retardation but none had malformations.

COMMENT: We should include warnings in ivabradine labeling similar to those in the ACE inhibitor and ARB labels.

7.2.6. Primary reviewers’ comments and conclusions

The primary clinical reviewers overall safety conclusion is noncommittal: “Ivabradine is an I_f channel blocker, whose adverse event profile is generally consistent with the location of HCN expression (the SA node, AV node, retina, and brain). The primary adverse events include bradycardia/HRR, atrial fibrillation, ventricular arrhythmias, sick sinus syndrome, AV block, and phosphenes. At the time of finalization of this review, ivabradine also appears to cause acute renal failure in subjects with symptomatic heart failure. This will be examined in more detail prior to the Advisory Committee meeting.”

7.2.7. Discussion of notable safety issues

7.2.7.1. Bradycardia

In this summary review I have focused on the most significant complication of bradycardia, i.e., CV death. Please see the primary clinical review for presentations and statistics on less severe bradycardia and related AEs.

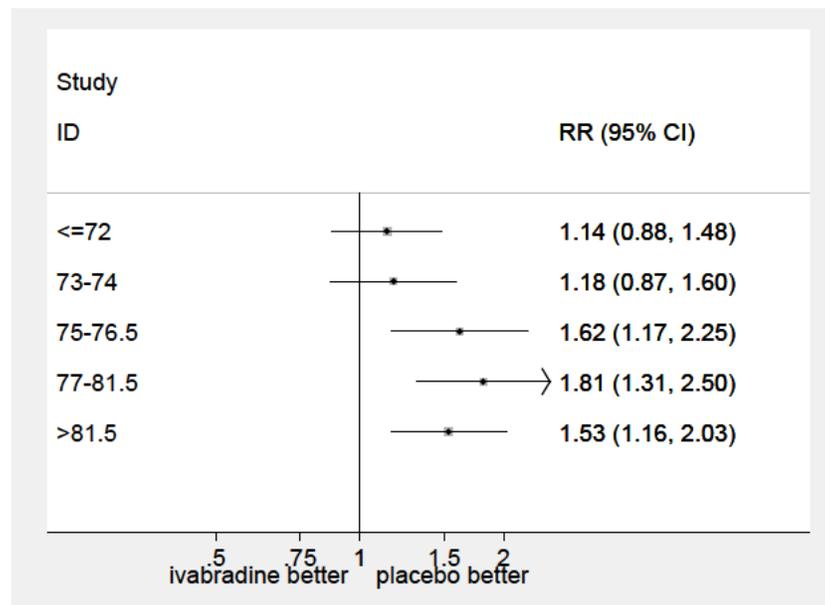
COMMENT: Reduced HR is the expected pharmacologic action of ivabradine. Bradycardia by the usual definition, i.e., <50 bpm, does appear to be associated with increased rates of endpoints and AEs. More extreme decreases in HR, i.e., >30 bpm, also are associated with increased rates of endpoints and AEs. The labeling and instructions to physicians should communicate these concerns clearly.

7.2.7.2. Atrial fibrillation (afib)

Afib was significantly more frequent in the ivabradine arms of all three trials. By my evaluations the risk ratio (RR) ivabradine/placebo for afib was about 1.25 in SHIFT, 1.2 in BEAUTIFUL, and 1.4 in SIGNIFY. Per the primary clinical review the placebo afib rates were higher in SHIFT (4.5%PY) and BEAUTIFUL (3.7%) than SIGNIFY (1.5%PY). There are some noteworthy characteristics of afib in the ivabradine trials:

- The incidence curves diverge early in SIGNIFY (1-2 months), later in SHIFT (6 months), and much later in BEAUTIFUL (12 months). The late divergence in the HF studies suggests an ivabradine effect upon atrial structure (structural or electrical remodeling?) but no studies have been done to verify this possibility.
- There does not appear to be any relationship to baseline or day 28 HR in SHIFT, although the patients with the highest drop from baseline (>30 bpm) had a slightly higher rate of afib (10.7% overall) than the patients with lower drops (about 9%). In BEAUTIFUL and SIGNIFY, the afib RRs were higher at the higher HR quintiles. I show the afib RRs by baseline HR quintile in Figure 20. The pattern for BEAUTIFUL is similar, again with a slight lower RR at the highest HR quintile than at the second highest. In BEAUTIFUL I also checked the pattern for HRs at 1 month and found the pattern to be similar.

Figure 21: Afib Risk Ratios by Baseline Heart Rate Quintile in SIGNIFY



- Afib was associated with 3- to 4-fold higher stroke rates in the ivabradine trials. Afib patients were also 3-4 years older and had 2- to 3-fold higher death rates than patients without afib. Despite the usual association of afib and stroke, stroke rates were neutral in SIGNIFY and BEAUTIFUL and

significantly lower in the ivabradine arm of SHIFT compared to its placebo arm. In SHIFT the difference in stroke rates was higher in the patients without afib than in those with afib (0.84% vs. 0.45%).

That afib rates were higher while stroke rates were neutral to lower raised the question to me of whether follow-up was adequate in the afib patients. Completeness of follow-up based on contact and visit documentation in the submitted datasets was similar to that reported for other recent CV outcome studies: about 4.8% of ivabradine patients and 4.1% of placebo patients who were not reported as dead had documentation of a last contact on or after the earliest last visit date (02/01/2010). About 7.9% of such ivabradine patients and 7.4% of such placebo patients did have documentation of a last visit on or after the earliest last visit date. Missing last contact rates were about 0.4% higher in afib patients regardless of arm while missing last visit rates were about 7% higher in placebo afib patients and 0.1% lower in ivabradine afib patients.

COMMENT: It is always somewhat concerning when completeness of follow-up is better in the control arm but the one standout statistic regarding SHIFT follow-up is the 7% higher missing visit rate in placebo afib patients. However, given that the poorer follow-up in placebo patients should favor placebo and last contact rates were similar regardless of arm or afib, missing follow-up does not appear to explain the stroke rates. Completeness of follow-up does not appear to be a major issue for SHIFT.

While a slight increase in afib rates is another complication with which patients taking ivabradine will have to deal, at least the afib is not associated with higher rates of the most feared complication of afib, stroke. The mechanism may be bradycardia allowing reentrant atrial rhythms to degenerate into afib but I can't claim that the HR associations in SIGNIFY and BEAUTIFUL confirm that mechanism. The delayed divergences of the afib incidence curves in BEAUTIFUL and SHIFT suggest that there may be a structural remodeling component. Confirmation of that by appropriate studies, e.g., electrophysiology and echocardiographic, would be ideal.

7.2.7.3. Statin interaction

The logistic regression results in Table 11 of CV mortality in SHIFT for multiple baseline factors suggested that there could be a detrimental interaction between ivabradine and statins. Because statins are the CV drugs with the best established mortality benefit, because ivabradine shows a possible signal of a detrimental effect of ivabradine on CV mortality in SIGNIFY, and because a detrimental interaction with statins should be correctable with dosage adjustment or statin selection, I believe that we should investigate the possible statin interaction exhaustively.

Because the interaction was suggested by the logistic regression of CV mortality in SHIFT, performing similar logistic regressions for BEAUTIFUL and SIGNIFY is

an appropriate next step. I show a simple logistic regression including the interaction term for BEAUTIFUL in Table 18 and for SIGNIFY in Table 19.

