30th September 2009

Dear Helen,

Firstly, we are delighted to be able to inform you that dronedarone has received a positive CHMP opinion. A press release from the EMEA of the agreed indication is attached along with a draft SPC and both are much as we anticipated. We do not feel that there is any need to revise the STA dossier that has been submitted to you on the 26th August. As previously discussed we will provide you with the final decision on price as soon as possible (anticipated prior to the 25th November 2009).


EMEA.pdf


Draft SPmC 29 09 09.doc

Secondly, we are pleased to provide below the sanofi-aventis responses to the clarification questions received on the 17th September 2009. We have addressed each question immediately below with more detailed responses provided within additional attachments (please see the attached confidentiality check list).

We would also like to bring to your attention a number of smaller errors that we discovered while pulling together the responses to your questions.

- For clarification the patient numbers for DIONYSOS are 255 patients randomised to amiodarone and 249 randomised to dronedarone. At times these numbers appear to have been mistakenly reversed within descriptive tables in appendices (5 – 9) - summaries of meta-analysis and MTC results.
- The detailed and corrected version of the search strategy for the clinical effectiveness has been attached to this document (see response to question C13).

With regards to the Simul8 errors that have been noted by the ERG – these have been corrected and we are pleased to inform you that they are all minor mistakes and their correction has had negligible impact on the ICER results. The full revised results are also attached (see response to question C7).

If any additional questions arise we would be grateful if you could let us know as soon as possible.

Kind regards

Phil Booth
Head of Health Outcomes
sanofi-aventis

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Section A: Clarification on effectiveness data

A1. The proposed treatment algorithms on p71 and p72 indicate that patients can be 're-treated' with dronedarone after treatment failure. Please clarify whether this is the correct interpretation and if so explain the rationale for assuming this.

RESPONSE: While we can see why the algorithms on p71 and p72 suggest that patients might be 're-treated' with dronedarone, this is not the intention within the submission for the following reasons. Sanofi-aventis take the assumption that the notion of treatment failure in the rhythm control strategy mostly consists of the persistence of a high level of AF symptoms or treatment intolerability which is deemed to require alternative therapy.

For a patient who receives dronedarone as an adjunct therapy – high CV risk corresponding to CHADS2 score ≥ 4, it is anticipated that they will continue with dronedarone treatment indefinitely unless the treating clinician and patient feel that there are persistent symptoms or adverse events that are unacceptable. AF recurrence or continuation of some AF symptoms should not necessitate the discontinuation of treatment given, given the potential symptomatic benefit of rate control during periods of recurrence of atrial fibrillation and the morbidity and mortality benefits demonstrated in ATHENA. It is important to recognise that the outcome benefits seen in the ATHENA study for patients in atrial fibrillation at entry into the study (HR for primary outcome: 0.74 vs. placebo, 95% CI 0.61-0.91) were of an equal magnitude as for patients in sinus rhythm at study entry (HR 0.76 vs. placebo, 95% CI 0.68-0.85). If a patient does unfortunately continue to experience persistent high levels of symptoms or treatment intolerability we would not recommend re-treatment.

For patients receiving dronedarone as a 1st line AAD alternative to amiodarone, sotalol or the class 1c agents again we anticipate they will continue with their treatment indefinitely unless one of the above factors occurs (persistent high levels of symptoms or treatment intolerability).

A2. Please provide any information available on how any beneficial effect of dronedarone on mortality and reducing the risk of stroke is mediated. For example, is this assumed to be via anti-arrhythmic effects alone, or via another mechanism, such as rate control?

RESPONSE: The main driver of benefit of dronedarone on mortality is CV mortality and arrhythmic deaths. Treatment with dronedarone was associated with a 30.2% lower risk of cardiovascular death (HR [95%CI] 0.698 [0.509; 0.958]) when compared to placebo.
The reduction of cardiovascular death with dronedarone 400 mg BID was mainly due to a reduction in the risk of sudden cardiac deaths (14 versus 35 in the placebo group) and stroke (11 versus 18). The reduction of sudden deaths can primarily be explained by direct ventricular anti-arrhythmic effects that were well documented in previous animal studies (Finance O, et al. Journal of Cardiovascular Pharmacology 1995;26: 570–576 – see attached). A high proportion of ATHENA patients had significant structural heart disease, including ischemic heart disease and heart failure. These patients were therefore more susceptible to develop life-threatening ventricular arrhythmias. Anti-arrhythmic properties of dronedarone at the ventricular level (e.g. inhibition of IK_r) may be, at least partly, responsible for this observed reduction of sudden deaths. There are several potential mechanisms by which dronedarone could reduce the risk of stroke. The most likely mechanism is by the suppression of AF.

However, there are other potential mechanisms that could play a role as there was a trend for reduction in stroke even in patients who appeared to be in AF throughout the study. [redacted]

In ATHENA, dronedarone was also associated with a modest reduction in blood pressure. Another potential mechanism of stroke reduction was heart rate slowing during AF with dronedarone. It is possible that a slower rate during AF recurrence could directly reduce the risk of stroke by preventing hypertension.

We are delighted to attach the very recent publication in Circulation on the analysis of stroke in ATHENA (Connolly, 2009).


Finance J Card Phar 1995.pdf


Connolly CIRCULATION 2009.

ATHENA trial

A3. Please provide the full clinical study report for the ATHENA trial.

RESPONSE: Submitted separately on the 22nd September 2009.

A4. On p36 and p37 of the submission, the composite endpoint of the number of hospitalisations due to any cardiovascular event or death from any cause is reported. Table 6.5 provides figures for first hospitalisation only. Please provide the number of hospitalisations (at any stage) due to any cardiovascular event.

RESPONSE: The number of hospitalisations at any stage within ATHENA due to any cardiovascular event was: [redacted] *log-rank asymptomatic test for repeated event time data).*

A5. On p39 of the submission, with regard to study discontinuation and adverse events, it states that the imbalance in the "other reasons" category was mainly due to the more frequent investigator initiation of study disallowed anti-arrhythmic medication or recurrent atrial fibrillation in the placebo group. This indicates that episodes of atrial fibrillation were recorded as part of the ATHENA trial. However, rate of recurrence of AF is not mentioned as an outcome measure in the submission nor in the article by Hohnloser et al., 2009. Please clarify whether data on AF episodes were measured in the ATHENA trial and also whether data on rate control data were measured?

RESPONSE: Recurrence of AF and rate control were not pre-specified end-points in ATHENA as the focus was on morbidity and mortality. However ECG's performed during scheduled and unscheduled visits can provide some information about rhythm

status and heart rate at some time points. As patients could be randomised in AF/AFL or in SR (and there was no mandatory cardioversion for patients entering in AF/AFL), a time to first recurrence of AF/AFL analysis is not feasible for the overall ATHENA population.

