sanofi aventis
Because health matters

Dr Carole Longson
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28th January 2010

Dear Dr Longson,

Re: NICE Technology appraisal of dronedarone for atrial fibrillation (AF)

Sanofi-aventis disagree with, and are disappointed by the Committee's preliminary decision in this appraisal. We believe the conclusions do not properly reflect the evidence presented and that the approach followed is contrary to the spirit of the NICE Atrial Fibrillation guidelines (CG36) which is based on outcomes. The Committee's decision is particularly surprising given the weight of evidence in support of dronedarone relative to the evidence available for other treatments. Dronedarone has, in sum, more high quality evidence than any other anti-arrhythmic drug (AAD), with 6285 AF patients studied within the clinical development programme. It is also the only AAD to have ever demonstrated efficacy on morbidity / mortality outcomes.

Dronedarone was initially developed to replicate the anti-arrhythmic benefits of amiodarone whilst minimising its significant toxicities; to achieve this, specific structural modifications were introduced to the chemistry of the medicine. During the development of dronedarone it became evident that the drug not only improved heart rhythm problems, but also reduced CV events leading to hospitalization and death. Dronedarone, represents an important new advance in the management of AF, addressing a major unmet need. These observations provided the rationale for conducting the ATHENA trial; with over 4600 patients with atrial fibrillation, ATHENA is the largest trial of an AAD ever conducted.

A 'not recommended' from NICE will deny UK patients access to the only AAD to have demonstrated improvement in major morbidity / mortality, thereby restricting patient and clinician choice to the older agents that are known to have less favourable benefit/risk profiles.

We disagree with the Committee's reasoning in reaching its conclusions. The Committee has not given appropriate consideration to the evidence-base and have adopted a highly conservative assumption that there is no effect on all-cause mortality, yet the balance of probability favours dronedarone. This would appear contrary to the established methodology of technology appraisals and the usual approach of NICE. We understand that decision modelling and, in particular, the use of probabilistic sensitivity analysis (PSA) is normally used by the Committee to deal with uncertainty and to allow estimation of the most likely outcomes and it is unclear why such an approach was not followed in this case. We ask that the Committee reconsider the balance of probabilities or provide an explanation of why they think the best interpretation of the evidence is that dronedarone has no mortality advantage relative to comparator AADs.

How did the Appraisal Committee reach its conclusions? In order of priority, the Committee appear to have concluded:

i) dronedarone has no overall mortality advantage over placebo or comparator drugs. This view is supported in the ACD by two main reasons:

   a. the lack of plausibility of the all-cause mortality benefit observed within the ATHENA trial and subsequent challenges to the statistical analysis of key trial data (i.e. the mixed treatment comparison (MTC)) supporting the all-cause mortality advantage of dronedarone over comparator drugs;

b. concern that a mechanism by which such an advantage might manifest itself has not been demonstrated, particularly as the mechanism would need to be independent of time to *first AF recurrence*;

ii) dronedarone is less efficacious than comparator drugs measured on time to *first AF recurrence*;

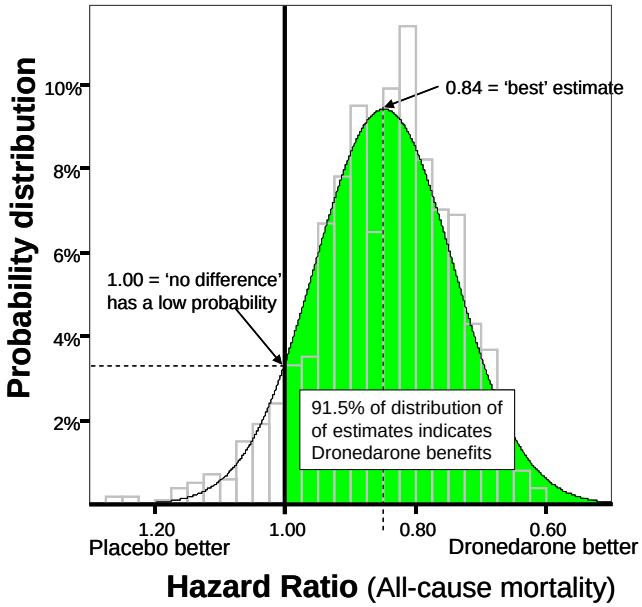
iii) without an all-cause mortality advantage there is no cost-effectiveness case for dronedarone

Summary of our response (see below and in the tabulated appendices for detailed comments):

i) We strenuously dispute the conclusion of there being no mortality advantage for dronedarone. The Committee's interpretation appears to selectively disregard the evidence to the contrary and their conclusion of no plausibility for any mortality benefit is very difficult to sustain. We request the Committee reverse their decision in light of the following:

a. There is evidence of an all-cause mortality advantage for dronedarone shown throughout the evidence base. Within the ATHENA trial the hazard ratio (HR) for the secondary endpoint of all-cause mortality was 0.84 with a 95% confidence interval (CI) 0.66 – 1.08[i]. The most appropriate interpretation of this evidence is one that uses estimation and uncertainty, and which looks to the point estimate to provide the best available estimate of effect and the confidence intervals to describe the level of uncertainty of that estimate. Such an approach suggests 91.5% likelihood that the true effect of dronedarone on all-cause mortality is beneficial as demonstrated in the Figure 1 below.

Figure 1: Plausible range of All-cause mortality benefit for dronedarone vs. placebo (ATHENA)



Evidence on the use of other AADs in the AF population has shown a trend towards an increased hazard for all-cause mortality as demonstrated in several independent publications (detailed within Appendix 1). The significant difference in all-cause mortality between dronedarone and amiodarone or sotalol, as found in the results of the MTC, is therefore entirely plausible;

b. It is commonplace in drug development for only a partial understanding of the mechanism by which a new medicine works to be available at the time its benefits are first demonstrated. As stated in previous communications we consider the combined unique features of dronedarone's activity offer a plausible explanation for the benefits observed (see also Appendices 1 and 2). We suggest that the Committee would find it equally challenging to specify the precise mechanism by which any of the other AADs used to treat atrial fibrillation deliver their benefits

ii) We recognise that time to *first AF recurrence* was shorter for dronedarone when compared to amiodarone and [redacted] More relevantly, in UK clinical practice *time to first AF recurrence* is not routinely used as a measure of treatment failure and should not therefore, be considered as the only means of determining efficacy of an AAD. In the context of the burden that AF represents in terms of health care consumption, it is no longer acceptable to define an AAD's efficacy purely on its ability to impact time to *first AF recurrence*.

iii) We acknowledge point iii); without the comparative all-cause mortality advantage for dronedarone a cost-effectiveness case has not been made. However, by assuming zero mortality benefit, the Committee have over-stated the uncertainty of the evidence and have, in effect, based their conclusions on a scenario which has a probability of only 0.035. It is of note that very little of the mortality benefit observed in the evidence-base is required (only around 7% of that observed in the MTC) for dronedarone to achieve cost-effectiveness at the £20,000/QALY threshold. The evidence is strongly supportive that at least that much mortality advantage is to be had. Indeed, given the various estimates of mortality benefit available from randomised trials, the conclusion that all agents have the same effect is simply not tenable. It should be noted in this regard that the Appraisal Committee may have been misled by a mistake which was found in the pre-briefing documentation given to the Committee prior to the Appraisal Committee Meeting. On page 24 of that document, it was reported that the likelihood of the incremental cost-effectiveness ratio (ICER) being greater than £20,000 was 96% in a comparison with sotalol. This should read likelihood of ICER being **less than** £20,000 was 96%; The probabilistic sensitivity analyses performed by sanofi-aventis indicates that the cost-effectiveness of dronedarone is highly likely to be in the acceptable range.

In conclusion, we wish to clarify the rationale behind our positioning of dronedarone at the forefront of the treatment pathway. The NICE Clinical Guideline, upon which we base our positioning, recommends warfarin and aspirin 'up front', not to retrain heart rhythm, but for reducing the risk of stroke and death – the major clinical outcomes associated with AF. It is clear from the NICE recommendation, preventing these clinical outcomes is of the utmost importance in the management of AF. Following beta-blockade, the AADs are recommended for patients depending on the pattern of AF symptoms and the presence/absence of structural heart disease. The underlying rationale in the guidelines for the choice of AAD is that the less effective, yet better tolerated treatment is preferred in the first case, with patients only graduating to the more effective and more toxic agents (e.g. amiodarone) as a later resort; in some patients, only one agent can be used (e.g. persistent patients with structural heart disease or paroxysmal patients with left ventricular dysfunction). In contrast with other agents, dronedarone can be used in all patients with non-permanent AF other than the small group of patients with unstable heart failure.

Dronedarone, with the largest dataset of any AAD, has demonstrated efficacy on *time to first AF recurrence,* is a well tolerated medicine without the treatment limiting (thyroid toxicity) or life-threatening (pro-arrhythmic) effects of the other AADs, and is the only AAD to have reported a positive effect on all-cause mortality and confirmed a benefit on the proxies for all-cause mortality, namely CV mortality, and unplanned CV hospitalisations. In contrast, the evidence indicates the other AADs have a negative effect on all-cause mortality and significant toxicities that make patients and clinicians wary of their use, especially over the longer-term.

Dronedarone offers a clinical and cost effective addition to current AF treatment options and we believe there is good evidence that the Committee should take into account in reaching a final decision to recommend that dronedarone should be made available within the NHS. For NICE to reject the first innovation in this therapy area for twenty years denies patients and clinicians an important choice.

Yours sincerely,

[redacted]

Inc.
Appendix 1 – Further considerations in addressing the Committee's concerns
Appendix 2 – Tabulated comments on the ACD documentation

Appendix 1 - Further considerations in addressing the Committee's concerns

Statistical evidence for an all-cause mortality benefit of dronedarone:

There are a number of studies which all support dronedarone having a mortality advantage over comparator AADs. The ATHENA trial provided evidence for an advantage on all cause mortality for dronedarone versus placebo in patients with AF; such an advantage has not been demonstrated for comparator drugs.

1) The systematic review and meta-analysis submitted by sanofi-aventis consistently found a trend for increased mortality in patients receiving amiodarone and sotalol versus control treatment arms with three separate analyses; direct, indirect and mixed treatment comparisons. These results were largely replicated by the ERG using their own approach. While the difference with amiodarone was only significant in the MTC analysis it is worth noting it was significant throughout all analyses of sotalol.

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
MTC comparison with control*	2.73 (1.00 – 7.41)	4.32 (1.59 – 11.70)	sanofi-aventis

* Control is either placebo or standard care

2) Independent systematic reviews in an AF population have also demonstrated a trend for increased all-cause mortality for amiodarone and sotalol as noted below.

Comparison type	Amiodarone OR (95% CI)	Sotalol OR (95% CI)	Source
Direct comparison with placebo	1.88 (0.54 – 6.56)	Not considered	Piccini 2009[ii]
Direct comparison with control*	1.96 (0.68 – 5.67)	2.09 (0.97 – 4.49)	Lafuente 2006[iii]

* Control is either placebo or standard care

3) The AFFIRM trial[iv], which randomised over 4000 AF patients to receive either rhythm or rate control, also found a trend for increased all-cause mortality and CV hospitalisation for those patients randomised to rhythm control. The hazard ratio for all-cause mortality at 5 years follow-up was 1.15 (95%CI 0.99 – 1.34; p = 0.08) and a subsequent analysis also noted that CV hospitalisation was more frequent in the rhythm-control arm (46% versus 36%, p < 0.001)[v]. The rhythm arm of this trial consisted primarily of amiodarone and sotalol treatment (approx. 70% of patients received either agent as initial therapy).