Table 18: Logistic Regression of CV Mortality for Statin Use at Randomization in the Indicated Subgroup of BEAUTIFUL

Logistic regression	Number of obs	=	1716
	LR chi2(3)	=	4.51
	Prob > chi2	=	0.2115
Log likelihood = -677.53917	Pseudo R2	=	0.0033

	cvd	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]
1.ivabradine		.7920489	.1948597	-0.95	0.343	.4890345 1.282816
1.statin0		.6679389	.1403519	-1.92	0.055	.4424625 1.008317
ivabradine#statin0						
1 1		1.260143	.3789231	0.77	0.442	.6989806 2.271825
_cons		.2142857	.0364359	-9.06	0.000	.1535536 .2990381

Table 19: Logistic Regression of Definite CV Mortality for Statin Use at Randomization in the Baseline HR \geq 75 bpm Subgroup of SIGNIFY

Logistic regression	Number of obs	=	9932
	LR chi2(3)	=	3.55
	Prob > chi2	=	0.3141
Log likelihood = -656.21033	Pseudo R2	=	0.0027

	h	cvd	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]
1.ivabradine			.6086707	.3421864	-0.88	0.377	.2022313 1.831961
1.statin0			.5036377	.1847229	-1.87	0.061	.2454239 1.033522
ivabradine#statin0							
1 1			2.045002	1.21673	1.20	0.229	.6371594 6.563559
_cons			.0212264	.0071502	-11.44	0.000	.0109685 .0410777

I show the logistic regressions for the subgroups most similar to the proposed indicated population except, for SIGNIFY, I omit the loop diuretic restriction because including it reduces the subgroup size to one too small to be informative; the results for the full studies are similar. Neither analysis statistically significantly confirms an interaction between ivabradine and statins. However, both are weakly suggestive that ivabradine use in the absence of a statin is beneficial while the concomitant use is detrimental.

Because statins vary significantly in their PK properties I judge it appropriate to analyze results by types of statins used in the three trials. I show the types of statins used and the CV mortality rates for each type for SHIFT in Table 20, for BEAUTIFUL in Table 21, and for SIGNIFY in .

Table 20: CV Death Rates by Statin Type at Randomization in the Indicated Subgroup of SHIFT

statin	%	age, mean	CV death		
			placebo	ivabradine	RR
none	51.6%	58.0	19.8%	13.9%	0.70
atorvastatin	19.8%	60.2	13.4%	13.5%	1.01
fluvastatin	1.2%	65.4	16.0%	13.6%	0.85
itavastatin	0.05%	66.9		0.0%	
lovastatin	1.3%	62.6	17.9%	19.2%	1.08
pravastatin	1.1%	65.0	28.0%	10.0%	0.36
rosuvastatin	3.7%	62.1	15.3%	20.0%	1.31
simvastatin	21.2%	61.5	13.4%	10.6%	0.79

RR = risk ratio ivabradine/placebo

Table 21: CV Death Rates by Statin Type at Randomization in the Indicated Subgroup of BEAUTIFUL

statin	%	age, mean	CV death		
			placebo	ivabradine	RR
none	28.7%	66.2	17.6%	14.5%	0.82
atorvastatin	22.6%	65.4	11.7%	13.5%	1.15
fluvastatin	3.2%	64.9	6.7%	16.0%	2.40
lovastatin	3.4%	62.8	10.3%	13.8%	1.33
pravastatin	4.4%	67.5	19.4%	12.8%	0.66
rosuvastatin	2.5%	62.6	0.0%	4.5%	
simvastatin	35.2%	65.0	13.9%	12.0%	0.86

RR = risk ratio ivabradine/placebo

Table 22: CV Death Rates by Statin Type at Randomization in the Baseline HR \geq 75 bpm Subgroup of SIGNIFY

statin	%	age, mean	CV death		
			placebo	ivabradine	RR*
none	8.3%	66.7	2.1%	1.3%	0.61
atorvastatin	46.9%	65.0	0.8%	1.2%	1.48
fluvastatin	1.3%	67.0	1.6%	1.5%	0.97
lovastatin	0.48%	66.1	0.0%	8.7%	
pitavastatin	0.2%	65.6	0.0%	0.0%	
pravastatin	1.7%	66.5	2.3%	2.4%	1.06
rosuvastatin	14.7%	64.8	1.0%	0.7%	0.69
simvastatin	26.5%	65.7	1.5%	1.7%	1.14

RR = risk ratio ivabradine/placebo

The two statins (atorvastatin and simvastatin) accounting for most of the statin use in both trials are also the statins accounting for most of the statin use in U.S. CV

outcome trial populations. I also included the mean age for each statin type because there is a significant difference for mean ages, with pravastatin used in older patients in SHIFT and BEAUTIFUL but not in SIGNIFY.

COMMENT: There appears to be some patterns to the CV death risk ratios: The RR in patients not taking a statin is favorable in all three studies. Regarding the two most highly used statins, the trend is from a more favorable to a less favorable RR from SHIFT to BEAUTIFUL to SIGNIFY. For atorvastatin the RR trends from neutral to substantially unfavorable; for simvastatin the RR trends from slightly favorable to slightly unfavorable. Pravastatin also shows the same general trend, although from a highly RR in SHIFT to a neutral one in SIGNIFY. Rosuvastatin is the one statin with increasing usage that does not show the similar trend: Its RR is unfavorable in SHIFT and BEAUTIFUL but favorable in SIGNIFY, the last trial where its use was greatest.

To explore further the possibility of differential statin interactions I also analyzed all cause mortality by baseline statin type. I show the all cause mortality RRs by statin type for SHIFT in Figure 21, for BEAUTIFUL in Figure 22, and for SIGNIFY in Figure 23.

Figure 22: All Cause Mortality Risk Ratios by Statin Type at Randomization in the Indicated Subgroup of SHIFT

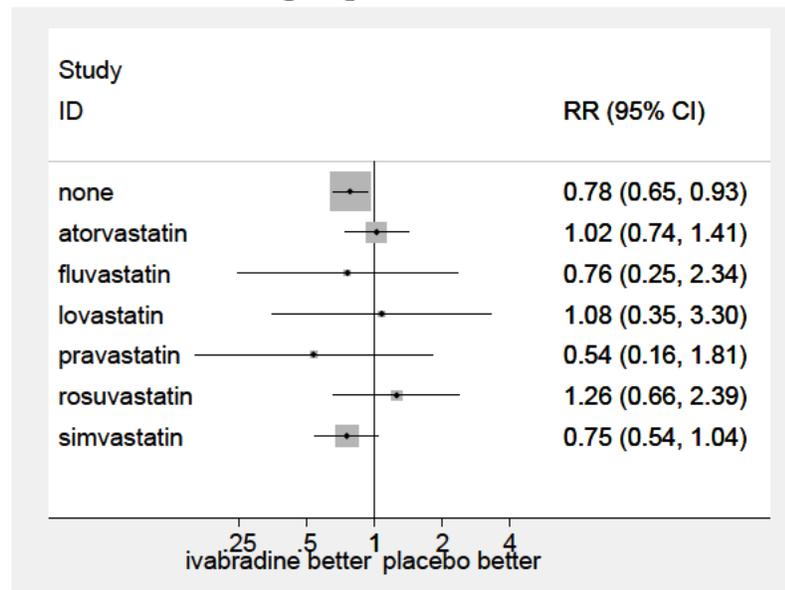


Figure 23: All Cause Mortality Risk Ratios by Statin Type at Randomization in the Indicated Subgroup of BEAUTIFUL.