Considering the subgroup of patients entering in SR, the recurrences were not systematically collected (there was no TTEMs nor reporting of episodes of AF/AFL that did not lead to hospitalisation or cardioversion not documented on a scheduled ECG). However in a published post-hoc analysis (RL Page, Circulation 2008 – see abstract attached) such an endpoint has been built by using one of the following events as an indication for AF recurrence:

- *Hospitalisation for AF/AFL*
- *Reported electrical cardioversion*
- *AF/AFL on an scheduled ECG (day 7, 14, months 1, 3, 6 and every 6 months thereafter)*

In this patient population the median time to AF was prolonged from 498 days in Placebo pts to 737 days in dronedarone pts (HR 0.75, 95% CI 0.68 – 0.82; p<0.001).

With regard to discontinuation due to the prescription of disallowed anti-arrhythmic drugs, a sub-classification of the main reasons for permanent study drug discontinuation in the groups "Subjects Request" and "Other Reason" was performed by the Sponsor. It used the investigator's "Verbatim" and a written guideline specifying the following subgroups "AF/AFL recurrence", "Treatment with a prohibited anti-arrhythmic concomitant medication", "Treatment with a prohibited non-anti-arrhythmic concomitant medication" and "Family request". Please see the table below directly from the clinical study report (Table 5 of the CSR provided on the 22nd September 2009).

Table A5.1

A6. On p42 of the submission, a post hoc analysis of subgroups categorised by risk of stroke of CHADS2 score ≥ 4 is described. Please provide:

i. A rationale for this post-hoc analysis

RESPONSE: Given the consistency of the main ATHENA results across a broad range of pre-specified subpopulations (patients with or without structural heart disease and with or without CHF) different exploratory post-hoc analyses were considered a logical next step. The findings of the pre-specified subpopulations were important because in addition to the expected effect on hospitalisations due to AF, dronedarone also reduced CV deaths and CV hospitalisations due to other reasons than AF, such as acute coronary syndrome or stroke. Given that stroke is one of the main clinical complications of AF (5-fold increase of stroke due to AF), the exploration of the effect of dronedarone on stroke reduction is extremely relevant.

The subsequent post-hoc analysis on stroke showed that patients with a CHADS score ≥2 had a significantly greater effect of dronedarone than those with a CHADS2 score ≤1 (P=0.03 for interaction; see Connolly 2009 attached above). Given that patients who had the higher level of risk appeared to derive greater benefit, it was deemed logical to further explore the relationship between the level of risk and the magnitude of the treatment effect. For that reason, the analysis was further extended to different values of the CHADS2 score corresponding to different levels of risk. While the statistical significance of CV mortality was demonstrated not only for the full population but across the range of CHADS2 scores, the statistical significance of all-cause mortality was only shown for those patients with a CHADS score≥4 (see following table), hence their inclusion in the submission as a possible position for dronedarone use as an adjunct to standard therapy.

Table A6.1

		Placebo (N=2327) n/N (%)	Dronedarone (N=2301) n/N (%)	HR [95% CI] (from Cox model)	P-value
CV death according to centralized classification	All patients	[redacted]	[redacted]	[redacted]	[redacted]
	Chads2 score >=2	[redacted]	[redacted]	[redacted]	[redacted]
	Chads2 score >=3	[redacted]	[redacted]	[redacted]	[redacted]
	Chads2 score >=4	[redacted]	[redacted]	[redacted]	[redacted]
Death from any cause	All patients	[redacted]	[redacted]	[redacted]	[redacted]
	Chads2 score >=2	[redacted]	[redacted]	[redacted]	[redacted]
	Chads2 score >=3	[redacted]	[redacted]	[redacted]	[redacted]
	Chads2 score >=4	[redacted]	[redacted]	[redacted]	[redacted]
All randomised patients. PGM= \\rpsf001\SOD\G-I\GHOMASAS\SR33589_Dronedarone\ATHENA\PGM\TimeToDeathChads.sas OUT= OUTPUT\TimeToDeathChads.1.rtf (20JUL2009 - 16:08)					

ii. Full details of the post hoc analysis

RESPONSE: Please see attached report on the full analysis

[redacted]

iii. Details of any other studies of anti-arrhythmic drugs that have used CHADS2 in their analysis

RESPONSE: A simply PubMed search (28/09/09) was undertaken using the following search strategies:

- *CHADS + anti-arrhythmic*
- *CHADS + atrial fibrillation*
- *Amiodarone + CHADS*
- *Sotalol + CHADS*
- *Flecainide + CHADS*
- *Propafenone + CHADS*

Only the first 2 searches identified any possible papers of interest (CHADS + anti-arrhythmic found 4 papers; CHADS + atrial fibrillation found 49 papers; results attached). Of these 7 looked potentially interesting and abstracts were considered but none were found to consider a specific anti-arrhythmic drug to a CHADS2 analysis (most considered anti-coagulation or some considered rate versus rhythm control).

In addition to the above the key studies used in the MTC analysis were re-visited to check if any analysis had been considered using CHADS2 but none were found. This may be due to their date of initiation which in many instances was pre-CHADS2 validation.

Finally, a simple Google search identified one study that specifically considered amiodarone and Class 1c agents and mentioned an analysis conducted by CHADS2 score. On review of the full paper (Gulizia, AHJ 2008 - see attached) this analysis was a post hoc evaluation of anticoagulation agent use as a function of stroke risk score following the CHADS2 rule and therefore of no specific interest.


Gulizia AHJ 2008.pdf


PubMed Search Results2.htm


PubMed Search Results.htm

ADONIS and EURIDIS trials

A7. Please provide a breakdown of the number of patients with atrial flutter in each study arm for ADONIS and EURIDIS separately and combined.

RESPONE: ***Number of patients with Atrial Flutter in EURIDIS and ADONIS***

-	-	Placebo n/N (%)	Dronedarone n/N (%)
Euridis & Adonis	Atrial fibrillation	[redacted]	[redacted]
	Atrial flutter	[redacted]	[redacted]
	Missing	[redacted]	[redacted]
Euridis	Atrial fibrillation	[redacted]	[redacted]
	Atrial flutter	[redacted]	[redacted]
	Missing		[redacted]
Adonis	Atrial fibrillation	[redacted]	[redacted]
	Atrial flutter	[redacted]	[redacted]
	Missing	[redacted]	[redacted]
Randomised and treated patients PGM= \\rpsf001\SOD\G-I\GHOMASAS\SR33589_Dronedarone\EURADO\PGM\AFAFL_repartition.sas OUT= OUTPUT\AFAFL_repartition.rtf (22SEP2009 - 11:13)			

A8. Please provide full details of the treatment-emergent adverse events in the ADONIS and EURIDIS trials.

RESPONSE: Please find full details in the attached report

[redacted]

Meta-analysis and mixed treatment comparison (MTC)

A9. Please provide full details of the MTC, including the code and raw data for the analysis. (The document provided does not contain sufficient details of the MTC).