   In addition, a further investigation on the predictors of mortality[v] found that CV hospitalisation was highly predictive of death regardless of treatment (rhythm or rate). Given the higher CV hospitalisation found in the rhythm arm of AFFIRM it is perhaps not surprising that there was a trend for higher mortality. In contrast to this, the ATHENA trial found a 26% reduction in CV hospitalisation demonstrated by dronedarone versus placebo. Given this evidence we question why the Committee have discounted any mortality benefit for dronedarone (especially when considering the study was not powered to detect an independent mortality difference, but showed a trend for improvement).

4) While there is no direct comparative data on dronedarone and the other AADs with regards to CV hospitalisation and all-cause mortality, the above evidence from a variety of independent sources supports a number of conclusions:

   - Firstly, the Committee's assumptions have over-simplified the available evidence, which indicates there is no simple relationship between the *time to first AF recurrence* and major clinical outcomes. AADs have never been shown to reduce all-cause mortality, nor has restoration and maintenance of sinus rhythm (SR) been associated with improvement of major clinical outcomes. In the landmark AFFIRM study[iv] more patients in the rhythm arm were maintained in SR but this did not translate into a reduction of mortality or CV events.

- Secondly, to consider dronedarone within the context of the *time to first AF recurrence* alone does not do justice to the evidence or the complexity of the disease area. The totality of the evidence on dronedarone challenges the assumption that improvement in *time to first AF recurrence* would translate to an improvement in major clinical outcomes. In the ATHENA trial, dronedarone reduced the composite end-point of unplanned CV hospitalisation or death, and the size of the effect was similar even for those who remained in AF for the entire duration of the study

- Finally, in UK clinical practice *time to first AF recurrence* is not routinely used as a measure of treatment failure and should not therefore, be considered to be the only means of determining efficacy of an AAD.

The plausibility of the all-cause mortality benefit:

While it may be understandable to question the plausibility of the mortality benefit of dronedarone when such an important clinical outcome has never been demonstrated for any other AAD, we believe the strength of the data from ATHENA and the MTC, together with the explanations we have provided as to the likely mechanism of such an effect means that this benefit should be taken into account. The Committee specifically questioned the plausibility of accepting **any** of the observed all-cause mortality benefit of dronedarone either from the ATHENA trial or from the evidence syntheses (i.e. MTC comparison). We would therefore ask the Committee to reconsider the evidence for dronedarone in relation to all-cause mortality especially within the context of the following points:

1) Comparator drugs to dronedarone have been known to be toxic for many years and the rationale behind the development of dronedarone was to replicate the effects of the AAD, amiodarone, while minimising its significant toxicity. During clinical development it became apparent that dronedarone had an impact on outcomes beyond *time to first AF recurrence.* A post-hoc analysis of EURIDIS/ADONIS demonstrated a significantly lower risk of hospitalisation or death compared to placebo. This observation was confirmed prospectively in the ATHENA trial with a highly significant primary endpoint of reduced risk of unplanned CV hospitalisation or death. It was impractical to conduct an event-driven clinical trial in this population with the lone endpoint of all-cause mortality because of the trial size demanded (for a study with 90% power over 25,000 patients would be required) and follow-up required, but we would suggest that the weight of the evidence supporting the mortality benefit for dronedarone, not just in the ATHENA trial adds to the plausibility of this benefit.

2) When looking at the secondary endpoint of all-cause mortality within the ATHENA trial, the Committee felt that the mortality benefit demonstrated (HR 0.84; 95% CI 0.66 – 1.08; p = 0.18) was only marginal until approximately 24 months of follow-up, and that the wide divergence in the curves after this point (an 'artefact' of the lower patient numbers available) was driving the observed difference. This interpretation is incorrect. The events which occur at the tails of the survival curves add very little weight to the summary statistics, so the divergence observed throughout the earlier part of the time-course is more influential on the results than the later periods of follow-up. The Cox Proportional hazards method used for this analysis appropriately accounts for the small patient numbers at the later time points (see Appendix 2, section 4.5), and the validity of the assumption of constant proportional hazards will, we are sure, allay the Committee's concern about the plausibility of the estimated mortality benefits demonstrated in the ATHENA trial;

3) A further consideration relevant to the robustness of the demonstration of the all-cause mortality effect is the significant difference in CV-mortality observed within the ATHENA trial. There were 63 deaths from CV causes in the dronedarone group and 90 in the placebo group (HR 0.71; 95% CI 0.51 – 0.98; p = 0.03). Given the additional 'noise' that is incorporated within the measure of all-cause mortality (as all-cause mortality inevitably includes deaths which are quite unrelated to the treatments) it is not surprising that this result has been diluted somewhat. The most appropriate interpretation of this evidence is one that uses estimation and uncertainty, and which looks to the point estimate to provide the best available estimate of effect, and the confidence intervals to describe the level of uncertainty on that estimate. By assuming no all-cause mortality advantage the Committee has chosen to accept that part of the confidence interval which has a likelihood of 8.5% or less. The uncertainty on the estimates of all-cause mortality is of course included in the fully probabilistic economic modelling, and reflected in the uncertainty on the cost

per QALY value derived from that model (within the PSA the probability of a cost per QALY < £20,000 is over 90% for all comparisons of dronedarone with amiodarone and sotalol).

4) The Committee noted the absolute rates for all-cause mortality of 5% and 6% for dronedarone and placebo, implying that the difference is rather small. People who work in other areas of cardiac care will be familiar with the importance of small reductions in absolute risk. By way of comparison, the RELY study looking at a composite primary endpoint of stroke or systemic embolism in AF patients, randomised to either dabigatran or Warfarin, found the absolute rates of the primary endpoint at 1 yr of just 1.69% versus 1.11%[vi]. For dronedarone, these absolute rates reflect a very important 23 excess deaths in the placebo arm of ATHENA. Considering the extremes of the confidence intervals around the all-cause mortality point estimate we estimate that per 1000 AF patients treated with dronedarone there may be as many as 21 deaths avoided or an additional 4 deaths incurred (the likelihood of there being a net benefit is 91.5%). The impact of dronedarone on all-cause mortality will in the majority of cases be positive as suggested by the distribution curve presented within the covering letter.

5) Finally, the all-cause mortality advantage demonstrated in the MTC analysis is highly plausible given the evidence available on dronedarone in comparison to that available for the current AADs. As noted above, the evidence for sotalol and amiodarone suggests either a neutral or increased trend for mortality compared to placebo whilst dronedarone has demonstrated a trend towards a reduction in all-cause mortality compared to placebo. It is therefore not surprising when available evidence is synthesised and combined in the MTC that a significant difference in all-cause mortality between dronedarone and amiodarone or sotalol is found.

It was asked of the manufacturer at the first Appraisal Committee Meeting on the 25th November if a claim for outcomes benefit to be recognised in the product indication (section 4.1) had been sought from the EMEA. We can confirm this was the case, but as reported in the European Public Assessment Report, EPAR (page 45) the inclusion of clinical endpoints in the indication section was not in line with the SPC guideline. However, the values of the ATHENA trial outcomes were fully described within section 5.1 of the SPC. In addition, when reading the therapeutic indication in 4.1 specific attention is made to section 5.1.

Adequacy of the explanation of dronedarone's mechanism of action

It is the case that exactly how the drugs under consideration here, including dronedarone, deliver their benefits is not completely understood. While the precise mechanism of action of dronedarone is still being investigated, a situation common for many drugs at such an early stage in their life cycle, it is believed that dronedarone may provide its demonstrated benefits because of particular features of its chemistry; as we reported in our original submission. Dronedarone has a broad pharmacological action which includes multiple ion-channel blockade and β-adrenoceptor antagonism which leads to a variety of tissue response in patients with arrhythmias. This includes a reduction in heart rate, improved rhythm control and haemodynamic effects such as lowering of blood pressure. It is likely that the unique combination of these effects (individually associated with reducing CV risk) explains in part at least the benefits of dronedarone beyond its anti-arrhythmic action. Additional detail is provided in Appendix 2, section 4.18.

The relative importance of the 'Time to first AF recurrence' endpoint

It is noted throughout the ACD that the Committee believe dronedarone to be the least efficacious of the AADs in respect to *time to first AF recurrence*. This conclusion is not completely accurate as stated in our covering letter.

More importantly however, we wish the Committee to consider the relevance of *time to first AF recurrence* within the wider context of patient care. While a key consideration of treatment for the patient will clearly be symptom relief, and time to *first AF recurrence* may be a useful surrogate for this, it is crucial to remember other outcomes associated with AF such as unplanned hospitalisation for cardiovascular events and mortality. The principal aim of AF treatment is the prevention of these major outcomes and this is reflected in the recommendations of the NICE clinical guideline CG36 in relation to appropriate anticoagulant or anti-thrombotic therapy as foundation treatment. Until now AADs have not demonstrated reduction in morbidity or mortality in patients with AF, and there is some evidence of negative outcomes with these older products. Dronedarone offers clinicians and patients

the opportunity to benefit from outcomes prevention while still maintaining significant efficacy in rate and rhythm control.

Long-term outcomes might not be at the forefront of patients' thoughts, as they are not an everyday occurrence. However, when unplanned hospitalisations occur they are typically very detrimental to the patients' quality of life, and are often precipitated by major cardiovascular events which may ultimately be fatal. The ATHENA trial demonstrated that dronedarone significantly reduced unplanned cardiovascular hospitalisation; major differences being 161 fewer supraventricular rhythm disorder hospitalisations, 13 fewer MI / unstable angina hospital events, 7 fewer stroke and 14 fewer CHF hospitalisations. The impact of such events will be significant for the patients; 50% of the patients experiencing an AF-related hospitalisation within the ATHENA trial remained in hospital for at least 4 nights, and 25% for at least 8 nights.

The outcome benefits reported for dronedarone in the ATHENA trial were achieved on top of the benefits to be expected from standard background therapy; 71% of the patients received beta-blockers and 60% received vitamin K antagonists.

Cost-effectiveness

As stated in the ACD document, the key driver of dronedarone's cost-effectiveness argument in our submission is the all-cause mortality benefit seen on top of standard therapy versus standard therapy alone (beta-blockers and anti-coagulation) for patients with multiple CV risk factors (corresponding to CHADS2≥4) and over current AAD products (i.e. amiodarone, sotalol and Class 1c agents) for other patients with AF where a first line AAD is to be introduced. The Appraisal Committee asserted that there was too much uncertainty to accept **any** of the mortality benefit observed with dronedarone versus amiodarone and sotalol, and by disregarding this benefit completely they have noted an ICER in excess of £1m/QALY. However, by assuming that there is evidence of **no** all-cause mortality advantage (or no evidence of **any** mortality advantage) the Committee is challenging the body of evidence. We would suggest it is untenable to argue that there is no evidence of all-cause mortality benefit, and that this position is unreasonable. On the balance of the evidence presented, and of the indications from proxies for all-cause mortality (e.g. CV hospitalisation and CV mortality) some benefit has clearly been demonstrated.