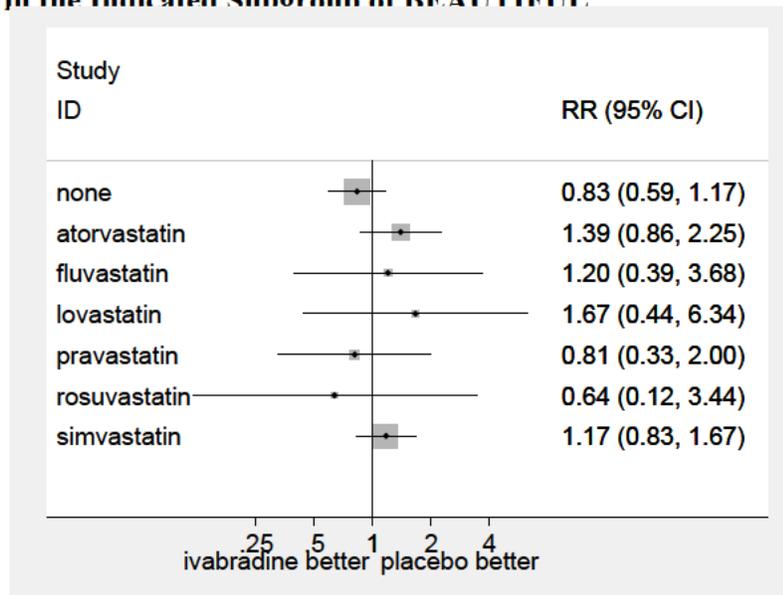
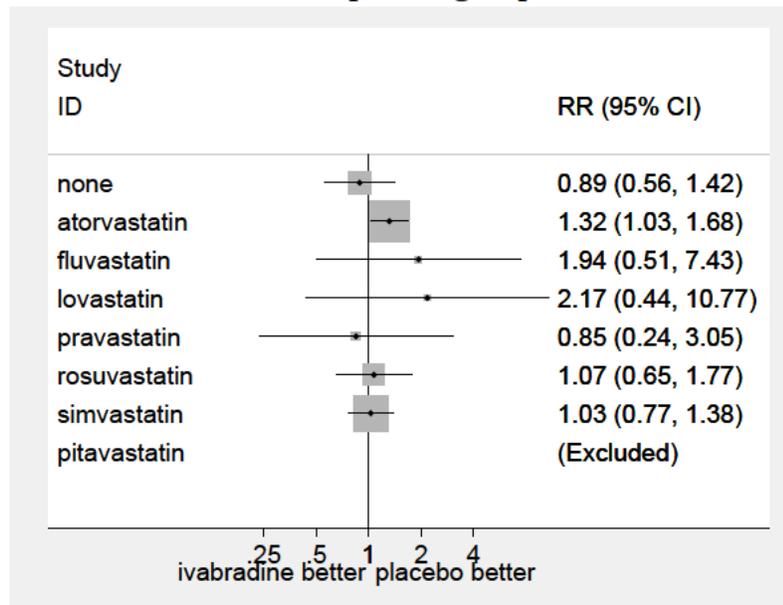
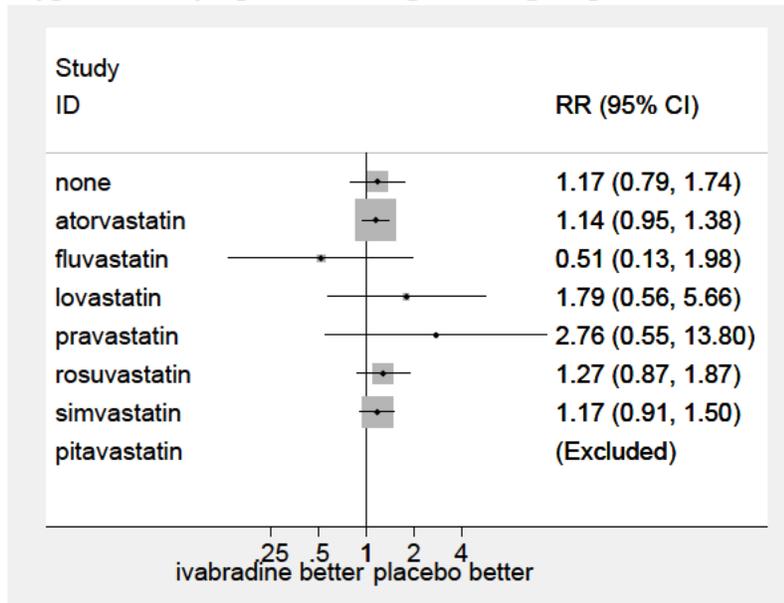


Figure 24: All Cause Mortality Risk Ratios by Statin Type at Randomization in the Baseline HR \geq 75 bpm Subgroup of SIGNIFY



By all cause mortality the differences in RRs by trial atorvastatin still fares poorly in BEAUTIFUL and SIGNIFY but the other statins appear less differentiated by trial. Because the recent concerning finding for ivabradine was the increased risk of the primary endpoint (CV mortality + MI) in the symptomatic angina subgroup of SIGNIFY, I analyzed that endpoint by baseline statin type and show the RRs in Figure 24.

Figure 25: Primary Endpoint (CV death+MI) Risk Ratios by Baseline Statin Type in the Symptomatic Angina Subgroup of SIGNIFY



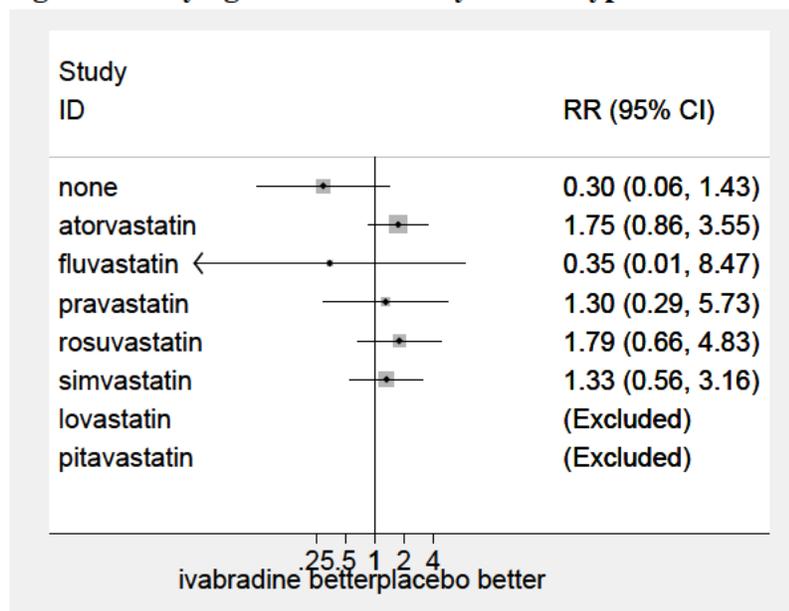
There appears to be no relationship between statin type or lack of use of a statin and the primary endpoint results in SIGNIFY.

As a different approach to determining whether there is an interaction between ivabradine and statins I analyzed myalgia AE rates in SIGNIFY. I counted myalgias if they were not reported as unilateral (e.g., “left shoulder muscle ache”) or a non-specific chest muscle pain. I used SIGNIFY because of its large size with finite rates (about 0.5) of patients with at least one myalgia AE. I show in Figure 25 the myalgia RRs by baseline statin type for SIGNIFY.

Ivabradine without concomitant statin use appears protective against myalgias while myalgia rates with concomitant statin and ivabradine use are increased regardless of statin type. However, none of these differences are statistically significant nor are there sufficient numbers of events to differentiate myalgia rates for different statins.

Statin use during the trial is more difficult to analyze and interpret because about 40% of patients in SHIFT taking a statin and 30% in BEAUTIFUL used more than one statin. However, for fewer than 100 patients in each trial the statin used for the longest duration was different than the statin used at baseline while only about 5 to 6% of patients not taking a statin at baseline subsequently received one. Hence the results for the statins used for the longest durations in the trials are similar to those for the statins used at baseline.

Figure 26: Myalgia Risk Ratios by Statin Type at Randomization in SIGNIFY



COMMENT: Statin dosages might be very informative but I did not have time to attempt to analyze them and their analysis would be even more complicated than the simpler analyses of post-randomization statin type. The analysis of statin dosages is a topic that the sponsor should pursue.