RESPONSE: Please find below a sample of the SAS coding that was used for the MTC (detailed in Freemantle report dronedarone 210609.pdf sent previously along with the raw data; submitted on the 22nd September 2009). The code remains the same for all outcomes with the exception of the study drugs listed.

Sample SAS code for the analyses is described below:

```
proc glimmix data=work.stroke;
Title stroke by Drug ;
class study;
model R/N =  study  Dronedarone  Amiodarone Sotalol   / dist=B solution CL;
NLOPTIONS tech=nrridg MAXITER=5000;
random _residual_ / sub=study ;
run;
```

A10. There seem to be inconsistencies in the inclusion/exclusion criteria applied between the meta-analyses and the MTC. Please provide clarification on whether additional inclusion/exclusion criteria were applied to the meta-analysis of non-active control and head-to-head data presented in Tables 6.9 - 6.13 over and above the inclusion criteria reported in Table 6.8, page 51.

RESPONSE: Results presented for the MTC are subject to pre-specified stepwise inclusion/exclusion based on convergence of the algorithm used. If convergence was not reached using the full dataset, then the dataset was restricted to studies including more than 25 patients with at least one event in one of its arm. Then the algorithm was run again. If convergence again failed, the dataset was further restricted to include studies with more than 50 patients per arm with at least one event in one of its arms and the algorithm was run again. If convergence was still not achieved the dataset was restricted to studies with more than 100 patients per arm with at least one event in one of its arms.

For clarity please note that for the outcomes all cause mortality and AF recurrence the primary analysis was performed using 12 months data. This was done in coherence with the previous Cochrane analysis and to gain homogeneity in the comparisons. It derives from this that if a study was of less than 12 months duration or did not report the outcome at a reasonable approximation of 12 months; the study was excluded from this particular analysis.

Our pre-specified criteria for the inclusion of trials in the mortality models (and their exclusion due to lack of convergence) was driven in particular by the presence of single trials for propafenone and flecainide. In further exploratory analyses we included trials of amiodarone, sotalol or dronedarone with at least 1 event in one treatment group, but without any restriction on patient numbers randomised. This led to the additional inclusion of DAFNE, 2003, and Fetsch, 2004. This model did converge, providing the following results:

Table A10.1 Supportive analysis including additional trials of amiodarone, sotolol or dronedarone on all cause mortality (odds ratio and 95% CI):

Drug	Odds Ratio	Lower 95% CI	Upper 95% CI	P value
Dronedarone	0.860	0.693	1.067	0.1423
Amiodarone	2.917	1.221	6.966	0.0227
Sotalol	4.660	1.968	11.035	0.0039

For stroke, the Aliott Study 1996 compared flecainide to propafenone however it had to be excluded as there was no other studies involving either product with a common comparator or control to allow the 'linkage' required to the network used in the analysis.


PAFAC Fetsch EHJ 2004.pdf


Aliot Am J Card 1996.pdf

A11. Please provide additional justification for restricting trials in the MTC to those with at least 100 subjects per randomised group and at least 1 event in either group. Also, provide the rationale for separate criteria for the outcome of stroke, i.e. at least 50 subjects per randomised group (page 57).

RESPONSE: Please see the response to question A10 which also provides the additional justification for stroke.

A12. Please explain the issue of not achieving convergence in the MTC analysis. Please report whether all outcomes were affected by this issue.

RESPONSE: Not achieving convergence means that the algorithm would actually either simply refuse to give estimations (both point estimate and uncertainty around the estimates) or that the convergence test would lead to the suspicion that likelihood based estimator did not reach the real extremum but is stuck in a sub-extremum of the parameter space therefore would lead to incorrect estimations.

All outcomes for which inclusion/exclusion criteria had to be strengthened were subject to this lack of convergence. In other words, all-cause mortality, treatment discontinuation and stroke outcomes were affected.

A13. Please clarify whether the MTC results are based on a fixed or random effects analysis.

RESPONSE: MTC analysis was performed using a random-effect model. To further clarify the procedure allows for parameterisation of the random part through the parameterisation of the variance/covariance matrix which is used to estimate the random part of the model (meaning it does not change the point estimations but only the uncertainty part).

A14. Please provide additional justification for assuming no treatment effect in the absence of results for the MTC, e.g. Class 1c for all cause mortality and stroke.

RESPONSE: It is assumed in the model that there is no mortality benefit for dronedarone compared to class 1c agents since there were insufficient data to conclude reliably the estimate of the odds ratio for all cause mortality in the MTC. The meta analysis of flecanide and propafenone reported an odds ratio of [redacted] *compared to non-active control if a 12 month time frame is considered (included in appendix 6 of the main submission) or* [redacted] *compared to non-active control if the whole study period is considered (see attached document on pooled 1c analysis). Furthermore if the meta-analysis results for flecanide and propafenone are considered separately then odds ratios of* [redacted] *for flecanide and* [redacted] *for propafenone are shown (see Table 3, pg 38 of the previously submitted updated priority report 050509 – full report of the meta-analysis). Clearly there is considerable uncertainty demonstrated in these results with the direction of the point estimates compared to dronedarone changing depending on the perspective of the*

analysis. It was felt that given this variability the assumption of no mortality benefit for dronedarone compared to Class 1c agents was appropriate.

There was no evidence available on which to base any assumption as to the value of the treatment effect for class 1c agents on stroke and so we assumed that there was no benefit compared to non-active control, but maintained the treatment effect for dronedarone which has demonstrated a statistically significant benefit on the endpoint of stroke. A sensitivity analysis has been added to the results addendum (see question C7 for attachment) as part of this response which assumes that class 1c has the same treatment effect on stroke as dronedarone, amiodarone and sotalol to demonstrate the effect on the ICER if class 1cs achieved the same preventative effect as the comparators (see analysis 9 in the results addendum response to question C7).

A15. Tables 6.9, 6.10, 6.11, 6.12, and 6.13 (p52-57) are difficult to interpret as they do not contain information with respect to the number of trials or the number of patients in each treatment comparison. Even though this information may be included elsewhere in the submission or appendices please redraft these tables and include:

i. The number of trials in each treatment comparison

ii. The number of patients in each treatment comparison

iii. Please provide the MTC results for each AAD vs. control, i.e. consistent with the data reported in Table 7.5, page 92 and subsequently used in the model.

RESPONSE: See attached document with revised tables. Please note that within the revised tables we have listed the number of treatment arms used for the analysis rather than the number of trials as requested in A15i as some trials had multiple treatment arms. The number of trials (and names/authors) can be derived from Tables 2 and 3 of the appendices 5 – 9 submitted to accompany the full dossier (26th August 2009).

A16. Although the raw data for the direct comparisons are included in the Abacus report, it is not clear which data are included in the indirect meta-analysis comparisons. Please provide these details (or state where they are in the report).