The evidence for a mortality effect from ATHENA is shown in Figure 1

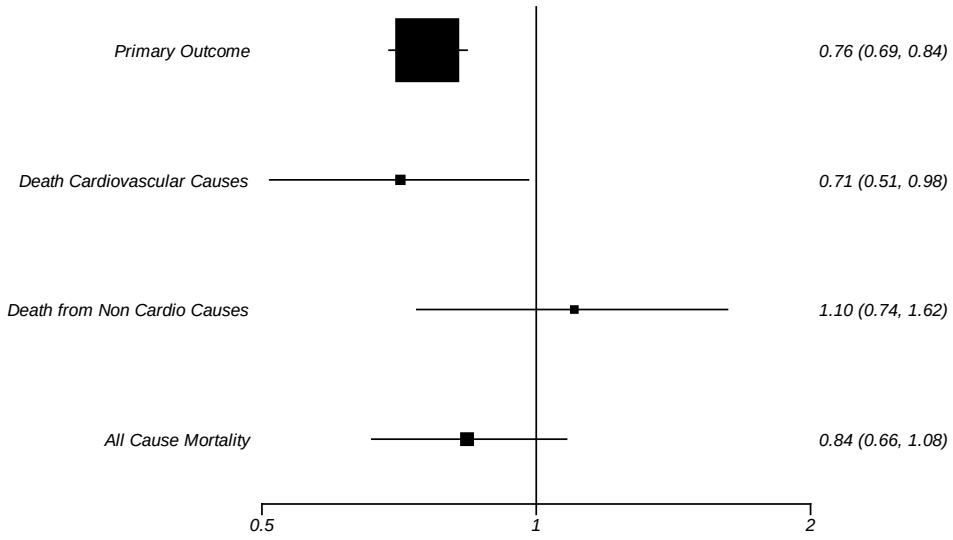


Figure 2: Primary and Secondary Results from the ATHENA trial

As indicated within our original submission, only a small percentage of the mortality benefit needs to be incorporated into the modelling for dronedarone to be cost-effective. On page 113 it was shown that if only 5% of the estimated mortality benefit associated with dronedarone relative to amiodarone

for persistent patients with structural heart disease were achieved, the ICER would be below £20,000/QALY. The probability of achieving this 5% mortality benefit is 96% according to our MTC. Across the various patient populations as dictated by the NICE clinical guidelines, only 7% of the potential mortality benefit indicated by the MTC is required for the cost per QALY to drop to under £20,000.

[i] Hohnloser SH, Crijns HJ van Eickels M Gaudin C Page RL Torp-Pedersen C Connolly SJ and ATHENA Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med.* 2009; 360: 668-678

[ii] Piccini, JP (2009) Comparative Efficacy of Dronedarone and Amiodarone for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation. J Am Coll Cardio, 54: 1089 – 1095.

[iii] Lafuente-Lafuente, C et al. (2006) Antiarrhythmic Drugs for Matinaining Sinus Rhythm After Cardioversion of Atrial Fibrillation. Archives of Internal Medicine, Vol. 166: 719 - 728.

[iv] A Comparison of Rate Control and Rhythm Control in Patients with Atrial Fibrillation (2002) NEJM, Vol 347; 23: 1825 – 1833.

[v] Wyse, G (2004) Alternative endpoints for mortality in studies of patients with atrial fibrillation: The AFFIRM study experience. Heart Rhythm, 1: 531 - 537

[vi] Connolly, S et al. (2009) Dabigatran versus warfarin in patients with atrial fibrillation. NEJM, 361; 12: 1139 – 1151.

[redacted]

Response to ACD document from sanofi-aventis 28th January 2010

APPENDIX 2	
Comment within ACD	**Comment**
Pg 3, section 1	No comment
Pg 3, section 2.1/2.2	While this section is factually correct we would suggest that the Committee also document the reference under the Therapeutic Indication wording of the SPC to section 5.1 which includes detailed reference to the benefits of reduced hospitalisation demonstrated with ATHENA. For example within 2.1 it may be appropriate to put: "Dronedarone has a marketing authorisation for the treatment of adult clinically stable patients with a history of, or current non-permanent atrial fibrillation to prevent recurrence of atrial fibrillation or to lower ventricular rate. Within section 5.1 of the SPC reference is also made to the reduction in the risk of AF hospitalisation."
Pg 3, section 2.3	While elevated blood creatinine levels and prolongation of QT interval are very common adverse reactions with dronedarone they are also the least serious as noted in Table 1, pg 8 of the SPC, requiring only investigation. Within this section, it would be more appropriate to clinicians and patients to refer to the common adverse events that are likely to require treatment such as bradycardia, gastrointestinal events such as diarrhoea and vomiting, rashes, pruritus, fatigue and asthenia.
Pg 4, section 2.4	No comment
Pg 4, section 3.1	Beta-blockers have multiple indications. While they do have mild to modest anti-arrhythmic properties making them an appropriate first-line treatment for patients with non-permanent AF (as noted within the NICE clinical guidelines CG36), for the sake of clarity it is confusing to define them as AADs (AADs are purely for rhythm management). As such the second-line treatment recommended within CG36 of amiodarone, sotalol and Class 1c agents are essentially first-line AADs. Can we suggest the following: "The choice of first-line anti-arrhythmic drug depends on the type of atrial fibrillation (persistent or paroxysmal) and the presence or absence of structural heart disease, left ventricular dysfunction or coronary heart disease. The manufacturer's submission considered the use of dronedarone as an alternative to amiodarone, sotalol and class 1c agents for people in whom a first-line anti-arrhythmic drug is indicated"
Pg 5, section 3.1	The company submitted position is as a first line alternative to current AADs which includes amiodarone, sotalol and class1c agents (please note comment pg 4 section 3.1).
Pg 5, 3.2	No comment
Pg 6, 3.3	No comment
Pg 6, 3.4	No comment
Pg 7, 3.5	While this section provides an accurate summary description of ATHENA there are a number of important aspects that have not been presented which would allow for a more balanced appreciation of the ATHENA trial results. For all endpoints discussed we feel it would be appropriate to list the actual number of events allowing the reader to appreciate the size of the ATHENA trial which is the largest AAD trial conducted to date. These numbers would include:

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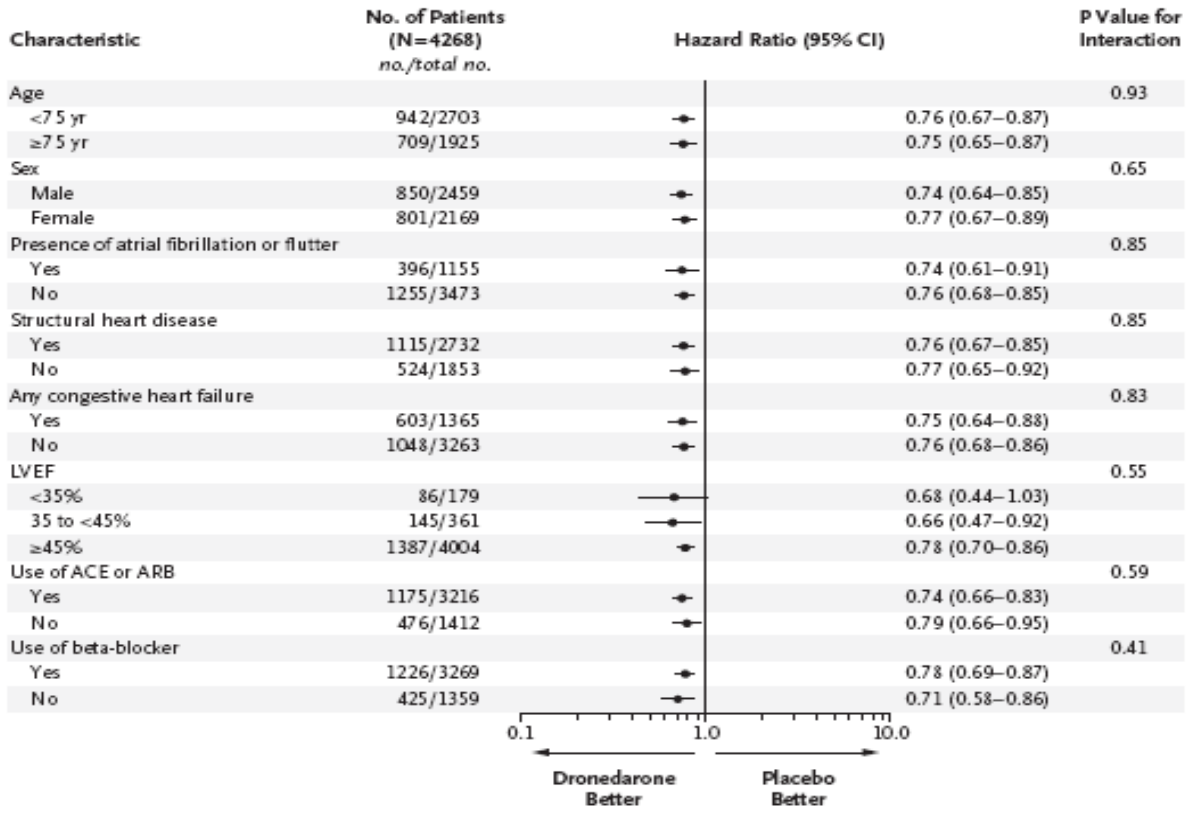
	• Primary endpoint: n = 734 events in the dronedarone arm and 917 events in the placebo arm; number of events avoided = 183 • Secondary endpoint of all-cause mortality: n = 116 in the dronedarone arm and 139 in the placebo arm; number of deaths avoided = 23 • Secondary endpoint of first hospitalisation due to cardiovascular event: n = 675 in the dronedarone arm and 859 in the placebo arm; number of CV hospitalisations avoided = 184 It is important to highlight that the hospitalisation noted in the primary endpoint was unplanned therefore we would suggest the following: "The primary outcome was a combination of first **unplanned** hospitalisation because of a cardiovascular event and death before hospitalisation." We would also suggest that the appropriate numbers, hazard ratio and confidence intervals around the unplanned hospitalisation endpoint be noted for consistency. For example: "For time to first hospitalisation due to cardiovascular events the number there were 675 events in the dronedarone arm and 859 in the placebo arm with a hazard ratio of 0.74 (95% CI 0.67 – 0.82; p<0.001)". Given the importance of all-cause mortality the suggestion that there was only a slightly lower rate of all-cause mortality and the presentation of the absolute percentages for both arms of the trial diminishes the value of this result. We would suggest the following amendment: "There was a lower rate of all-cause mortality in the dronedarone group than the placebo group (n = 116 versus 139); although this difference was not statistically significant (hazard ratio 0.84, 95% CI 0.66 – 1.08, p = 0.18)." We would also request that there is a clear reflection that the difference in CV-mortality is significant, for example: "There were significantly fewer deaths (n = 63 versus 90) from cardiovascular causes in the dronedarone group than the placebo group (2.7% and 2.9% respectively, hazard ratio 0.71, 95% CI 0.51 to 0.98, p = 0.03)".
Pg 8, 3.6	It would be appropriate to also note within this section that there was no significant difference between dronedarone and placebo on the incidence of serious treatment emergent adverse events (n = 456 in the dronedarone arm compared to 489 in the placebo arm).
Pg 8, 3.7	For complete accuracy it should be noted that the primary endpoint of DIONYSOS was: "The primary endpoint of DIONYSOS was a combined endpoint of **first occurrence** of either recurrence of AF or premature study drug discontinuation for intolerance or lack of efficacy" In addition, more detailed information from DIONYSOS is now available in the public domain within the EMEA Assessment Report from DIONYSOS (published 16.12.09) which may add value to this section. For example: "This difference was mainly because of fewer incidences of atrial fibrillation recurrence in the amiodarone group (63.5% for amiodarone versus 42% for dronedarone)."
Pg 8, 3.8	This paragraph appears to switch between the results of the meta-analysis and the mixed treatment comparison (MTC) which does not present a consistent view of the analyses. Given that the economic model was based on the MTC analyses we would suggest that these results be presented throughout this paragraph. For example [redacted] The results from DIONYSOS on risk of first AF recurrence were lower for amiodarone than dronedarone reflecting these results."
Pg 10, 3.9	Within the NICE clinical guidelines for the management of atrial fibrillation (CG36) section 6.2, pg 52, it states that the need for AADs has to be balanced against adverse effects and a higher mortality in some patients. Given this recommendation, the relevance of the similar incidence of serious adverse events (SAEs) between dronedarone and placebo based on the pooled data from over 6000 patients as