I don't judge that an ivabradine-statin interaction is well established. The sponsor did perform one drug interaction PK study with a statin (simvastatin at 20 mg QD). For the beta-hydroxy acid metabolite of simvastatin (the pharmacologically active species), the ratio of the AUC was 0.88 (90% CI: 0.70 to 1.1) with co-administration of ivabradine relative to administration of simvastatin alone. That magnitude of difference should not affect efficacy but I believe that there are the possibility of other interactions, i.e., hepatic ion transporter interactions, that would not necessarily be reflected in serum PK. I discuss them next.

Because statin use and statin types were not randomly assigned, these results may all be due to statin use being associated with another baseline factor, such as severity of ischemia, that has a real interaction with ivabradine use. However, because a statin interaction could be a modifiable risk, I would recommend that the sponsor pursue a possible ivabradine-statin interaction further.

7.2.7.4. OCT inhibition

Per the sponsor's Summary of Clinical Pharmacology, (b) (4). Because the IC₅₀ for OCT2 is close to the mean steady-state C_{max} value for unbound ivabradine at high dosing, (b) (4) cannot exclude a clinically significant interaction between ivabradine and concomitantly administered drugs that are OCT2 substrates. The IC₅₀ for OCT1 is

175-fold higher than the high dosing C_{max} , so the sponsor considers an interaction with OCT1 substrates to be unlikely. The sponsor reported no substantial inhibitory effect of ivabradine or its metabolite S18982 on the other efflux transporters BCRP and MRP2 or on the uptake transporters OATP1B1, OATP1B3, OAT1, or OAT. The sponsor also conducted a drug interaction study with metformin (a drug excreted by OCT2) that did not show an effect upon metformin pharmacokinetics.

Creatinine is a substrate for OCT2, so drugs that inhibit OCT2 at therapeutic drug levels typically show a slight increase in serum creatinine levels following drug administration. Ivabradine demonstrates this effect: In both SHIFT and BEAUTIFUL the median change in serum creatinine from baseline to the first post-treatment measurement was 0 in the placebo arms; in the ivabradine arms the median change was 0.011 mg/dL in SHIFT (at 4 months, 95% available) and 0.023 mg/dL in BEAUTIFUL (at 1 year, 12% available). For comparison, for another OCT inhibitor ranolazine, mean serum creatinine in the ACS outcome trial MERLIN increased about 0.06 mg/dL more in the ranolazine arm than in the placebo arm. (See Attachment 1.)

We don't attribute any adverse effects to OCT inhibition other than the potential for drug interactions.¹ In SHIFT, renal failure or impairment AEs were numerically less frequent in the ivabradine arm (OR 0.84, $p = 0.11$) while renal failure SAEs were more balanced (OR 0.93, $p > 0.7$). There is no interaction between ivabradine and loop diuretics for renal AEs. However, because heart failure worsening is associated with renal function worsening, the differences in renal impairment AEs may be related to beneficial effects of ivabradine on heart failure.

In BEAUTIFUL renal failure or impairment AEs were more frequent with ivabradine (3.5 vs. 2.8%, $p = 0.034$ by Chi square, OR 1.26). Renal failure SAEs were also more frequent with ivabradine (0.99% vs. 0.68%, $p = 0.08$ by Chi square, OR 1.45) although not statistically significantly so as for renal failure or impairment AEs. Creatinine increase AEs were only slightly and insignificantly more frequent with ivabradine (OR 1.1, $p > 0.5$). While, not surprisingly, loop diuretic use at randomization is a significant risk factor (OR about 5) for a subsequent renal failure event, the interaction between ivabradine and loop diuretics is not significant for renal AEs. There also do not appear to be interactions with other drugs associated with increased risks of renal AEs, e.g., ARBs, ACEIs, and MRAs.

In SIGNIFY renal failure or impairment AEs were more frequent with ivabradine (3.3 vs. 2.8%, $p = 0.047$ by Chi square, OR 1.2). Renal failure SAEs were only slightly more frequent with ivabradine (0.8% vs. 0.7%).

¹ I am not convinced that conventional wisdom is correct. OCTs likely play a role in excreting charged wastes that, when increased, contribute to the symptoms of renal failure. Renal impairment AEs were more frequent in the ranolazine arm of MERLIN than in the placebo arm. Of course, there may be explanations other than OCT inhibition for this latter finding.

COMMENT: Whether OCT2 inhibition is an important mechanism for ivabradine effects or just a minor sideshow remains to be determined. My experience with ranolazine, another OCT2 inhibitor, suggests that OCT2 inhibition likely plays some role for ivabradine as well. Ranolazine did produce in its MERLIN trials increased rates of renal failure AEs compared to placebo. (See Attachment 1.) Whether the increases are directly related to OCT2 inhibition or related to interactions with other drugs is not clear. Ranolazine also produced increases in the types of AEs associated with ACEIs, including angioedema, cough, renal impairment, and anemia. The complicating factor is that ACEIs (and ARBs) are handled by organic anion—rather than cation—transporters. Ranolazine is extensively metabolized into a wide range of charged metabolites so, for ranolazine, is possible that a metabolite is an OATP inhibitor rather than ranolazine itself. The sponsor describes ivabradine metabolism as less extensive so different transporter inhibition by metabolites other than ivabradine and its identified major metabolites may be less likely. I still propose that we consider OCT2 inhibition or other transporter inhibition as contributory mechanisms until we fully understand the various effects and interactions of ivabradine

8. Advisory Committee Meeting

We have scheduled an advisory committee meeting for January 14, 2015. This review is documentation for that meeting.

9. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

10. Financial Disclosure

Please see the primary clinical review for a complete discussion of financial disclosures. The trials were conducted outside of the U.S. without the contemporaneous collection of the U.S. specified financial disclosures from the sites. The sponsor attempted to collect complete information prior to the NDA submission but failed to collect much information. The primary reviewer's conclusion is the following: "the missing financial disclosure information from SHIFT should not impact the approvability of this application."

11. Labeling

11.1. Proprietary name

We have tentatively accepted the proposed proprietary name Corlanor.

11.2. Physician labeling

We have begun discussions of physician labeling with the sponsor to be completed after the Advisory Committee meeting and after we decide about approval.

11.3. Carton and immediate container labeling

The review of carton labeling is pending along with the CMC review.

11.4. Patient labeling/medication guide

The patient labeling discussion are proceeding along with the physician labeling discussions.

12. OSI Audits

OSI audits are pending.

13. Conclusions and Recommendations

13.1. Recommended regulatory action

I recommend approval of ivabradine to reduce the risk of cardiovascular mortality and hospitalizations for worsening heart failure in patients with chronic heart failure (b) (4) in sinus rhythm with either non-ischemic etiology and a heart rate ≥ 70 beats per minute (bpm) or with ischemic etiology and a heart rate ≥ 75 bpm and taking a loop diuretic, (b) (4) including maximally tolerated doses of beta blockers or when beta blocker therapy is contraindicated (b) (4). The SHIFT trial overall was successful for its primary endpoint of CV mortality and HF hospitalizations. The subgroup defined by the indication identifies patients who have substantial benefits for both CV mortality and HF hospitalization while balancing out the detrimental effects shown in the SIGNIFY study in ischemic patients not taking a loop diuretic. The CV benefits outweigh the risks of bradycardia events, increased atrial fibrillation, small increases in renal impairment, and phosphenes such that the benefit-risk in the indicated population is highly favorable. I recommend that the beneficial impact upon both HF hospitalizations and CV mortality be recognized in the labeling.

13.2. Safety concerns to be followed postmarketing

I do not have any safety concerns that warrant special postmarketing surveillance.

13.3. Risk Minimization Plan

The risks of ivabradine, including the management concerns like evaluating pre-treatment eligibility and titration and the risks of teratogenicity, appear similar to other drugs, such as ACE inhibitors and MRAs. Hence I judge that a more restrictive REMS plan is not needed.