RESPONSE: In the full meta-analysis report (updated priority report 050509 – submitted to NICE on the 8th September), section 3.3, page 37 Table 2 provides a list of all the studies considered for the direct and indirect analysis. For example below are a list of the studies considered when looking at amiodarone and sotalol compared to placebo/control. The indirect analysis was conducted by linking these studies through the placebo therefore when comparing amiodarone to sotalol all of the below studies were included in the indirect analysis.

Direct comparisons	**Placebo/control**
Amiodarone	6 studies (Boos, 2008; Channer, 2004; Galperin, 2001; Kochiadakis, 2000; SAFE-T, 2005; Vijayalakshmi, 2006)
Sotalol	12 studies (A-COMET-II, 2006; Bellandi, 2001; Benditt, 1999; Brodsky, 1994; Carunchio, 1995; Fetsch, 2004; Kochiadakis, 2000; Kochiadakis, 2004b; SAFE-T, 2005; Singh, 1991; SOPAT, 2004; Vijayalakshmi, 2006)

Section B: Clarification on cost-effectiveness data

B1. Please provide the full report of cost-effectiveness studies as offered on p65 of the submission.

RESPONSE: Submitted 22nd September 2009

Risk of mortality

B2. Please provide additional explanation of the approach used for estimating time to mortality (p91). Please clarify whether this approach was applied to the entire model period or just to the period beyond the follow-up of the ATHENA trial?

RESPONSE: Additional explanation on the approach and methodology used for estimating the time to mortality is provided within an attached Excel based simulation. This simulation is used to estimate absolute mortality rates for standard care and the approach is applied throughout the entire model.

Survival Simulation.xls

We have also adapted the Simul8 model to allow an analysis where mortality benefit is only applied for the trial period and then all interventions revert back to the standard care risk of mortality. The results of this sensitivity analysis are included in the results addendum accompanying this response (see analysis 11 in the attachment for question C7)

B3. Please provide the coefficients for the equations estimating time to mortality. Please clarify whether alternative curve fits were examined based on Akaike's Information Criterion and Bayesian Information Criterion goodness of fit criterion for time to mortality.

RESPONSE: The coefficients for time to all-cause morality are presented in the updated appendix 12 attached in response to question C1. These are presented again in table B3.1 below. The all-cause mortality data is based on the life tables produced by the government actuarial department and is only cut by age and mortality. We calculated all-cause mortality from entry into the model which is for patients aged 72 so there is no age co-efficient as all patients are assumed to be 72. No alternate curve fits were considered in the main submission, however a new sensitivity analysis examining the second best fit based on the AIC has been added

to the results addendum accompanying this response (see analysis 10 in the attachment for question C7).

***Table B3.1:** All cause mortality Weibull curve coefficients*

All-cause mortality coefficients	Mean	SE
Sex	-0.04	0.02
Constant	-4.00	0.03
Weibull shape	1.69	0.01

B4. On p90, all cause mortality is adjusted for CHADS2 score. Please clarify whether this risk of mortality includes mortality from stroke. Please also clarify whether the inclusion of an additional mortality effect through adding stroke to the model constitutes double counting. Is the treatment effect applied to both mortality and stroke?

RESPONSE: The mortality effect associated with stroke is removed from the all-cause mortality data to ensure that there is no double counting of effect in the model. The methodology for this is included in the simulation submitted in response to question B2.

The treatment effect is only applied to all cause mortality and not to stroke mortality.

B5. Please provide 95% confidence intervals for the relative risk of mortality reported in table 7.4 (p90).

RESPONSE: Please see revised table 7.4 below.

***Table 7.4:** Increased risk of mortality based on $CHADS_2$ score*

$CHADS_2$	RR of mortality (95% CI)
0	*1.00(reference)*
1	*2.52 (2.24 – 2.83)*
2	*3.14 (2.80 – 3.52)*
3	*3.99 (3.56 – 4.48)*
4	*4.25 (3.78 – 4.77)*
5	*5.13 (4.55 – 5.79)*
6	*6.05 (5.26 – 6.95)*

B6. Please explain why alternative curve fits were not explored for the outcomes ACS and AF recurrence (Appendix 14).

RESPONSE: All survival models including variation over time (Weibull, Gamma, Lognormal, etc) use a common baseline (usually the entry time into the cohort) from which the time is modelled. When modelling recurrence and ACS, we allow for more than one event to occur, which makes the assignment of such common entry point problematic for the following events. The theoretical underpinnings of the use of more advanced functional forms for the hazard were questionable, therefore it was felt appropriate to use the simplest form of parameterisation i.e. exponential.

<u>Quality of life</u>

B7. Please provide additional clarification on the derivation of the health state and event utility weights presented in table 7.7 (p96). Are these values derived from published studies or new analyses?

RESPONSE: These values were derived from new analyses of the European Heart Survey; please see the attached document for additional clarification.

Costs

B8. Please provide additional information on the resource use and unit cost assumptions associated with adverse events, and the sources of this information (table 7.16, p104).

RESPONSE: The cost of treating treatment related adverse events are based on assumptions made by consulting clinical experts to obtain an estimate of the proportion of patients that would be expected to be treated as inpatients and as outpatients based on the adverse event. These are then costed using 2006/7 reference costs for inpatient stay and outpatient visits and the BNF to cost drug use for outpatient visits (inpatients reference costs include drug acquisition costs) A summary of these assumptions and costs are presented in table B8.1 below

The value used in the model for eye events and fatigue assumed that there were no inpatient costs (as shown in table B8.1), but did not include the outpatient cost associated with treatment. This has been updated in the amended version of the model that accompanies this response and has had a negligible effect on the ICER.

Table B8.1: Adverse events assumptions and costs

Event	% inpatient	HRG	% outpatient	Outpatient care*	Cost (£)
Cardiac events (bradychardia, proarrythmia, tachycardia)**	10%	EB07H-I	90%	2 outpatient visits	£390
Eye events (photophobia, blurred vision)	0%	na	100%	Referral to ophthalmologist	£154
Fatigue	0%	na	100%	1 outpatient visit	£158
Gastrointestinal (diarrhoea, nausea, vomiting)	10%	FC05C	90%	1 outpatient visit	£217
Hepatic events	100%	CC07C	0%	na	£919
Hyperthyroidism	10%	KA02Z	90%	2 outpatient visits, L-tyroxin	£542
Hypothyroidism	10%	KA02Z	90%	2 outpatient visits, carbimazole	£552
Neurological events (tremor, sleep disorder)	20%	AA25Z	80%	1 outpatient visit	£441
Pulmonary (interstitial lung disease)	80%	DZ25B	20%	1 outpatient visit	£1,011
Skin events (photosensitivity, rash etc)	5%	JD06B	95%	1 outpatient visit	£178

*Outpatient care assumed to be in cardiology unless otherwise specified.
**Costing for bradychardia used – this was the most common cardiac side effect in ATHENA.