	noted in section 3.9 is worth highlighting again for future discussions.
Pg 11, 3.10	The description of dronedarone as an alternative second-line anti-arrhythmic agent is potentially confusing (see section 3.1). Whilst the position in question is a second-line treatment it is the first time a specific AAD is introduced, therefore we request that dronedarone is described as an alternative first line anti-arrhythmic agent.
Pg 11, 3.11	No comment
Pg 12, 3.12	Adverse event rates used in the economic model for dronedarone were taken from a pooled analysis of 6 RCTs: ATHENA, EURIDIS, ADONIS, DIONYSOS, ERATO and DAFNE – this is different from the pooled analysis mentioned in section 3.9 which does not include DIONYSOS.
Pg 12, 3.13	The treatment initiation cost for dronedarone should be £213 which is comprised of the reference cost of a consultant led first attendance outpatient face to face visit (£158) inflated to 2008 (£165) plus the cost of a creatinine test at a GP visit (£47). This was clarified to NICE on 7th October 2009.
Pg 13, 3.14	No comment
Pg 14, 3.15	No comment
Pg 14, 3.16	While ATHENA did include patients with a higher risk of a major cardiovascular event than people in other trials the generalisability of this evidence to a lower-risk and younger population is a reasonable assumption given the following evidence: • The ATHENA trial results are supported by the results of a post-hoc analysis of unplanned hospitalisation or death within the very low-risk population recruited for EURIDIS and ADONIS (mean age 63.5 yrs; 42% of population had SHD; 60% hypertension, etc.). The magnitude of the reduction in the outcome was consistent across the studies (HR 0.73; 95% CI 0.57 – 0.93, p = 0.01 for EURIDIS/ADONIS compared to HR 0.76; 95% CI 0.69 – 0.84, p < 0.001 for ATHENA). • Looking specifically at the ATHENA trial population, patients had a range of risk which was reflected in the sub-group analyses which considered age, sex, structural heart disease, heart failure, etc. It was found that the treatment effect was consistent within these important subgroups as noted in Figure 3 of the publication (Hohnloser, S. 2009, NEJM; 360: 668 - 678) and replicated below. The same magnitude of benefit was seen whether or not each individual risk factor was present, suggesting there is no reason to believe that populations with different risk factor profiles than that enrolled in the ATHENA trial would have a meaningful difference in response.

Response to ACD document from sanofi-aventis 28th January 2010

	 [redacted] It is fair to say that the benefit of dronedarone is irrespective of background therapy or risk factors. • In addition, adverse event (AE) rates between EURIDIS/ADONIS, ATHENA and DIONYSOS are all consistent which again reflects the consistency of dronedarone results across populations with a range of risks. It should be noted that although patients may be characterised as low, medium or high risk, patients who are in cohorts that are considered to be 'high risk' may be very different. The high risk patient population seen in ANDROMEDA (who were not primarily AF patients) had very different background CV risk factors or concomitant disease compared to the high risk patients seen in ATHENA. It is important to clarify the differences between these patient populations.
Pg 15, 3.16	In response to the ERG noted criticisms of the meta-analyses and mixed treatment comparison (MTC) we would like to take this opportunity to respond:

1. a lack of consideration of clinical and statistical heterogeneity of the studies included in the analysis
Response: To account for the variabilites/heterogeneities between the trial design and patient characteristics, two methodologies were considered, a random effects model and a multivariate analysis. The multivariate analysis which adjusts the observed differences in the baseline characteristics was considered inappropriate. This was because there were too few studies in the analyses which would lead to issues in estimating all of parameters in the model. Moreover this approach did not take into account unobserved confounders hence might not remove all the biases. The random effects model was used which takes into account the between study variability (due to observed but also unobserved differences) through a random variable (the between study variance) that is estimated in the model separately from the treatment effect. This methodology limits these biases from the estimated treatment effect and was considered to be the most scientifically sound approach. We would suggest the Appraisal Committee consider this in their future discussions.

2. Uncertainty about the validity of pooling the individual studies in the different analyses
3. Few events in the studies
4.The use of outcomes that were neither pre-specified endpoints nor centrally adjudicated
Response: Points 2, 3 and 4 above are common limitations of every evidence based medicine work and not specific to the manufacturers' submission. This should be noted within the text perhaps by removing these specific points from the bulleted text which are specific to the manufacturers submitted work and by including a broader sentence subsequent to the bullets: "As with all such studies there are limitations about the validity of pooling individual studies, studies with few events and using outcomes that were neither pre-specified endpoints nor centrally adjudicated."

5. inconsistencies in the selection of studies across the different analyses
Response: The study selection protocol for each outcome measure was clearly explained. Each outcome was explored using various methods for the meta-analyses to assess importance of methodological choices.

6. the restriction of randomised controlled trials in the MTC
Response: Restriction of the RCTs in the MTC was driven by the methodological approach used which resulted in the best quality, most powerful studies being included in the dataset. Taking into account the concerns that have been raised by the ERG group about the restriction of the dataset for the MTC, additional analyses have been run which relax the previous restrictions allowing smaller studies to be included. The results show that the direction of effect remains consistent with the previous analysis, with only the precision of the estimation being affected by additional study inclusion. The inclusion of additional smaller trials with low event rates increases the between study variability and thus the width of confidence intervals on the treatment effects. The table following demonstrates how the point estimates remain in the same direction as the number of studies included in the analysis is increased. The results of ERG re-analysis of the MTC, which used a different methodological approach, are also presented in the below table. All the point estimates support a favourable mortality benefit for dronedarone versus placebo and a negative mortality benefit for amiodarone and sotalol versus placebo. The main differences between the results are the width of the confidence intervals.

	Original MTC based on 7 studies (95% CI)	Revised MTC based on 18 studies (95% CI)	ERG results including 12 studies (fixed effects model)*
Dronedarone vs control	0.86 (0;67 – 1.09)	[redacted]	0.8399 (0.66 – 1.07)

	Amiodarone vs control	2.73 (1.00 – 7.41)	[redacted]		1.302 (0.68 – 2.567)
	Sotalol vs control	4.32 (1.59 – 11.70)	[redacted]		1.865 (1.01 – 3.57)

* as detailed in Appendix 2 of the ERG report, page 123

It should also be noted that there have been a series of analyses that have all come to broadly the same findings (Cochrane 2006 (1), Piccini 2009 (2)) with more or less precise estimates depending on the assumptions. See immediately following section for additional detail.

The ERG also noted inconsistency of direction of effect between results of the direct and indirect analyses and the MTC using the example of all-cause mortality – this is incorrect. All the results in the submission meta-analysis and MTC are in the same direction except for treatment discontinuation due to any cause which is driven by DIONYSOS. Not all of the results are statistically significant therefore we would suggest the following wording

"The ERG noted the inconsistency of the statistical significance between results of the direct and indirect analyses and the MTC, however the direction of all results was consistent with the exception of treatment discontinuation from any cause which was driven by DIONYSOS."

(1) Lafuente-Lafuente, C et al. (2006) Antiarrhythmic Drugs for Maintaining Sinus Rhythm After Cardioversion of Atrial Fibrillation. Archives of Internal Medicine, Vol. 166: 719 - 728.

(2) Piccini, JP (2009) Comparative Efficacy of Dronedarone and Amiodarone for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation. J Am Coll Cardio, 54: 1089 – 1095.

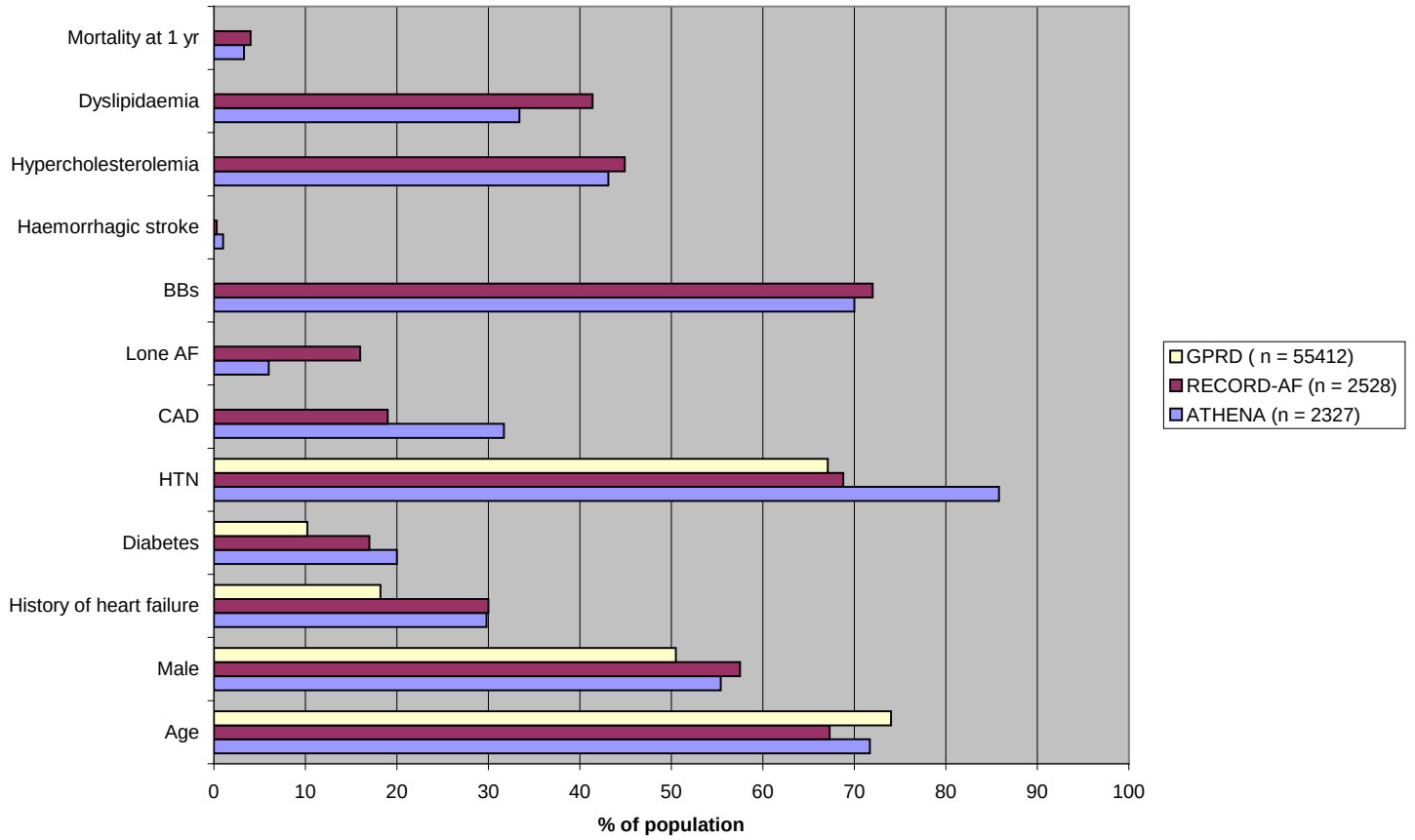
Pg 16, 3.16

It seems unreasonable for the ERG group to conclude that the efficacy of dronedarone relative to other AADs remains uncertain given the consistency of the results of the meta-analysis with other published works such as the Cochrane systematic review (2006) and the recent Piccini meta-analysis (2009) plus other pivotal trials:

- The Cochrane systematic review and meta-analysis consider all-cause mortality and noted an odds ratio for amiodarone versus placebo of 1.96 (0.68 – 5.67), while for sotalol the odds ratio was 2.09 (0.97 – 4.49). While neither were statistically significant the trend for increased all-cause mortality over placebo as indicated in the submitted analysis is consistent.
- Piccini (2009) undertook a meta-analysis focused on amiodarone and dronedarone. The results showed a trend for increased mortality with amiodarone compared to placebo and a trend in favour of dronedarone compared to placebo. In an indirect comparison (Figure 2B, page 1093) there was a trend for increased mortality with amiodarone over dronedarone (OR 2.20; 95% CI 0.61 – 7.88).
- The SAFE-T trial enrolled 267 patients receiving amiodarone, 261 receiving sotalol and 137 receiving placebo for a 12 month period. The risk of death was greater in the amiodarone group when compared with placebo. The OR was equal to 2.0 (p=0.11). There was also a greater risk of death when comparing sotalol with placebo (OR 1.8; p=0.20) (1).
- The AFFIRM trial enrolled 4,060 patients and at 5 years showed a hazard ratio for mortality of 1.15 (p=0.08) for treatment with anti-arrhythmic drugs(2).
- The RACE trial randomly assigned 522 patients with atrial fibrillation to receive either anti-arrhythmic therapy or rate control and showed more primary endpoints including deaths, in the group undergoing an anti-arrhythmic therapy (3).

	Given the trend for reduced all-cause mortality for dronedarone coupled with the trend for increased mortality with the current AADs, it is not surprising that the results of the MTC are statistically significant. It should also be noted that the uncertainty within the MTC analysis as reflected by the confidence intervals is fully taken into account in the economic model which is a fully probabilistic model. (1)Singh SN, Singh BN, Reda DJ et al. Comparison of sotalol versus amiodarone in maintaining stability of sinus rhythm in patients with atrial fibrillation (Sotalol-Amiodarone Fibrillation Efficacy Trial [Safe-T]). Am J Cardiol. 2003 Aug 15;92(4):468-72. (2)The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002 Dec 5; 347(23):1825-33. (3) Van Gelder IC, The Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med. 2002 Dec 5; 347(23):1834-40. Finally, with regards to the evidence on rate control this was included within the submission in the description of the EURIDIS/ADONIS trials (manufacturer submission, page 32). In the European trial the mean ventricular rate during the first adjudicated recurrence was 102.3 ± 24.7 beats per minute in the dronedarone group and 117 ± 29.1 beats per minute in the placebo group ($p < 0.001$). In the corresponding non-European trial the results were 104 ± 27.1 beats per minute versus 116.6 ± 31.9 beats per minute for dronedarone versus placebo respectively ($p<0.001$). The other trial which considered rate control, ERATO (4) was specific to permanent AF patients therefore while mentioned in the submission it was not detailed as permanent AF patients are not within the licensed indication. The ERATO trial clearly demonstrated the benefits of dronedarone versus placebo for ventricular rate control in patients with permanent AF with, at day 14 a reduction of 11.7 beats per minute ($p<0.0001$) and comparable reductions sustained throughout the 6-month trial. The effects of dronedarone were additive to those of other rate-control agents including beta blockers, calcium antagonists and digoxin. Given that rate control is one of the contributing factors to the improved clinical outcomes with dronedarone it is implicit within the overall efficacy of dronedarone which was included in the economic model. (4) Davy, J-M eta al. (2008) Dronedarone for the control of ventricular rate in permanent atrial fibrillation: The Efficacy and safety of dRondeArone for The cOntrol of ventricular rate during atrial fibrillation (ERATO) trial. American Heart Journal, Vol. 156, No. 3: 527.e1 – 527.9
Pg 16, 3.17	This section notes a number of issues identified by the ERG about the cost-effectiveness analysis which we would like to take the opportunity to respond to: 1. Full range of treatment pathways not presented: The treatment pathways submitted did not represent the full range of treatment strategies or sequences for dronedarone simply because we followed the logic within the NICE clinical guidelines of assessing the benefit/risk profile such that an escalating approach to drug therapy could be recommended based on associated co-morbidity and the need for increasingly effective AADs (section 6.2.3, pg 54). Within the guidelines it is noted that the approach to AAD treatment is not totally in keeping with the evidence on efficacy (related in this instance to time to first AF recurrence) which is in favour of amiodarone. The approach in the guidelines tries to balance efficacy with concerns regarding the adverse effects which for amiodarone may become apparent only after the long-term use and include pulmonary, hepatic, ophthalmic and thyroid toxicity. The submitted pathways for dronedarone - dronedarone as an add-on to 1st line treatment on top of beta-blockers for patients with multiple CV risk factors (CHADS2

	≥4) and as an alternative 1st line AAD to amiodarone, sotalol and Class 1c agents when they are to be introduced, are appropriate given the approach taken by the Guidelines Development Group. 2. Generalisability of ATHENA to the NHS: To demonstrate that the ATHENA trial results are representative of a likely NHS population we have compared the baseline characteristics of the placebo arm to two different databases, the RECORD-AF international registry and a UK specific database analysis of AF patients within the GPRD database. The GPRD database (data on file) is very relevant when considering how representative the ATHENA population is to the NHS especially as it is based on the records of almost 55,500 AF patients in the UK. However, it must be recognised that this database sample includes all types of AF. Currently, within the GPRD database coding it is not possible to differentiate permanent and non-permanent AF patients. While the RECORD-AF (1) is an international registry conducted in over 21 countries it includes over 5600 non-permanent AF patients who were either in sinus rhythm or AF at the time of recruitment, and is therefore more reflective of the non-permanent AF population in whom dronedarone will be used in clinical practice. Both examples clearly show that the ATHENA population is representative of a real life AF population and one that clinicians within the NHS would likely see. (1) Heuzey, J-Y et al. (2009) The RECORD-AF Study: Design, Baseline Data and Profile of Patients According to Chosen Treatment Strategy for Atrial Fibrillation. Am J Cardio (available online 7 Dec. at www.AJConline.org)



3. Methodology of the meta-analysis and MTC: The meta-analysis and MTC have been conducted to a high standard and their results are robust. As detailed in section 3.16, the results of the meta-analyses are consistent with other published works (Cochrane 2006, Piccini 2009). Even when the ERG group replicated the MTC with a Bayesian approach the results for all-cause mortality remained significantly different in favour of dronedarone over both amiodarone and sotalol (ERG report, Appendix 2, page 123). One aspect the ERG picked up as a concern with the MTC analysis was the exclusion of studies with no events especially around the all-cause mortality endpoint. The exclusion of zero event trials is scientifically sound (Sweeting, 2004 (2); Whitehead 1991 (3)). Even when including all studies with an inclusion of 12 months (despite zero events) the results of the ERG MTC analysis still found a significant difference in favour of dronedarone over sotalol and while not statistically significant the result for amiodarone was in the same direction (ERG report, Appendix 2, page 124). Thus despite the different methodological approaches taken by the manufacturer and the ERG, the MTC results are consistently in favour of an all-cause mortality benefit for dronedarone over amiodarone and sotalol.

<table>
<tr><td></td><td>(2) Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004 May 15;23(9):1351-75.
(3) Whitehead A, Whitehead J. A general parametric approach to the meta-analysis of randomized clinical trials. Stat Med. 1991 Nov;10(11):1665-77.</td></tr>
<tr><td>Pg 17, 3.17</td><td>We feel it is unjustified for the costs attributed to dronedarone and comparators to be a point of concern as they were based on the most appropriate information available (in many cases the specific product SmPC recommendations), and were also subject to a full sensitivity analysis which demonstrated that there was marginal impact on the cost-effectiveness results which remained robust.
Again the concern over the modelling benefits of dronedarone are unjustified as within a sensitivity analysis it was demonstrated that stopping the all-cause mortality advantage of dronedarone over the comparators at the end of the ATHENA trial period (just under 2 years) still demonstrated that dronedarone was cost-effective, as shown in the following table:

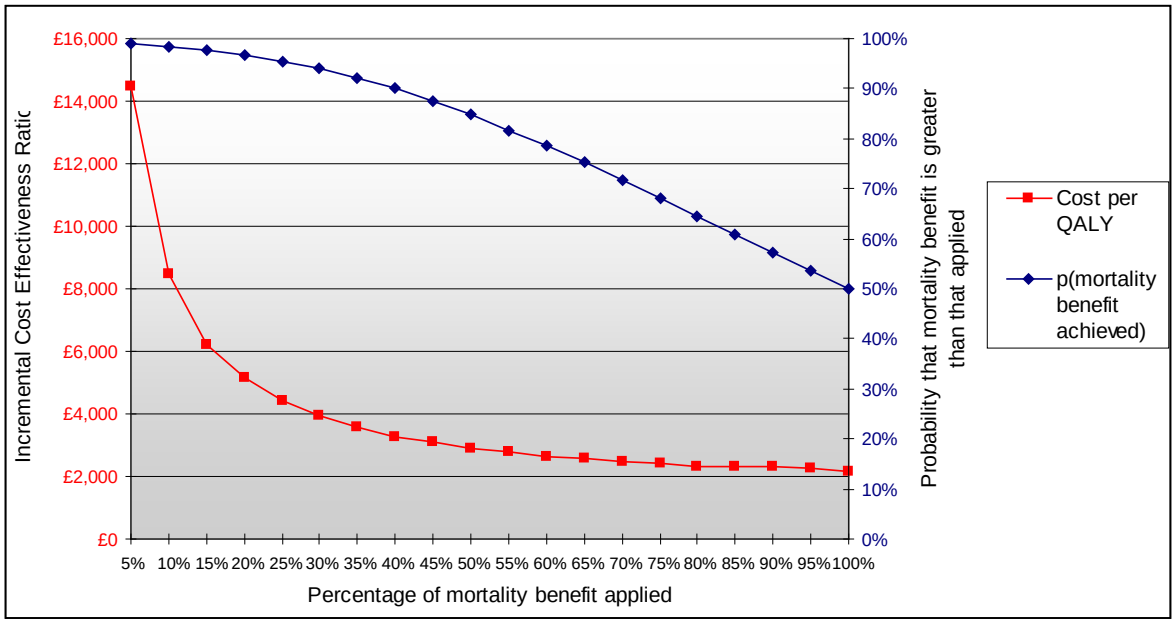
<table>
<tr><th>Patient Type</th><th>Base case ICER</th><th>ICER with mortality benefit stopped at 2 years</th></tr>
<tr><td>Paroxysmal</td><td></td><td></td></tr>
<tr><td>No structural heart disease (1st line $CHADS_2$ ≥4)</td><td>£4,364</td><td>£6,845</td></tr>
<tr><td>No structural heart disease</td><td>£1,953</td><td>£3,036</td></tr>
<tr><td>CAD (1st line $CHADS_2$ ≥4)</td><td>£4,494</td><td>£7,049</td></tr>
<tr><td>CAD (replacing sotalol)</td><td>£2,111</td><td>£3,311</td></tr>
<tr><td>LVD (1st line $CHADS_2$ ≥4)</td><td>£4,715</td><td>£7,395</td></tr>
<tr><td>LVD (replacing amiodarone)</td><td>£2,064</td><td>£3,327</td></tr>
<tr><td>Persistent</td><td></td><td></td></tr>
<tr><td>No structural heart disease (1st line $CHADS_2$ ≥4))</td><td>£3,776</td><td>£5,907</td></tr>
<tr><td>No structural heart disease (replacing sotalol)</td><td>£2,096</td><td>£3,287</td></tr>
<tr><td>Structural heart disease (1st line $CHADS_2$ ≥4)</td><td>£3,632</td><td>£5,697</td></tr>
<tr><td>Structural heart disease (replacing amiodarone)</td><td>£2,818</td><td>£4,420</td></tr>
</table>
</td></tr>
<tr><td>Pg 17, 3.18</td><td>No comment</td></tr>
<tr><td>Pg 17, 3.19</td><td>No comment</td></tr>
<tr><td>Pg 18, 3.19</td><td>We welcome the ERG exploration of the submitted model and the recognition that in the majority of the exploratory analyses the ICERs remain below £20,000 per QALY. In the instances quoted that lead to ICERs >£30,000 we question the rationale of the assumptions and therefore balance of the presented results. Available evidence suggests that there being no mortality benefit for dronedarone versus amiodarone or sotalol is unlikely (see discussions in section 3.16). Even assuming sotalol and amiodarone have no effect on mortality relative to standard therapy but keeping the mortality benefit of dronedarone, the ICER remains below £20,000 as noted by the ERG.
While the evidence on the incidence of stroke is limited, the evidence on dronedarone is from the largest AAD trial conducted and is much</td></tr>
</table>