13.4. Postmarketing studies

There are a number of studies that I believe would be advantageous for the applicant to do. They include:

- The ivabradine trials included minimal uses of devices, such as intracardiac defibrillators (ICDs) and biventricular pacers or cardiac resynchronization therapy (CRT) that are frequently employed in the U.S. to treat HF patients. It would be valuable to know whether ivabradine supplements either type of therapy or whether it could, in some patients, replace the device therapy.
- Ivabradine appears to add to beta blocker effects, at least at lower BB dosages. We do not know whether BBs add to ivabradine efficacy. Use of one drug rather than two could be advantageous.
- The afib incidence curves suggest a possible structural (anatomic or electrical) remodeling. Electrophysiological and echocardiographic studies could elucidate the etiology and suggest management approaches.
- Whether there is a mechanistic explanation for the loop diuretic interaction remains to be determined. Ideally we should know how loop diuretics, ivabradine, MRAs, and other measures to maintain potassium balance can be optimized to minimize mortality in HF patients. I consider optimizing HF care to be a public health issue and not the responsibility of the applicant.
- While a statin interaction is not definite, analyses of statin dosages in the three trials should elucidate whether additional studies would be useful. Knowing conclusively whether there is a statin interaction is important because an interaction should be surmountable by dosage adjustments or statin selection. Given the results of the SIGNIFY study in symptomatic angina and the findings of increased CV mortality with ivabradine in patients not on a loop diuretic in all three trials, I would not recommend ivabradine for the treatment of angina and I would advise against the off-label use of ivabradine for angina.
- Regardless of the metformin drug interaction study ivabradine OCT2 inhibition appears to have clinical effects. It would be valuable to know the clinical basis for the increase in renal impairment AEs and how to manage them. Given the findings with ranolazine, which is an OCT2 inhibitor that has clinical evidence for inhibition of organic cation transporters (OAT) as well, I would recommend study all ivabradine metabolites with nontrivial exposures (>1% of total exposure?) for OCT and OAT inhibition.

While I believe the studies suggested above would be useful, I don't judge that they are needed for approval or for clinical use of ivabradine in HF. I judge we know enough from the three trials to label ivabradine adequately for its HF indication. I do not recommend requiring any post-marketing studies.

13.5. Comments to be conveyed to the applicant

We have various recommendations regarding the proposed label that we will communicate to the applicant during the label negotiations.

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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: July 24, 2014

Reviewer: Thomas A. Marciniak, M.D.
Medical Team Leader

IND/NDA: (b)(4)/12-151/21-437

Drugs: spironolactone (Aldactone) and eplerenone (Inspra)

Subject: (b)(4) MRA trial results

Summary and Recommendations

(b)(4)

(b)(4)

- MRA use appears to be associated with higher lung cancer rates similar to those seen with angiotensin receptor blocker (ARB) use.
- MRA use appears to be associated with lower prostate cancer rates.

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Baseline Potassium Levels and CV Death

Striking findings in both RALES (the placebo-controlled trial of spironolactone in class III-IV heart failure) and EPHESUS (the placebo-controlled trial of eplerenone in MI patients with left ventricular systolic dysfunction) were that the reductions in CV deaths for the MRA compared to placebo were observed at lower baseline potassium levels. I show these comparisons for RALES in Figure 1 and for EPHESUS in Figure 2.

Figure 1: CV Mortality by Baseline Serum Potassium in RALES

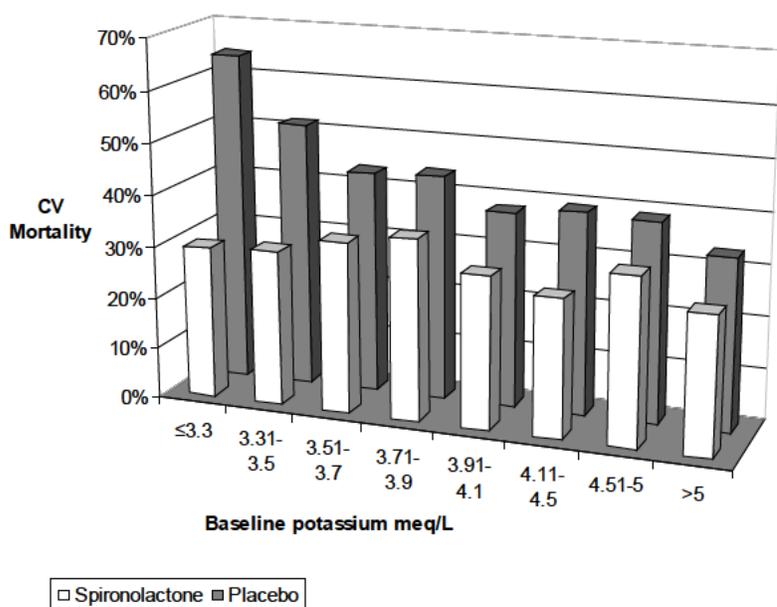
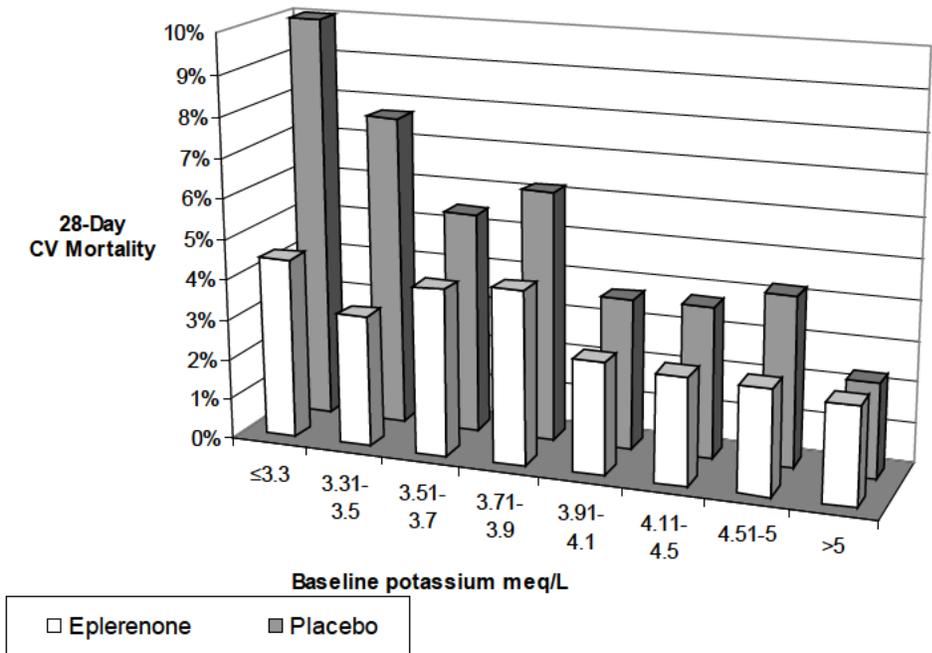


Figure 2: 28-Day CV Mortality by Baseline Serum Potassium in EPHESUS



These figures are taken from my review of the eplerenone submission for EPHESUS, NDA 21-437, Supplement 2. Please see that review for more details on these two trials. While the interaction tests for dichotomized baseline potassium levels are not statistically significant, the trends shown by the figures are striking and I do not know of a standard statistical test for testing them robustly.



(b) (4)

COMMENT: While the effect sizes vary among the (b) (4) studies, there does appear to be a consistent relationship that the use of an MRA eliminates the excess CV mortality at low baseline potassium levels. We have a reasonable mechanistic explanation for this relationship: Low serum potassium levels are associated with tachyarrhythmias so raising potassium levels may alleviate this risk. That something as crude as a single baseline serum potassium measurement provides evidence for this effect supports that the effect is real. It is possible that all of the benefits of aldosterone blockers in heart failure are mediated through this mechanism because the single baseline serum potassium measurement is not robust and the risk of arrhythmias could be more highly correlated with some other measure of potassium balance, e.g., ratio of intracellular to extracellular potassium, rather than the serum level.