Table B9.1: Adverse events assumptions and costs

	Dronedarone		Amiodarone		Sotalol		Class 1c	
Event	**Rate**	**Cost**	**Rate**	**Cost**	**Rate**	**Cost**	**Rate**	**Cost**
Cardiac events (bradychardia, proarrythmia, tachycardia)**	[redacted]	£14.27	[redacted]	£24.57	15.00%	£58.50	7.00%	£27.30
Eye events (photophobia, blurred vision)		£1.05		£3.08	2.60%	£4.00	15.90%	£24.49
Fatigue		£10.11		£3.79	19.60%	£30.97	7.70%	£12.17
Gastrointestinal (diarrhoea, nausea, vomiting)		£32.57		£16.06	13.00%	£28.21	8.90%	£19.31
Hepatic events		£31.34		£50.55	0.00%	£0.00	0.00%	£0.00
Hyperthyroidism		£1.52		£8.67	2.60%	£14.09	0.00%	£0.00
Hypothyroidism		£3.59		£21.53	0.00%	£0.00	0.00%	£0.00
Neurological events (tremor, sleep disorder)		£4.06		£44.98	0.00%	£0.00	4.70%	£20.73
Pulmonary (interstitial lung disease)		£2.02		£0.00	0.00%	£0.00	10.00%	£101.10
Skin events (photosensitivity, rash etc)		£5.75		£5.70	0.00%	£0.00	0.00%	£0.00
Total cost		**£106.28**		**£178.92**		**£135.77**		**£205.09**

B9. Please indicate how the costs presented in table 7.17 (p104) relate to those in table 7.16.

RESPONSE: Table 7.17 is calculated by multiplying the rate of the event presented in table 7.6 by the cost of the event presented in table 7.16. These calculations are summarised in table B9.1.

Results

B10. Please explain the reasons for different costs and QALYs gained for treatment with dronedarone between positions 2 and 3 in table 7.18 (p108), i.e. only the comparator drug has changed between position 2 and position 3.

RESPONSE: In the comparison between dronedarone and sotalol (position 2) there is an all cause mortality benefit achieved with treatment with dronedarone. This is calculated using the absolute risk of all cause mortality for standard care patients and adjusting for dronedarone and sotalol based on the comparison with placebo in the MTC. In the comparison with treatment with class 1c therapies, there is no evidence of a mortality benefit. We therefore assume that there is no difference between standard care and dronedarone and class 1c. This means that compared to position 2, dronedarone has a different all-cause mortality rate. An alternate way of presenting this analysis would be to assume that class 1c drugs have the same mortality benefit compared to standard care as dronedarone so that the results for dronedarone remain the same between positions 2 and 3. This approach has been used in the updated analysis included in the attached addendum.

B11. Please clarify why the absolute QALYs gained in table 7.20 (patients with paroxysmal AF with left ventricular dysfunction; p109) are higher than the absolute QALYs gained in table 7.18, where patients have no structural heart disease. Please also clarify this point for tables 7.21 and 7.22 (p110-111).

RESPONSE: The risk equations from the ATHENA trial that are used for the absolute risk values for standard care patients in the model show that the presence of structural heart disease increases the risk of AF recurrence, CHF and ACS, but has a preventative effect on the risk of stroke. The utility detriments and mortality effect associated with stroke give rise to the increase in QALYs gained for patients with SHD or LVD. The patients underlying utility value is also not adjusted for the patient's heart condition, i.e. patients with no structural heart disease have the same baseline utility as those with SHD or LVD.

B12. Please provide the results of the analysis where the model has been validated against the ATHENA trial as offered in the submission (p115).

RESPONSE: The results of this analysis are presented analysis 12 of the results addendum.

Section C: Textual clarifications and additional points

Discrepancies

C1. The baseline CHADS2 score distributions presented in table 7.3 (p90) do not correspond with the values presented in appendix 12. Please clarify which values are correct.

RESPONSE: The values presented in appendix 12 are the record AF values for the UK. The values presented in table 7.3 for ATHENA are the correct base values. Appendix 12 has been updated to ensure the values are in line with main report (see attached).

Appendix 12 CIC Dec 09v2.doc

(Please note parts of this document as CIC and as such have been blanked out)

C2. The treatment effects reported in appendix 12 do not correspond with the values presented in the main report. Please clarify which values are correct.

RESPONSE: The values presented in the report are the correct values. Appendix 12 has been updated to ensure the values are in line with main report (see attachment in response to question C1).

C3. The treatment effect on AF recurrence for class 1c reported in table 7.5 (p92) does not match the value used in the model. Please clarify which value is correct.

RESPONSE: The value used in the model ([redacted]) is the correct value.

C4. The standard deviation for AF symptoms presented in table 7.7 (p96) does not match the value used in the model. Please clarify which value is correct.

RESPONSE: The value in the report is correct and the value in the model has been updated. The effects of this change are reflected in the results presented in the addendum.

C5. The initialisation cost for dronedarone presented in table 7.12 (p101) does not match the value used in the model. Please clarify which value is correct.

RESPONSE: The value presented in the report has not been inflated to 2008 prices. The value used in the model has been inflated and is the correct value.

C6. The cost of regular monitoring for amiodarone presented in table 7.14 (p102) does not match the value used in the model. Please clarify which value is correct.

RESPONSE: The cost of regular monitoring for amiodarone used in the model does not include the cost of an x-ray, which is included in the report. The model has been updated with the correct cost and the amendment reflected in the results presented in the addendum.

Simul8 code

C7. In the a_NextEvent code, the code beginning if lbl_TimeofACS has the + and - transposed compared with the other lines. Please clarify whether this is an error and provide the correct code and revised results accordingly.

RESPONSE: This is an error in the Simul8 code. The – value should be a + value. The Simlu8 code has been amended and the updated model results supplied with this response (see attachment).

C8. In the a_OneOffCosts code, please clarify whether the discounting is done correctly. The number of 'monitorings' is calculated, based on 2 per year, and this is discounted at the rate when the transition / initiation occurred. Therefore at start up, all 6 monitorings would be assumed to happen in Yr 1. Please clarify whether this is an error and provide the correct code and revised results accordingly.

RESPONSE: sanofi-aventis acknowledge that the calculation used in section a_OneOffCosts is incorrect and a corrected version has been included in the updated model supplied with this response.

C9. The number of patients per run, selected from the Model Controls input sheet in Excel, is divided by 10 (see 'Selecte4d Values' B8 in the Excel sheet). Please can you clarify why the number of patients per run is divided by 10.

RESPONSE: The number of patients is divided by 10 to improve the efficiency of the Simul8 engine. The model runs at an optimum speed if approximately 4000 to 5000 patients are run through the simulation. The model is run 10 times utilising the trial functionality in Simul8, using different random set for each trial. Running 10 trials of 4000 patients gives the same result as running one big run of 40,000 patients, it is simply that the former runs significantly faster.