<table>
<tr><td></td><td>more convincing than that for other agents.
Finally, there is no robust evidence to justify an assumption of greater mortality benefit for the Class 1c agents over dronedarone. Looking at the results of the ERG MTC analysis which included an analysis of all-cause mortality for the Class 1c agents (ERG report, Appendix 2, page 124) both the random effects and fixed effect model results for all-cause mortality found an odds ratio of 1.23 (0.42 – 3.49) and 1.212 (0.37 – 3.91) for Class 1c agents versus dronedarone. When considering the confidence intervals around these results it is clear that there is a much higher likelihood of Class 1c agents having a detrimental effect on all-cause mortality compared to dronedarone than for them to have a great mortality benefit.</td></tr>
<tr><td>Pg 18, 3.20</td><td>While it is appropriate for a full exploration of the economic model to be considered within any technology appraisal, the reference to the ICER of £1m in this section and subsequently should be clearly noted as a particularly extreme scenario assuming no mortality benefit and no stroke prevention benefit for dronedarone. Using the alternative results from the ERG MTC on all-cause mortality (as presented in our response to section 3.16), two things are very clear. Firstly, dronedarone remains very cost-effective, with a high probability of cost-effectiveness; greater than 80% at the £20,000 threshold as shown in the table below:

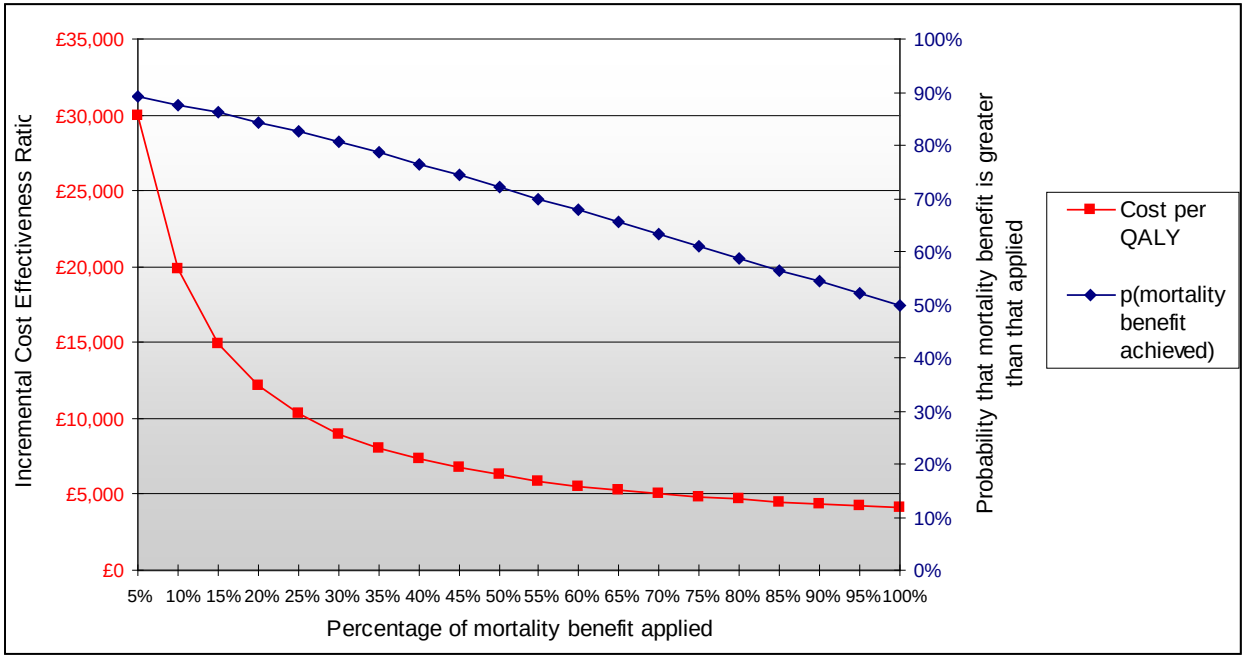
Probability of Cost-effectiveness at £20,000 per QALY
<table>
<tr><th>Patient Type</th><th>Base Case MTC (point estimate ICER)</th><th>ERG MTC (point estimate ICER)</th></tr>
<tr><td>Paroxysmal</td><td></td><td></td></tr>
<tr><td>No structural heart disease (replacing sotalol)</td><td>98% (£1,953)</td><td>88% (£2,149)</td></tr>
<tr><td>CAD (replacing sotalol)</td><td>97% (£2,111)</td><td>90% (£2,457)</td></tr>
<tr><td>LVD (replacing amiodarone)</td><td>96% (£2,064)</td><td>89% (£3,258)</td></tr>
<tr><td>Persistent</td><td></td><td></td></tr>
<tr><td>No structural heart disease (replacing sotalol)</td><td>95% (£3,776)</td><td>84% (£2,315)</td></tr>
<tr><td>Structural heart disease (replacing amiodarone)</td><td>97% (£2,096)</td><td>93% (£4,096)</td></tr>
</table>

Furthermore, based on the results of the ERG MTC analysis of all-cause mortality, it is evident that even a small mortality benefit (approximately 7% of that observed) is all that is required to achieve cost-effectiveness (see Figures below). The likelihood of achieving at least this level of benefit is high and should give the Committee confidence in the cost-effective results.

Paroxysmal Patients with no structural heart disease</td></tr>
</table>



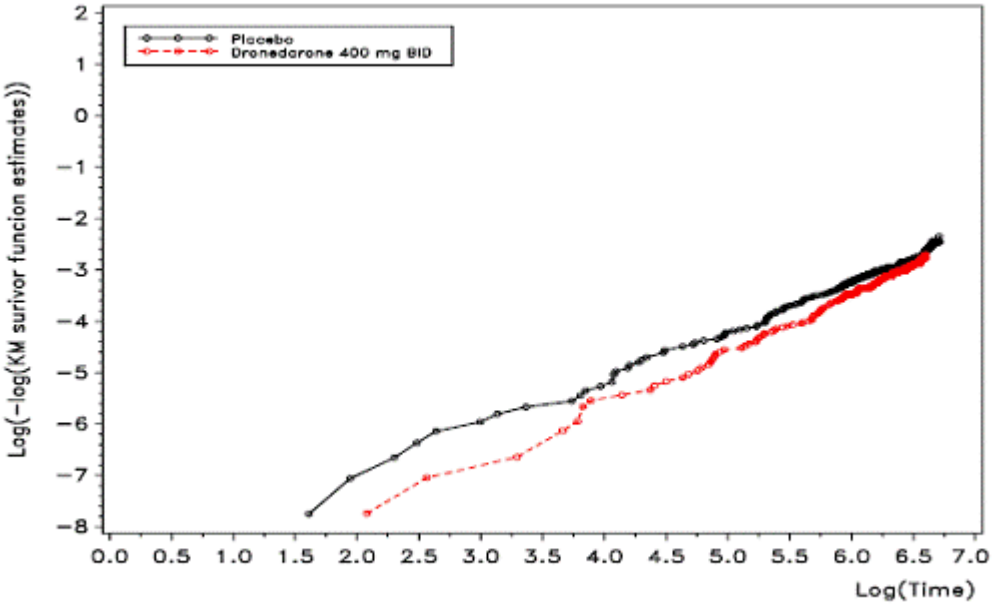
Persistent patients with structural heart disease



	We would recommend that in considering the effect of all-cause mortality on the economic model results, the Committee should give consideration to how the ERG have approached the sensitivity analysis. The ERG's approach has been to turn 'on' and 'off' this and other parameters in sequence to ascertain the broad impact of the all-cause mortality parameter. A more detailed exploration of the mortality benefit and how it impacts the model would suggest that the decision outcome is relatively insensitive to the all-cause mortality data and dronedarone is in fact cost-effective over a wide range of assumed all-cause mortality benefit. Indeed, when only a small percentage of the potential mortality benefit (approximately 7% dependent upon the patient characteristics) was included in the economic model, the ICER's for dronedarone decreased to below £20,000.
Pg 19, 3.20	We agree with the ERG group that the key driver of the cost-effectiveness is all-cause mortality, the introduction of this parameter decreasing the ICERs to below £10,000 per QALY. However to enhance the transparency of the argument it is appropriate to highlight the small magnitude of mortality benefit required to achieve cost-effectiveness at a £20,000 threshold (see suggestion above). The clinical evidence described previously (section 3.16) must provide a level of confidence that dronedarone offers a mortality advantage over amiodarone and sotalol, and the economic analyses conducted also demonstrates that it does not require much of this mortality benefit for dronedarone to become cost-effective. When considering the comparison with Class 1c agents we recognise that the data is more limited from the perspective of the Class 1c agents themselves rather than dronedarone.
Pg 19, 3.21	No comment
Pg 19, 4.1	It was noted that there was no statistical support for the Appraisal Committee at the meeting on the 25th November which may have not