(b) (4)

The majority of patients in these HF studies were taking diuretics. The rates of diuretic use range from 100% loop diuretic use in RALES (an entry criterion) through (b) (4) 60% in EPHEBUS. Most of the patients (80-95%) were also taking an ACE inhibitor or an ARB. I believe the message regarding the relationship between baseline serum potassium levels and CV mortality is that we have not been paying close enough attention to potassium homeostasis in HF patients receiving diuretics, particularly loop diuretics. I believe that the results in these four studies should be disseminated—perhaps by NHBLI? Ideally a trial should address this question, e.g., intensively targeting potassium levels in a HF population vs. a control population with usual care. We should also consider the relevance of these results to the hypertensive population, for whom diuretic use is also common.

Malignancies

The MRAs are sex hormonally active, e.g., they cause gynecomastia in men and menstrual irregularities in women. Spironolactone is more active than eplerenone at least regarding the incidence of gynecomastia. Because sex organ tumors are usually responsive to sex hormone levels, we should monitor the rates of malignancies, particularly sex organ tumors, in all studies testing an MRA.

Spironolactone is an old drug that does not have a formal development program. Its label mentions only RALES in the Clinical Studies section. The development program for the antihypertensive indication for eplerenone, while large for an antihypertensive, is nonetheless too small with studies of too short duration to be informative regarding cancer promotion. While overall the randomization in its controlled trials was 1.7 eplerenone to controls, 6 malignancies were reported in the eplerenone arms compared to 2 in the control arms. The malignancies in the eplerenone arms included 2 breast cancers and 1 prostate cancer with none of these cancers in the control arms.

I analyzed malignancy rates in the (b) (4) MRA outcome trials (b) (4) RALES, EMPHEBUS, (b) (4) using the methodology I developed for analyzing malignancy rates in the

angiotensin receptor antagonist (ARB) trials. I have included a description of that methodology as Attachment 1. I present the results of these analyses of malignancies below.

All (b) (4) of the trials were placebo-controlled with 1:1 randomization between MRA and placebo. I show selected characteristics of the trials in Table 1.

Table 1: Selected Characteristics of the MRA Outcome Trials

	(b) (4)	RALES	EPHESUS	(b) (4)
MRA	(b) (4)	spironolactone	eplerenone	(b) (4)
Age, mean	(b) (4)	65.7	64.4	(b) (4)
Female, %	(b) (4)	27%	29%	(b) (4)
Current smokers, %	(b) (4)	NA*	31%	(b) (4)
Ex smokers, %	(b) (4)	NA*	30%	(b) (4)
N	(b) (4)	1,633	6,632	(b) (4)
Years, mean	(b) (4)	1.8	1.3	(b) (4)
PEY ¹	(b) (4)	2,987	8,351	(b) (4)
Deaths/100PEY:	(b) (4)			(b) (4)
placebo	(b) (4)	26.40	13.20	(b) (4)
MRA	(b) (4)	18.30	11.11	(b) (4)
Solid cancers/100PEY:	(b) (4)			(b) (4)
placebo	(b) (4)	1.03	1.24	(b) (4)
MRA	(b) (4)	1.17	1.23	(b) (4)

*NA = not available

The trial populations differed somewhat particular regarding cardiac risk because of their different entry criteria, e.g., RALES in class III-IV HF has the highest mortality rate (b) (4). However, regarding cancer risk, the studies differ little and have similar solid cancer rates per 100 PEY.

COMMENT: The solid cancer rates differ little between studies and between the placebo and MRA arms. (b) (4)

I analyzed all malignancies, not just sex organ tumors. I show the counts of patients with solid cancer events in Table 2.

¹ PEY = person exposure year. However, I calculated PEY in a nonstandard way: Rather than time on treatment I used ITT time, i.e., time from randomization to the first of death or the earliest last visit date (regardless of whether the patient discontinued the study earlier than the earliest last visit date.) I used this variation on PEY, which perhaps should be abbreviated pITTY, to facilitate evaluating whether events are underreported after the patient discontinues treatment.

Table 2: Solid Cancers in the MRA Outcome Trials

	(b) (4)		(b) (4)	
	RALES		EPHESUS	
	P	S	P	E*
anus	(b) (4)	(b) (4)	(b) (4)	(b) (4)
bile duct	0	1	2	0
bladder	2	1	3	5
breast	1	1	1	3
carcinoid	1	0		
cervix			0	1
colon	1	3	9	10
esophagus	2	1	0	2
head & neck			0	2
kidney	1	0	2	1
liver			3	0
lung	3	7	11	15
melanoma			2	2
mesothelioma	1	0		
other			0	1
ovary			0	1
pancreas	1	1	0	1
prostate	2	2	10	1
sarcoma			1	0
stomach	0	1	0	3
thyroid			0	1
unknown			4	3
uterus				
vagina			2	0
vulva			1	0
total	15	18	51	52

*P = placebo; S = spironolactone; E = eplerenone

Note that the numbers in Table 2 are patients with at least one adverse event involving the solid cancer site specified. The majority of events are new solid cancers but, because histories of cancers are not always available, I did not attempt to distinguish new cancers from recurrent ones.

COMMENT: Despite having four large outcome trials, the numbers of cancer events are still too low to draw definitive conclusions based on these four trial results alone. There are several interesting observations regarding the counts in Table 2:

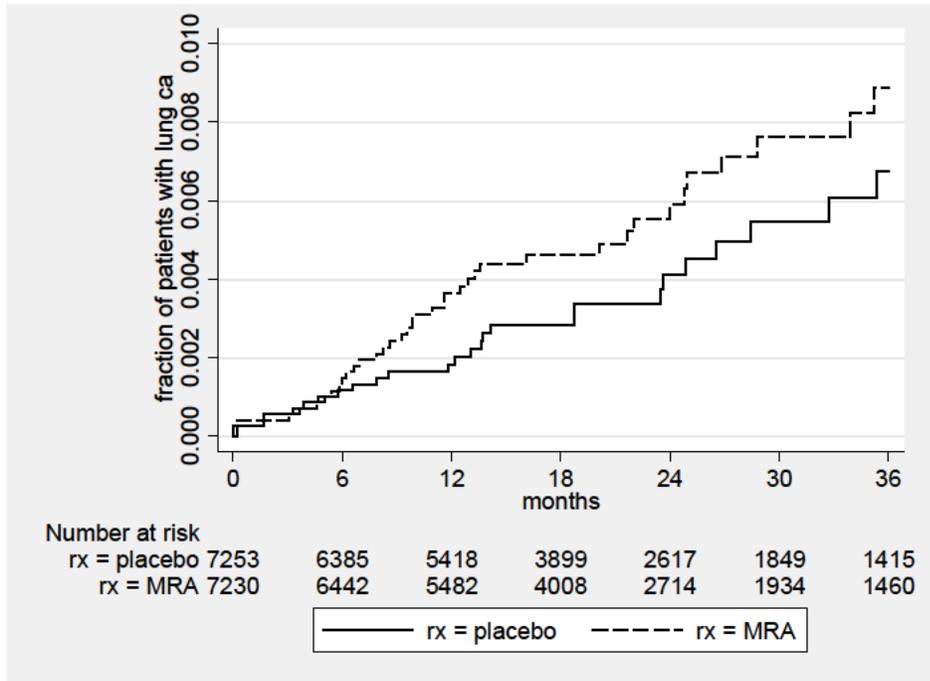
- [REDACTED] (b) (4)

- *The evidence is much stronger that MRAs may be protective against prostate cancer. Only RALES is neutral for prostate cancer while EPHESUS is strongly suggestive of a benefit (b) (4). Both drugs reduce prostate weight in dogs when given at dosages somewhat higher than the human dosages. Spironolactone has actually been tried as an antiandrogen for the treatment of prostate cancer. (Crawford and Nabors 1991)*
- *The surprise for me was lung cancer. (b) (4) studies suggest that lung cancer is more frequent with MRA use and the (b) (4) is neutral. Alone these results would not be very suggestive, but in view of the increased rates of lung cancers with ARBs, whose blockade is only one step earlier in the renin-angiotensin-aldosterone system (RAAS), these results are concerning. I believe examining the incidence curves should be informative, which I do below.*
- *There are other imbalances in solid cancer counts but, of course, we cannot definitively separate real effects from chance imbalances. All studies show a higher rate of colon cancers in the MRA arms. Conversely, the two studies reporting liver cancers reported them only in the placebo arms.*

The two observations that have some support from other data are the increased rates of lung cancer and decrease rates of prostate cancer with MRA use. To explore further I analyzed the incidence curves and meta-analysis statistics for them and present them below.