C10. The second choice of survival curves does not seem to work, i.e. changing cell J43 from the Model Controls input sheet in Excel from 1st to 2nd reproduces the same model results. Please provide a corrected version of the model.

RESPONSE: This functionality is provided in the updated version of the model results supplied with the response.

C11. Errors reported by Simul8. There are 5 times where Simul8 reports that the router label was greater than the number of routes. Normally, the label takes a number 1 to x, and then sends the entity down the appropriate route from 1 to x. Where this is a mismatch, i.e. router =8 and there were only 5 routes, Simul8 defaults to the greatest number route (i.e. 5). Please clarify whether this is an error and provide the correct code and revised results accordingly.

RESPONSE: This is not an error in the model but occurs when there is only one exit available from the work centre. The router is not set for these states and so can have

a value greater than 1 which causes Simul8 to report a warning. This has no effect on the results of the model.

Search clarifications following initial submission

C12. Appendix 2: Search strategy for section 6, clinical effectiveness; the search description states that Medline, EMBASE and the Cochrane Library were accessed in March 2009. However the search strategies listed in the Appendix show searches carried out in May 2009. Please confirm the date each database was searched.

RESPONSE: The search was conducted in May 2009.

C13. Appendix 4: Search strategy for meta-analysis and MTC; The search description states that the Cochrane Library, OVID EMBASE and OVID Medline were searched. However only one search strategy is listed in the Appendix and it is not marked which database this search strategy was used for.

i. Please confirm the date each database was searched.

REPONSE: The databases were initially access in September 22nd 2008, however a follow-up search was undertaken on the 8th April 2009 to identify any new publications of relevance.

ii. Please provide the search strategy used for each database.

RESPONSE: please see attached document and note that we discovered an error in the search strategy submitted on the 26th August 2009. The correct search strategy for each database is in the attached document which we hope will be acceptable.

Search Strategy.doc

iii. The search strategy listed in the Appendix contains lines (45, 46, 51, 52, 53, 54, 55 and 56) that are not incorporated into the final combined results. Please confirm that the strategy shown is complete and that these lines were purposely excluded.

RESPONSE: Please see response above and the correct search strategy attached.

C14. Appendix 10: Search strategy for health economic evaluations of dronedarone; the search description states that the Cochrane Library, Medline (PubMed) and EMBASE were searched. Please confirm the following:

i. The date each database was searched.

RESPONSE: All of the databases (Medline, EMBASE and Cochrane Library) were searched from 1990 – 12 Dec. 2008. For the Cochrane Library this was done on Issue 4, 2008. Conference abstracts were searched from 2005 to 16 January 2009

(full criteria is available in report submitted on 22nd September 2009 in response to question B1).

ii. That the first strategy listed in the Appendix is the EMBASE strategy.

RESPONSE: Table A-1 lists the general search strategy; Tables A-2 and A-3 list the Medline and Cochrane search strategies respectively. The search strategy is Table A-4 of the full report (recently submitted in response to question B1) however apologies are in order as this table was incorrectly excluded from the Appendix 10.

iii. Which host (e.g. OVID) was used to search EMBASE.

RESPONSE: Dialog Platform was used to search EMBASE (please see Section 3.1 of the full report recently submitted in response to question B1).

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Issues addressed from the comments on Appendix 12:

CHADS score: 'The values reported in this appendix are from GPRD. It is unclear where the values in the model are coming from. According to the report and clarifications response, the base case values are from ATHENA as given in Table 7.3 of the report. The values in the model do not correspond to ATHENA as presented in Table 7.3. Also note that the model does not correctly update these values if you only change cells W29-35 of worksheet 'Input Sheet'. You must also change cells G13-19 of worksheet 'Lists'. The two worksheets should be linked but they are currently not.'

The default values in the Excel sheet should be the ATHENA values as presented in Table 7.3 of the full submission. Due to the issue with the two Excel list selectors interacting these can be changed to the GPRD values in error. The Excel model has been updated so that the ATHENA values are always the base case values whatever the scenario combination selected.

***AF recurrence treatment effect (ORs):* 'These values are used in the model but they do not correspond to the updated Table 6.9 of the clarifications response.'**
The values presented in Table 6.9 of the clarification response letter contained errors caused by cutting and pasting rows. The values in the main submission and Appendix 12 are the correct values and are reflected in Table 6.9 below.

Table 6.9: Meta-analysis summary of comparison between treatments: Odds ratio (OR) for AF recurrence

Meta-analysis	**No treatment arms (no patients)**	**Peto OR (95% CI)**	**Peto OR (95% CI)**
Non-active control		**Direct analysis**	**Indirect analysis**
amiodarone v control	[redacted]	[redacted]	[redacted]
Class 1c v control**	[redacted]	[redacted]	[redacted]
sotalol v control	[redacted]	[redacted]	[redacted]
dronedarone v control	[redacted]	[redacted]	[redacted]
Head to head			
amiodarone v dronedarone	[redacted]	[redacted]	[redacted]
Class 1c v dronedarone**	[redacted]	[redacted]	[redacted]
sotalol v dronedarone	[redacted]	[redacted]	[redacted]
Mixed treatment comparison*			
		OR (95% CI)	**P value**
Dronedarone v Control	[redacted]	[redacted]	[redacted]
Amiodarone v Control	[redacted]	[redacted]	[redacted]
Sotalol v Control	[redacted]	[redacted]	[redacted]
Class 1c v Control	[redacted]	[redacted]	[redacted]
Amiodarone v dronedarone	[redacted]	[redacted]	[redacted]
Sotalol v dronedarone	[redacted]	[redacted]	[redacted]
Class Ic v dronedarone** combined	[redacted]	[redacted]	[redacted]

[redacted]

All-cause mortality coefficients: **'The appendix values do not correspond with the model values or Table B3.1 of the clarifications response. Also, note that the coefficient for sex is 0.04 in the model, while it is -0.04 in Table B3.1.'**

The values in appendix 12 had not been updated in line with the clarification response and the model. These have now been corrected in response to this further clarification. The coefficient for sex is 0.04 and is correct in the model.

Treatment effect on All-cause mortality(OR) Sotalol: '**This value is 4.52 in the updated Table 6.10 of clarifications response.'**

4.52 is the correct value and has been updated in appendix 12

Treatment discontinuation coefficients: 'The appendix values do not correspond with the values used in the model. It is unclear where these values are coming from.'
The values stated in appendix 12 were not updated in line with the final version of the submission. The curve with the best AIC fit for treatment discontinuation and used in the model and the main submission is the gamma. The coefficients for the gamma fit have been updated into appendix 12. These values were also incorrect in appendix 14 of the main submission. These have been amended in the table below (highlighted in red text).

Table 14.2: Coefficient (standard error) used to construct risk equations for time to events in the model. Based on the ATHENA baseline treatment arm.