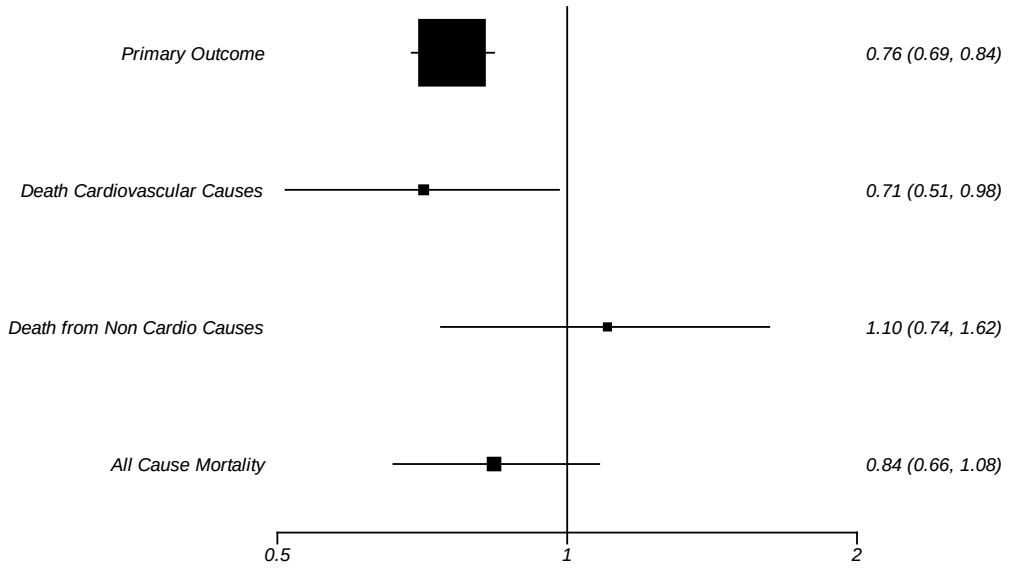
	given the Committee the full opportunity to explore the evidence presented to them given the complexity of the disease area and the product. We have already registered our concern that the clinical specialists attending the meeting on the 25th November were not the most appropriate given their experience in atrial fibrillation. Therefore we would request the Committee seek out additional support in these areas to ensure their full understanding of the evidence presented before reaching a final recommendation.
Pg 20, 4.2	It is correct that the licensed indication for dronedarone is to prevent recurrence of AF or to lower ventricular rate but it should be noted that the EU approval is based on the European SPC guidelines. These guidelines do not allow inclusion of outcomes in the indication. The EMEA recognises the relevant benefits demonstrated in the ATHENA trial, referring to them directly within the indication to Section 5.1 of the SPC
Pg 20, 4.3	As noted in our comment on 3.17, the treatment positions considered within the submission are in line with the NICE guidelines on the management of AF and with the clinical profile of dronedarone. Dronedarone will offer an important new treatment to patients who are on current AADs and are unable to tolerate them. However to consider dronedarone for this position alone ignores the important clinical benefits dronedarone can offer to patients who may be suitable for an AAD but are not currently receiving one. As previously mentioned the aim of treatment is not just to reduce time to first AF recurrence, but to balance the symptoms of AF, the adverse events associated with the treatments and ultimately is aimed at reducing major morbidity and mortality. Amiodarone is the most effective AAD at controlling AF in terms of time to first recurrence but it is also the most toxic. Once again, the drug escalation is based on increased morbidity and symptoms and more toxic drugs are normally reserved for more severe symptoms that are not treatable by safer options. Dronedarone is a valuable addition to a limited therapeutic armamentarium. Even if considered less efficacious than some existing AADs in terms of time to first recurrence, dronedarone is undeniably effective as an anti-arrhythmic, in contrast to other AADs it has demonstrated significant outcomes benefits, and has advantages over other AADs in terms of tolerability and toxicity. Being relatively safe, it provides an attractive option early in the sequence of treatment, with clinicians safe in the knowledge that a more effective, albeit more toxic, alternative remains available for those patients in whom dronedarone is not effective in terms of AF recurrence. Regardless, the evidence available from the ATHENA trial shows that the improvement in health outcomes states is independent of the effect on rhythm, the benefits being just as prominent even in the group who remained in AF for the duration of the trial. With respect to patients who are unable to tolerate other AADs, in particular amiodarone we would expect the efficacy of dronedarone to be unchanged however we stand by our assertion that the correct place for dronedarone is prior to current AADs given its combination of efficacy and safety characteristics.
Pg 21, 4.3	We fully support the patient experts who noted that dronedarone may be particularly important for younger patients given its better adverse event profile than amiodarone. Amiodarone is associated with significant adverse events such as pulmonary toxicity, thyroid disorders and hepatic toxicity which can lead to drug discontinuation and/or serious complications during long-term treatment. One of the objectives of the DIONYSOS trial was to evaluate the safety of dronedarone compared to amiodarone therefore it was designed to capture most of the expected AEs of amiodarone (occurrence of thyroid, hepatic, pulmonary, neurological, skin, eye AEs). The results found an advantage for dronedarone driven by the occurrence of significantly fewer thyroid and neurological events and a trend for less skin or ocular events. The EMEA assessment report noted that the CV safety profile of dronedarone appears comparable if not better to that of amiodarone, especially regarding bradyarrhythmia and effect on QT-interval. Given the benefits noted in the above section, dronedarone can offer younger patients an effective AAD with significant outcomes benefits plus advantages over other AADs in terms of tolerability and toxicity.
Pg 21, 4.4	We agree with the Appraisal Committee that dronedarone is efficacious considering time to first AF recurrence compared to placebo but

	not as effective as amiodarone. [redacted]
Pg 21, 4.5	No comment
Pg 22, 4.5	The DIONYSOS trial was a head to head trial of amiodarone and dronedarone with a composite endpoint of recurrence of AF or premature discontinuation. It was not designed with all-cause mortality as an endpoint and as such there were only 7 deaths recorded throughout the trial. It is inappropriate to draw any conclusions from this evidence alone. It was noted that the Committee discussed the cumulative incidence curves for all-cause mortality in the dronedarone and placebo groups of ATHENA and felt these indicated a marginal difference between the curves until approximately 24 months of follow-up. They therefore considered the result for all-cause mortality to be driven by the number of deaths after 24 months when a relatively small number of people were followed-up. It is inappropriate to interpret the curves for all-cause mortality in ATHENA in this way. • It should be observed that the smaller the sample size, the bigger the jumps in a survival curve. This is precisely what is observed after 24 months in this analysis. The separation seen in the associated all-cause mortality figure is merely an artefact due to the decrease in sample size rather than an increase in the effect. • As a proportional hazards analysis has been utilised, the estimation of effect takes into consideration the sample size shift throughout time. As the sample size is very small after 24 months, what occurs after this time contributes only very little to the actual estimation of the difference between the treatment arms. • If the risk of death in the arms of ATHENA was the same for dronedarone and placebo before 24 months and higher in the placebo arm after 24 months, this would imply that the instantaneous risk of death is different before and after 24 months. It is possible to test that the risk of death remains constant throughout time with a test of proportional hazards. This was conducted for by both the FDA and EMEA and presented below to provide the Committee with confidence that the difference in all-cause mortality was not driven by a divergence after 24 months. The distribution of the 95% CI for all-cause mortality indicates there is an 8.5% likelihood that the true effect on mortality is neutral or detrimental. **ATHENA - All cause mortality - Graphical check for Proportional hazards**

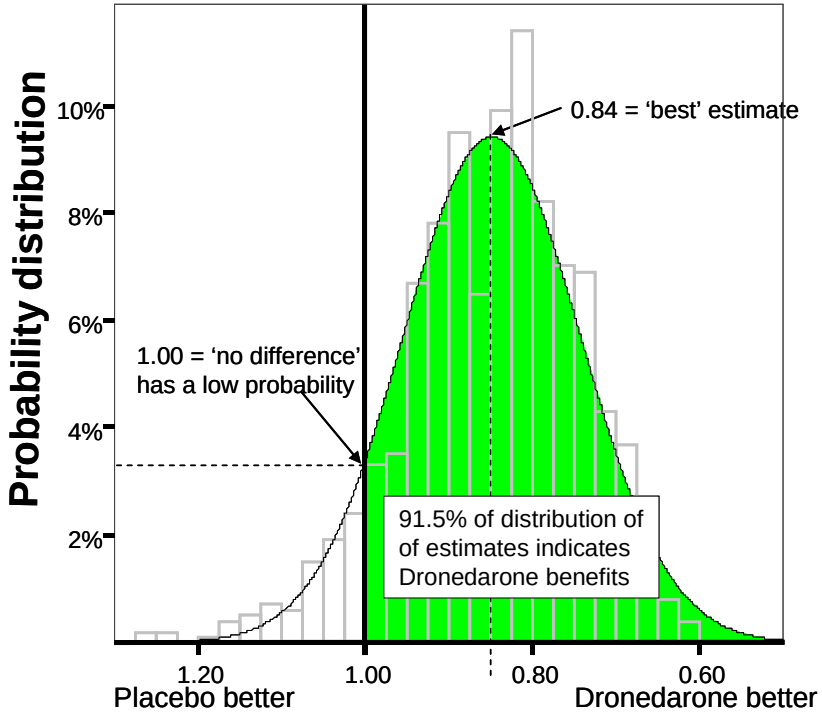


This graph and associated test for deviation from constant proportional hazards is very clear and demonstrates that it is not appropriate to make statements about there being a delayed response to treatment with dronedarone (p=0.23). Graphically, it is reasonable to accept the assumption of constant proportional hazard.

Thus the data on all cause mortality was appropriately analysed from the ATHENA trial, and does not unduly reflect the small number of events which occurred late among subjects with the longest follow up when the denominator (the number if subjects at risk) was small. In addition, the Committee should reflect on the results of the ATHENA trial for all mortality endpoints as demonstrated in the below forest plot. By assuming there is no plausible mortality benefit the Committee appear to be challenging the body of evidence from ATHENA.

	 **Figure: Primary and Secondary (mortality) results from the ATHENA trial**
Pg 22, 4.6	It was noted that no evidence had been presented to validate the use of CHADS2 score for more generally predicting all-cause mortality in people with AF. The CHADS2 algorithm is still a relatively recent introduction to assess the risk of stroke therefore it is not surprising that there is little evidence for its more general use. However this does not negate the value of the current work presented by Henriksson IJC 2009 based on over 100,000 patients with a previous stroke and considering the relationship between CHADS2 and all-cause mortality differentiated by the presence or not of AF. We feel that this evidence has been too readily dismissed.
Pg 23, 4.7	This section again presents the concerns the Appraisal Committee have on the methodology of the MTC analysis and the plausibility of the all-cause mortality in ATHENA. We would refer you back to our responses in section 3.16 and section 4.5 but in addition would like to add the following points: In response to the note that the results of the MTC and meta-analysis are largely based on the difference in all-cause mortality between dronedarone and placebo in the ATHENA trial this is in essence correct given that the ATHENA trial is the largest AAD trial to have ever been conducted. The ATHENA trial randomised 4628 patients to either dronedarone or placebo (in addition to standard background therapy) and in addition included all-cause mortality as part of the composite primary endpoint. It is both expected and valid that such an RCT has an important influence on the results of the meta-analysis and MTC. In addition, we would re-iterate that while the point estimate for all-cause mortality within ATHENA was not statistically significant it is more useful to look at the uncertainty around this as shown with the confidence intervals. For all-cause mortality the 95% confidence

intervals was 0.66 – 1.08 demonstrating that there is 91.5% likelihood that the true effect of dronedarone on mortality is beneficial.



The uncertainty around the point estimates are fully reflected in the probabilistic economic model which demonstrates that the probability of cost-effectiveness for dronedarone compared to amiodarone and sotalol is over 90% at a threshold of £20,000.