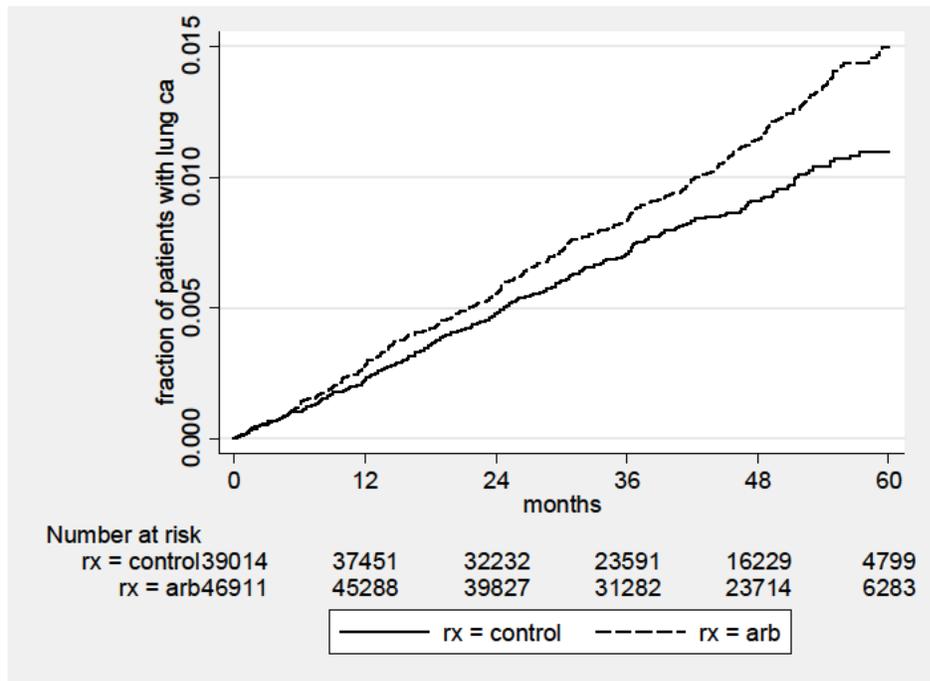
For the MRA trials and lung cancer events I show the incidence curves in Figure 9 and the risk ratios for the trials in Figure 11. For comparison to the incidence curves I show incidence curves for lung cancer events in the ARB trials in Figure 10. For the MRA trials and prostate cancer events I show the incidence curves in Figure 12 and the risk ratios for the trials in Figure 13.

Figure 9: Times to First Lung Cancer Events in the MRA Outcome Trials



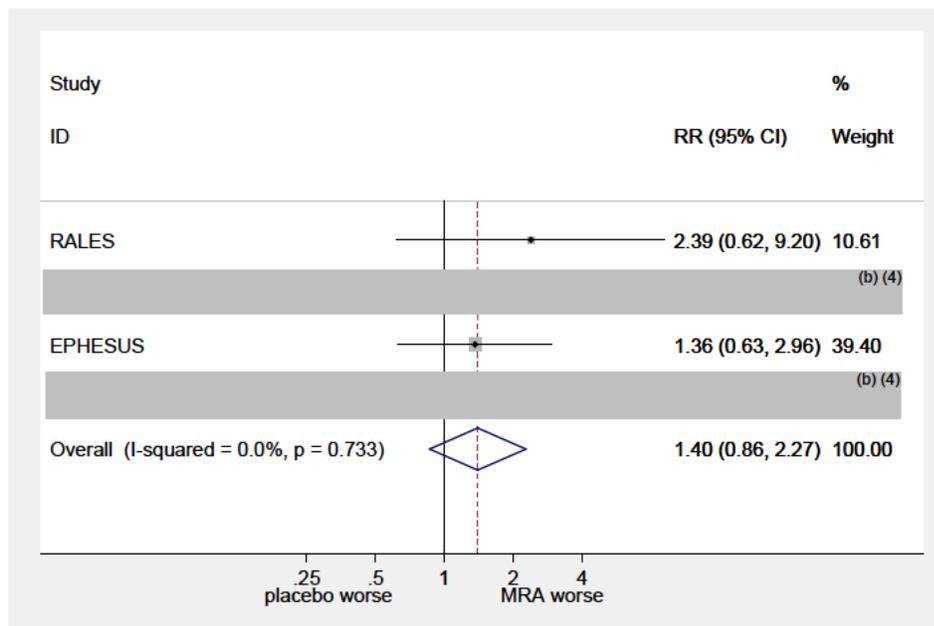
p = 0.21 by log rank stratified by study

Figure 10: Times to First Lung Cancer Events in the ARB Outcome Trials



p = 0.0033 by log rank stratified by study

Figure 11: Risk Ratios of Patients with Lung Cancer Events by MRA Trial



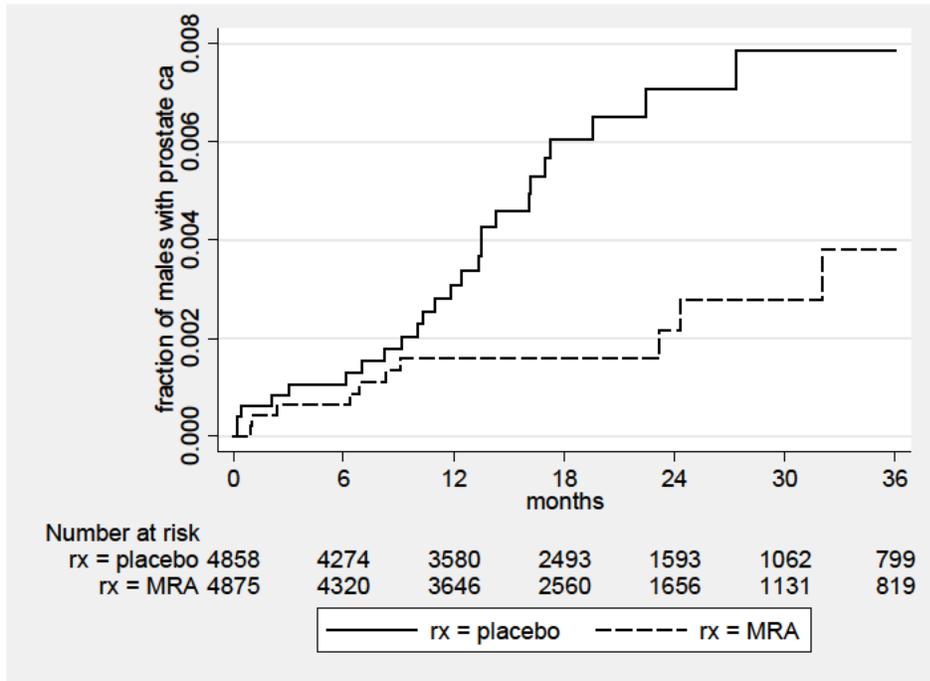
While by themselves the lung cancer event differences in the MRA trials are not statistically significant, the similarities of the results between the MRA trials and the ARB trials are striking. The incidence curves for the first 36 months (the overlapping duration) are very similar, both diverging at about 6 months. The hazard ratios or risk ratios are similar, about 1.36-1.4 for the MRAs and 1.24-1.27 for the ARBs. There is no significant heterogeneity in the results among the trials.