Covariate	**Stroke**	**CHF**	**ACS**	**AF recurrence**	**Treatment discont.**
Curve fit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline SHD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline CAD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline CHADS-2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Class 1c discontinuation rate: This value is used in the model but the updated Table 6.11 of the clarifications response has a different value: 1.64 (0.96, 2.79)

The discontinuation for any cause value reported for class 1c in the clarification response accidentally stated the value for withdrawal due to adverse event. Both tables from the clarification response have been corrected and are shown below (please note that discontinuation any-cause is the data used within the economic model).

.

Table 6.11: Meta-analysis summary of comparison between treatments: Odds ratio for treatment discontinuations any-cause

	No treatment arms (no patients)	Peto OR (95% CI)	Peto OR (95% CI)
Non-active control		**Direct analysis**	**Indirect analysis**
Sotalol v control	[redacted]	[redacted]	[redacted]
Dronedarone v control	[redacted]	[redacted]	[redacted]
Amiodarone v control	[redacted]	[redacted]	[redacted]
Class 1c v control**	[redacted]	[redacted]	[redacted]
Head to head			
Amiodarone v dronedarone (1)	[redacted]	[redacted]	[redacted]
Sotalol v dronedarone	[redacted]	[redacted]	[redacted]
Class 1c v dronedarone**	[redacted]	[redacted]	[redacted]
Mixed treatment comparison*			
		OR (95% CI)	**P value**
Amiodarone v dronedarone	[redacted]	[redacted]	[redacted]
Sotalol v dronedarone	[redacted]	[redacted]	[redacted]
Class 1c v dronedarone**	[redacted]	[redacted]	[redacted]
Control v dronedarone	[redacted]	[redacted]	[redacted]
Amiodarone v control	[redacted]	[redacted]	[redacted]
Sotalol v control	[redacted]	[redacted]	[redacted]
Class 1c v control	[redacted]	[redacted]	[redacted]

[redacted]

Table 6.12: Meta-analysis summary of comparison between treatments: Odds ratio for treatment discontinuations due to AEs

	No treatment arms (no patients)	Peto OR (95% CI)	Peto OR (95% CI)
Non-active control		**Direct analysis**	**Indirect analysis**
Sotalol v control	[redacted]	[redacted]	[redacted]
Dronedarone v control	[redacted]	[redacted]	[redacted]
Amiodarone v control	[redacted]	[redacted]	[redacted]
Class 1c v control**	[redacted]	[redacted]	[redacted]
Head to head			
Amiodarone v dronedarone (1)	[redacted]	[redacted]	[redacted]
Sotalol v dronedarone	[redacted]	[redacted]	[redacted]
Class 1c v dronedarone**	[redacted]	[redacted]	[redacted]
Mixed treatment comparison*			
		OR (95% CI)	**P value**

Amiodarone v dronedarone	[redacted]	[redacted]	[redacted]
Sotalol v dronedarone	[redacted]	[redacted]	[redacted]
Class 1c v dronedarone**	[redacted]	[redacted]	[redacted]
Dronedarone v control	[redacted]	[redacted]	[redacted]
Amiodarone v control	[redacted]	[redacted]	[redacted]
Sotalol v control	[redacted]	[redacted]	[redacted]
Class 1c v control	[redacted]	[redacted]	[redacted]

[redacted]

Adverse event rates:
The values reported in appendix 12 were incorrect values and have been updated to be in line with the main submission (see Table 7.6, pg 94) and the economic model.

% of patients hospitalised on Adverse event:
The updated values presented in table B8.1 of the clarification response are the correct values for the cost of treating adverse events. These have been updated in the revised Excel sheet and included in this response.

Dronedarone Initiation cost.
This value is correctly reported in appendix 12, but had not been updated in the main submission or the economic model. The cost of £213 is made up from the reference cost of consultant led first attendance outpatient face to face (£158) inflated to 2008 prices (£165) plus the cost of a creatin test at a GP visit (£47).

Appendix 12: List of variables used in the model: Based on paroxysmal patient with no structural heart disease, replacing sotalol as 1st line AAD.

Variable	**Details**	**Value**	**Standard error**
Time Horizon		Lifetime	
Disc Rates Cost	Costs	3.50%	
Disc Rates QALY	Qalys	3.50%	
No patients per run		40000	
Population starting age	Mean	72	
Percentage of males	Male	34%	
Percentage of females	Female	66%	
$CHADS_2$ distribution - ATHENA			
Score 0		3%	
Score 1		32%	
Score 2		36%	
Score 3		18%	
Score 4		8%	
Score 5		3%	
Score 6		1%	
AF recurrence coefficients			
Age	Age	[redacted]	0.002
Gender	Gender	[redacted]	0.036
Baseline Chads	Baseline Chads	[redacted]	0.017
Baseline SHD	Baseline SHD	[redacted]	0.043
Baseline CAD	Basline CAD	[redacted]	0.045
Constant	Constant	[redacted]	0.143
AF recurrence treatment effect (ORs)			
Beta Blocker	Beta Blocker	[redacted]	
Dronedarone	Dronedarone	[redacted]	
Amiodarone	Amiodarone	[redacted]	

Sotalol	Sotalol	[redacted]	
Class1c	Class1c	[redacted]	
Proportion of recurrences resulting in hospitalisation		29%	
Treatment assessments for non hosp AF recurrence			
no GP visits		1	
no OP visits		0.33	
Paroxysmal patients			
P(AF recurrence remains paroxysmal)		90%	
Days spent in symptomatic AF		2	
Persistent patients			
P(patient has cardioversion)		90%	
P(patient has 2nd Cardioversion)		90%	
P(patient has ablation)		6%	
Cardioversion parameters			
P(patient receives electrical cardioversion)		90%	
P(patient receives pharmacological cardioversion)		10%	
P(electrical cardioversion attempt successful)		77%	
P(pharmacological cardioversion successful)		81%	
Days waiting			
1st electrical cardioversion		7	
1st pharmacological cardioversion		7	
2nd electrical cardioversion		7	
2nd pharmacological cardioversion		7	
Ablation parameters			
P(ablation success)		74.50%	
Days waiting for Ablation		7	
Coefficients for time to ACS			
Age	Age	[redacted]	0.009
Gender	Gender	[redacted]	0.153
Chad score	Chad score	[redacted]	0.064
Baseline SHD	Baseline SHD	[redacted]	0.269