The comment about including DIONYSOS in the MTC analysis is contradictory – the submitted MTC has been criticised for excluding studies that did not have any all-cause mortality events. This approach was taken because inclusion of such studies in reality adds very little information to the analysis but increases the uncertainty (see above references that advise to exclude zero event trials [Sweeting 2004; Whitehead 1991]]. While DIONYSOS is not yet published it would be inappropriate to exclude the results from the MTC given that these are very relevant events which have been considered by the regulatory authorities. The approach taken to the submitted MTC analysis is both robust and appropriate. It demonstrates that dronedarone has a reduced all-cause mortality trend versus placebo while the other AADs have an increased trend versus placebo. With the comparison of active AADs, it is not surprising that these opposite trends become modestly statistically significant and fits with some of the key results of other studies such as noted previously (see section 3.16).

We feel that the uncertainty around all-cause mortality is within an acceptable range and it is in any case accounted for in the economic model. By rejecting the evidence presented and making the strong assumption that the effects of different treatments are the same, the

	Appraisal Committee will be denying patients and clinicians the choice of using an AAD that offers outcomes beyond just maintenance of sinus rhythm. Dronedarone is associated with maintenance of sinus rhythm with fewer adverse effects and reduced hospitalisation and mortality.
Pg 23, 4.8	No comment
Pg 24, 4.8	While we agree that the data on stroke are limited we feel that it should not be disregarded given the increased risk of stroke associated with AF and therefore the importance of any product that might be able to provide additional preventative benefits over and above current use of anti-coagulation which dronedarone has suggested in the post-hoc analysis of ATHENA. The NICE clinical guidelines for the management of AF clearly position stroke prevention as a priority for AF patients. That dronedarone might provide additional preventative benefit over currently recommended anti-coagulation is something that has not been shown with any other AAD.
Pg 24, 4.9	While the most common adverse event associated with dronedarone is gastrointestinal we would request that the Committee remember that this is a very manageable adverse event. Within ATHENA only 3.2% of the dronedarone arm discontinued treatment due to GI disorders compared to 1.8% of the placebo arm. While the evidence of the DIONYSOS trial is short term due to the design of the trial there is a wealth of additional clinical trial evidence that demonstrates the favourable adverse event profile of dronedarone. The safety profile of dronedarone 400 mg twice daily in patients with AF or AFL was evaluated on 5 pooled placebo-controlled studies, ATHENA, EURIDIS, ADONIS, ERATO and DAFNE. In these studies, a total of 6285 patients were randomized and treated. Of these, 3282 patients were treated with dronedarone 400 mg twice daily, and 2875 received placebo. The mean exposure across studies was 12 months making dronedarone the most studied of all of the AADs. In ATHENA, the mean and maximum follow-up was 21 months and 30 months, respectively. The main AEs identified with dronedarone were diarrhea, nausea or vomiting, serum creatinine increase (shown to be related to inhibition of creatinine secretion at kidney tubular level without decrease in glomerular filtration), rash, and cardiac effects consistent with the pharmacodynamic profile of dronedarone (bradycardia, QT prolongation). There was no evidence of a proarrhythmic effect of dronedarone; one case of torsades de pointes (TdP) was identified during the overall clinical development program and this was a non-fatal event which occurred in a protocol violator. Assessment of intrinsic factors on the incidence of any treatment emergent AEs (TEAEs) did not suggest any excess of AEs in a particular sub-group. The incidence of serious AEs (SAEs) was similar in the dronedarone 400 mg BID and placebo groups (18.0% and 19.7%, respectively). Those were mainly related to system organ classes (SOCs) of infections and infestations, GI disorders, and cardiac disorders, with similar incidences in the dronedarone 400 mg BID and placebo groups. When considering the safety profile of dronedarone the EMEA noted specific measures for heart failure, drug-drug interactions and the correct management of serum creatinine increase. However, within the risk minimisation strategy no other safety issues were raised that could not be dealt with by appropriate labelling in the SPC. Of specific interest is the mention within the EMEA assessment report of the amiodarone-like effects – interstitial lung disease, severe skin disorders, neuropathy, and hepatic injury with a recommendation that no minimisation action is proposed as there is no evidence of such risks with the use of dronedarone. It should also be noted that dronedarone is the only AAD that will have an ongoing Risk Minimisation Plan in place to ensure appropriate prescribing. This is not the case with other currently available AADs.
Pg 25, 4.10	We feel that it is important for patients and clinicians to have a choice on what their treatments might offer – the current AADs might prevent AF recurrence but they are also associated with a higher incidence of adverse events which can be fatal in some cases. The higher incidence of adverse events also results in higher discontinuation therefore the potential benefit of maintenance of SR is no longer available. Dronedarone offers a balance between the conventional efficacy of prevention of AF recurrence and adverse events but also

	offers patients and clinicians a treatment that leads to reduced CV hospitalisation and important clinical events such as stroke and all-cause mortality.
Pg 25, 4.11	The concerns raised by the ERG about the key assumptions of the model have been addressed in previous comments but will be summarised again: • Mortality benefit included in the model: see section 4.5 • Costs of dronedarone and other AADs: this was fully considered in the submitted sensitivity analysis was not found to be the key driver of cost-effectiveness • Utilities: while Quality of Life (QoL) and patient utilities were not measured within the clinical trial programme the utility values used within the model were from robust sources and even when additional analysis was conducted by the ERG on utility values dronedarone remained cost-effective. • Pair-wise comparison: the economic model was based directly on the recommendations of the NICE clinical guidelines therefore we believe that our approach was appropriate • All possible uses of dronedarone: all possible uses were not submitted as the model followed the recommendations of the NICE clinical guidelines therefore all possible uses were not considered necessary. To use dronedarone after the failure of other AADs would not be in keeping with the NICE guidelines on the management of AF as noted in our comments on section 3.9.
Pg 26, 4.12	We believe that the mortality benefit with dronedarone is plausible and therefore essential to consider within the cost-effectiveness analysis of dronedarone. Within the ERG consideration of the economic model they approached the dronedarone benefit as either on or off, however it is important to consider the magnitude of mortality benefit that is needed for dronedarone to achieve cost-effectiveness. As submitted within the original dossier, on average only 7% of the mortality benefit suggested in the MTC is required before the ICER for dronedarone reaches less than the NICE threshold of £20,000 for comparisons with amiodarone and sotalol
Pg 26, 4.13	It should be clear that the cost-effectiveness scenario including only time to first AF recurrence with an ICER of over £1m is an extreme scenario. Accepting 100% of the potential mortality benefit leads to ICERs of <£10,000 but more importantly only a small percentage of the mortality benefit is required for dronedarone to become cost-effective which has not been presented.
Pg 26, 4.14	The comment on the fact that the MTC is largely based on the results of ATHENA seems to be presented as a criticism, especially given that the concerns on the difference in all-cause mortality within this one trial. It is logical that ATHENA has a big influence on the results of the MTC analysis as it is the largest AAD trial ever conducted, recruiting over 4600 patients. It should also be remembered that even when the ERG group did additional analyses on the MTC analysis for all-cause mortality adding in additional smaller studies, the overall trend in the results did not change and the difference in all-cause mortality between dronedarone and sotalol remained significant. In response to the comment that no comparison was made between the predicted mortality over time included in the model and the mortality reported in the ATHENA trial additional analyses with the model were conducted. The model has been run using the same time horizon as the ATHENA trial period and the predicted mortality compared to the observed mortality in ATHENA. The model estimates a slightly higher mortality rate than ATHENA (8% for Dronedarone and 9% for standard care vs ATHENA 5% for Dronedarone and 6% for standard care) but maintains the observed hazard ratio between treatment arms (HR = 0.85). This is caused by having to use evidence of mortality rates from sources external to the trial data. A sensitivity analysis has been performed to adjust the risk of mortality in the model by multiplying with a factor of 0.75 so that the modelled mortality matches the ATHENA rates (i.e. reducing the overall risk profile). The results are presented in the following table:

	Patient Type	**Base case ICER**	**ICER with ATHENA baseline mortality risk**
	Paroxysmal		
	No structural heart disease (1st line $CHADS_2$ ≥4)	£4,364	£5,214
	No structural heart disease	£1,953	£2,578
	CAD (1st line $CHADS_2$ ≥4)	£4,494	£5,475
	CAD (replacing sotalol)	£2,111	£2,967
	LVD (1st line $CHADS_2$ ≥4)	£4,715	£5,634
	LVD (replacing amiodarone)	£2,064	£2,847
	Persistent		
	No structural heart disease (1st line $CHADS_2$ ≥4))	£3,776	£4,134
	No structural heart disease (replacing sotalol)	£2,096	£2,745
	Structural heart disease (1st line $CHADS_2$ ≥4)	£3,632	£4,214
	Structural heart disease (replacing amiodarone)	£2,818	£3,412
Pg 27, 4.15	No comment		
Pg 27, 4.16	No comment		
Pg 28, 4.17	The licensed indication for dronedarone is to prevent recurrence of atrial fibrillation or to lower ventricular rate which is consistent with the European SPC guidelines on the development of AADs which do not currently allow inclusion of outcomes in the indication. However, the value of the ATHENA outcomes have been recognised and referenced within section 5.1 of the product licence. The consistent evidence of mortality benefit demonstrated for dronedarone in individual studies and in the MTC should negate the Committee's concern about the inclusion of this benefit for the subgroup of CHADS2 ≥4. The uncertainty for this subgroup as for any population considered within the submission has been incorporated within the probabilistic design of the economic model. These results demonstrate that there is over 70% chance of dronedarone being cost-effective at a threshold of £20,000 for the CHADS2 ≥4 group.		
Pg 28, 4.18	Given the available evidence base on dronedarone and that accumulated for the current AADs there is no evidence to negate the benefits of dronedarone – dronedarone is an efficacious AAD considering time to first AF recurrence plus reducing major morbidity and mortality as clearly demonstrated in both the ATHENA trial and within the submitted MTC analysis; current AADs are efficacious at time to first AF recurrence but with a trend for increased impact on morbidity and mortality (see covering letter). There is no evidence that effect on outcomes is mediated through recurrence. To the contrary, given that the outcomes benefits demonstrated in the ATHENA trial were apparent even in the group of patients who remained in AF for the duration of the trial, there is evidence that this outcomes benefit is specifically not related to recurrence. While the mode of action for dronedarone might not yet be fully understood, we believe an adequate explanation has been submitted. It is unjust to dismiss the current evidence simply because the mode of action of a product is not fully understood yet the results of the trials are very clear. Dronedarone inhibits a broad spectrum of ion channels which is different from single channel blockers such as sotalol and drugs with single Vaughan Williams class action such as flecainide and propafenone. Amiodarone is also a multi-channel blocker but does not display as good blood pressure lowering properties. The mechanism by which coronary arteries are dilated is different between amiodarone and dronedarone. It is likely that the unique combination of effects associated with dronedarone explains its specific effects		

	on clinical events beyond its anti-arrhythmic action. Previous evidence such as AFFIRM suggests that current AADs result in an increase in all-cause mortality and hospitalisation. Given the differences in mode of action described above between dronedarone and other AADs and the significant reduction in CV hospitalisation or death despite AF recurrence demonstrated in ATHENA, we do not understand the reluctance of the Committee to accept the evidence presented on clinical outcomes beyond AF recurrence. The all-cause mortality benefit for dronedarone based on the MTC analysis is robust and as previously noted only a small percentage of the potential benefit is required within the economic model for dronedarone to become cost-effective. While there will always be a level of uncertainty we fully believe that this has been addressed through the MTC analysis and its use within the economic analysis and sensitivity analysis such that there should be no hindrance to the acceptance of dronedarone as an efficacious and cost-effective AAD.
Pg 29, 5.1	No comment
Pg 29, 5.2	No comment
Pg 30, 6	No comment
Pg 31, 7.1	No comment