Reported survival after a lung cancer event was poor, about 30% at one year. It was extremely poor in the placebo arms, about 20%. However, follow-up was also poor in the lung cancer patients in the eplerenone arms of EPHESUS (b) (4) about 75% complete in the eplerenone arms compared to about 90% in the placebo arms.

Regarding smoking and lung cancer, RALES did not capture smoking status. (See Table 1 for rates in the other trials.) The majority of lung cancers (85%) (b) (4) occurred in smokers, either current or former, with the higher relative risk in the current smokers. The interaction terms between smoking status and MRA use for lung cancer are not statistically significant.

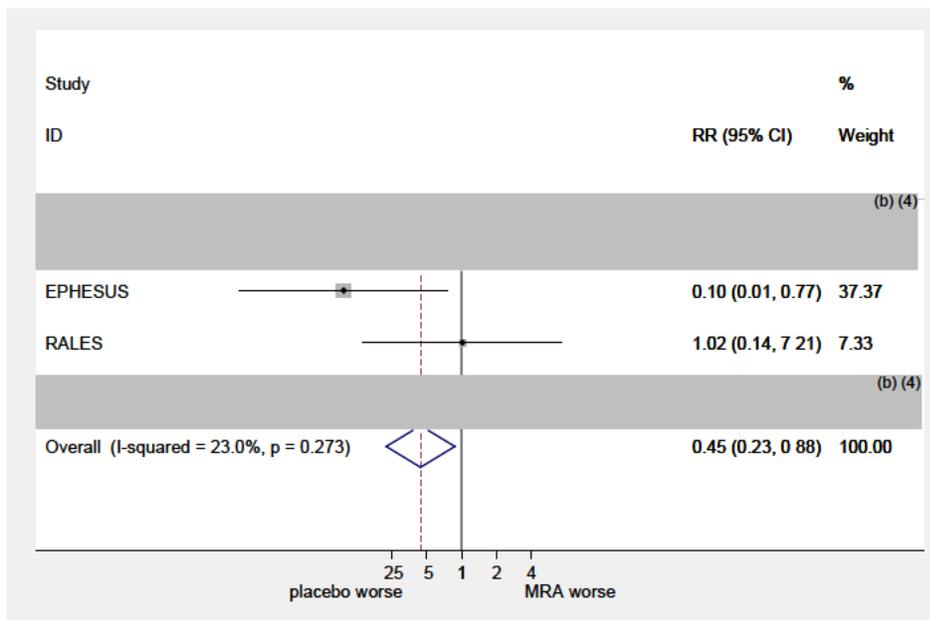
The prostate cancer event results in the MRA trials are nominally statistically significant. While the heterogeneity is not statistically significant by the I-squared test, (b) (4) EPHESUS for eplerenone. The other two trial results are (b) (4). The overall risk reduction is moderate, i.e., about 50%. Reported survival after a prostate cancer event was fair, about 70% at one year, and similar in the placebo and MRA arms.

Figure 12: Times to First Prostate Cancer Events in the MRA Outcome Trials



p = 0.014 by log rank stratified by study

Figure 13: Risk Ratios of Patients with Prostate Cancer Events by MRA Trial



COMMENT: I interpret these results as suggesting that MRA use is associated with both decreased risk of prostate cancer and increased risk of lung cancer. The evidence is stronger for the association with decreased risk of prostate cancer particularly because there is a reasonable mechanism and preclinical support for an effect upon prostate cancer. The evidence for an association with an increased risk of lung cancer is perhaps weaker, although the incidence curves are still striking and the similarity to ARB effects is supportive.

Because the MRAs may be behaving similar to the ARBs regarding lung cancer, I also analyzed hematologic malignancies because I have a hypothesis that ARBs may reduce their incidence. I present those analyses next.

I show in Table 3 the counts of hematologic malignancies in the MRA outcome trials.

Table 3: Hematologic Malignancies in the MRA Outcome Trials

	(b) (4)	RALES		EPHESUS		(b) (4)
		P	S	P	E	
leukemia	(u) (4)	1	0	3	1	(u) (4)
lymphoma		1	1			
leukemia/lymphoma		2	1	3	1	
myelodysplasia				0	1	
myeloma		1	0			
total		3	1	3	2	

While hematologic malignancies are rare and hence the counts in these trials are low, there appear to be fewer leukemias and lymphomas more myelodysplasia in the MRA arms.

COMMENT: My rationale behind analyzing hematologic malignancies for ARBs is that ARBs (and ACEIs) produce mild myelosuppression, e.g., hemoglobin levels drop slightly with their use. The effect is consistent enough that ACEIs have been used to treat the erythrocythemia that can follow a successful renal transplant. However, the MRAs are not reported to produce this myelosuppression, at least in eplerenone hypertension and HF trials. The numbers of hematologic malignancies in the MRA outcome trials are too small for any firm conclusions. Perhaps the most reasonable conclusion is that the results suggest that we should not lump myelodysplasia with leukemias and lymphomas.

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Pitt, B., M. A. Pfeffer, et al. (2014). "Spironolactone for Heart Failure with Preserved Ejection Fraction." New England Journal of Medicine **370**(15): 1383-1392.

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, and censored 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 ascertainment 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 ascertainment 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 ascertainment 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 HLG) 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 hypotheses 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	<ol style="list-style-type: none">1. Added LIFE lung and prostate ca statistics2. Updated count of ARB trials with data in-house from 14 to 153. Added explicit ACEI exclusion criterion4. Clarified use of dates of last treatment5. Added discussion of ITT vs. on-treatment analyses6. Added discussion of dosage issues
1.2	08/18/12	<ol style="list-style-type: none">1. Added Revision History2. Updated count of ARB trials with data in-house from 15 to 16 and added an appendix table identifying the 16 trials3. Clarified that, if FDA staff identify other eligible trials, they will be added to the analyses4. Added an appendix table of MedDRA preferred terms with site classifications5. 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)	(b) (4)
	IDNT	N20757S021
	IRMA 2	N20757S021
losartan	LIFE	N20386S032
	RENAAL	N20386S028
olmesartan	(b) (4)	(b) (4)
telmisartan	ONTARGET	N20850S025
	PRoFESS	N20850S025
	TRANSCEND	N20850S025
valsartan	(b) (4)	(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	lymphoma
hodgkin's disease	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
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
	extraskkeletal chondrosarcoma	sarcoma
	extraskkeletal chondrosarcoma metastatic	sarcoma
	extraskkeletal chondrosarcoma non-metastatic	sarcoma
	extraskkeletal chondrosarcoma recurrent	sarcoma
	extraskkeletal osteosarcoma	sarcoma
extraskkeletal osteosarcoma metastatic	sarcoma	

HLGT	Preferred Term	Site
	extraskkeletal osteosarcoma non-metastatic	sarcoma
	extraskkeletal 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 your 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.

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Finally, given your 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

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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

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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

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Sent: Sunday, August 19, 2012 2:31 PM
To: Stockbridge, Norman L
Subject: Emailing: ARB ca review plan v1p2.doc

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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.

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/s/

THOMAS A MARCINIAK
07/24/2014

36 Pages have been Withheld in Full. This CDTL review for
021526s004 can be found on Drugs@FDA

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this page is the manifestation of the electronic signature.**

/s/

Thomas Marciniak
10/23/2008 11:28:15 AM
MEDICAL OFFICER

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/s/

THOMAS A MARCINIAK
12/08/2014