Baseline CAD	Basline CAD	[redacted]	0.209
Constant	Constant	[redacted]	0.681
Coefficients for time to CHF			
Age	Age	[redacted]	0.009
Gender	Gender	[redacted]	0.132
Chad score	Chad score	[redacted]	0.056
Baseline SHD	Baseline SHD	[redacted]	0.181
Baseline CAD	Basline CAD	[redacted]	0.150
Constant	Constant	[redacted]	0.644
Weibull shape	Weibull shape	[redacted]	0.047
Coefficients for time to Stoke			
Age	Age	[redacted]	0.013
Gender	Gender	[redacted]	0.203
Chad score	Chad score	[redacted]	0.089
Baseline SHD	Baseline SHD	[redacted]	0.251
Basline CAD	Basline CAD	[redacted]	0.255
Constant	Constant	[redacted]	0.951
Treatment effect on ACS (OR)			
Beta Blocker	Beta Blocker	1.00	
Dronedarone	Dronedarone	1.00	
Amiodarone	Amiodarone	1.00	
Sotalol	Sotalol	1.00	
Class1c	Class1c	1.00	
Treatment effect on CHF (OR)			
Beta Blocker	Beta Blocker	1.00	
Dronedarone	Dronedarone	1.00	
Amiodarone	Amiodarone	1.00	
Sotalol	Sotalol	1.00	
Class1c	Class1c	1.00	
Treatment effect on Stroke (OR)			
Beta Blocker	Beta Blocker	1.00	

Dronedarone	Dronedarone	0.69	
Amiodarone	Amiodarone	0.89	
Sotalol	Sotalol	0.80	
Class1c	Class1c	1.00	
All-cause mortality coefficients			
Sex	Sex	0.040	0.014
Constant	Constant	-3.998	0.027
Weibull shape	Weibull shape	1.686	0.010
Treatment effect on All-cause mortality(OR)			
Beta Blocker	Beta Blocker	1.00	
Dronedarone	Dronedarone	0.86	
Amiodarone	Amiodarone	2.73	
Sotalol	Sotalol	4.52	
Class1c	Class1c	1.00	
Mortality associated with stroke			
Age		0.097	0.001
Constant		-10.461	0.084
Weibull shape		1.568	0.007
Post CHF Mortality		**Male**	
Males			
age band 45-54			
30 days		0.04	
1 Yr		0.09	
3 Yrs		0.11	
age band 55-64			
30 days		0.05	
1 Yr		0.15	
3 Yrs		0.11	
age band 64-74			
30 days		0.07	
1 Yr		0.22	

3 Yrs		0.41	
age band 75+			
30 days		0.14	
1 Yr		0.35	
3 Yrs		0.41	
Treatment withdrawal stand care AF			
Females			
age band 45-54			
30 days		0.04	
1 Yr		0.08	
3 Yrs		0.19	
age band 55-64			
30 days		0.06	
1 Yr		0.16	
3 Yrs		0.19	
age band 64-74			
30 days		0.08	
1 Yr		0.22	
3 Yrs		0.36	
age band 75+			
30 days		0.12	
1 Yr		0.30	
3 Yrs		0.36	
Treatment discontinuation coefficients			
Age	Age	[redacted]	0.007
Gender	Gender	[redacted]	0.115
Chad score	Chad score	[redacted]	0.055
Baseline SHD	Baseline SHD	[redacted]	0.141
Baseline CAD	Baseline CAD	[redacted]	0.147
Constant	Constant	[redacted]	0.490
Shape	Weibull shape	[redacted]	0.176

Treatment effect on discontinuation (OR)			
Beta Blocker		[redacted]	
Dronedarone		[redacted]	
Amiodarone		[redacted]	
Sotalol		[redacted]	
Class1c		[redacted]	
Rate of adverse events			
Cardiac events			
Beta Blocker		1.9%	
Dronedarone		[redacted]	
Amiodarone		[redacted]	
Sotalol		15.0%	
Class1c		7.0%	
Eye events (photophobia, blurred vision)			
Beta Blocker		0.6%	
Dronedarone		[redacted]	
Amiodarone		[redacted]	
Sotalol		2.6%	
Class1c		15.9%	
Gastrointestinal (diarrhea, nausea, vomiting)			
Beta Blocker		9.7%	
Dronedarone		[redacted]	
Amiodarone		[redacted]	
Sotalol		13.0%	
Class1c		8.9%	
Fatigue			
Beta Blocker		5.5%	
Dronedarone		[redacted]	
Amiodarone		[redacted]	
Sotalol		19.6%	
Class1c		7.7%	

Hepatic events			
Beta Blocker		2.4%	
Dronedarone		[redacted]	
Amiodarone		[redacted]	
Sotalol		0.0%	
Class1c		0.0%	
Hyperthyroidism			
Beta Blocker		0.4%	
Dronedarone		[redacted]	
Amiodarone		[redacted]	
Sotalol		2.6%	
Class1c		0.0%	
Hypothyroidism			
Beta Blocker		0.2%	
Dronedarone		[redacted]	
Amiodarone		[redacted]	
Sotalol		0.0%	
Class1c		0.0%	
Neurological events (tremor, sleep disorder)			
Beta Blocker		0.7%	
Dronedarone		[redacted]	
Amiodarone		[redacted]	
Sotalol		0.0%	
Class1c		4.7%	
Pulmonary (interstitial lung disease)			
Beta Blocker		0.2%	
Dronedarone		[redacted]	
Amiodarone		[redacted]	
Sotalol		0.0%	
Class1c		10.0%	
Skin events (photosensitivity, rash etc)			

Beta Blocker		1.7%	
Dronedarone		[redacted]	
Amiodarone		[redacted]	
Sotalol		0.0%	
Class1c		0.0%	
Days AE is assumed to incur utility detriment			
Cardiac events		28	
Eye events (photophobia, blurred vision)		28	
Fatigue		28	
Gastrointestinal (diarrhea, nausea, vomiting)		28	
Hepatic events		28	
Hyperthyroidism		Life time	
Hypothyroidism		Life time	
Neurological events (tremor, sleep disorder)		28	
Pulmonary (interstitial lung disease)		Life time	
Skin events (photosensitivity, rash etc)		28	
Unit costs	Class1c	**Av unit costs**	
% Patients receiving each concomitant medicine			
Beta-blocker		71	
Calcium antagonists		14	
Digitalis		14	
ACE inhibitors or ARB		70	
Statins		38	
Unit cost of concomitant medicine			
Beta-blocker		£0.03	
Calcium antagonists		£0.23	
Digitalis		£0.05	
ACE inhibitors or ARB		£0.03	
Statins		£0.05	
Events			
% of patients hospitalised on Adverse event			

Cardiac events (brady, tachy, proarrhythmia)		10%	
Eye events (photophobia, blurred vision)		0%	
Fatigue		0%	
Gastrointestinal (diarrhea, nausea, vomiting)		10%	
Hepatic events		100%	
Hyperthyroidism		10%	
Hypothyroidism		10%	
Neurological events (tremor, sleep disorder)		20%	
Pulmonary (dyspnea)		80%	
Skin events (photosensitivity, rash etc)		5%	
Unit cost of AE			
Cardiac events (brady, tachy, proarrhythmia)		£390	
Eye events (photophobia, blurred vision)		£154	
Fatigue		£158	
Gastrointestinal (diarrhea, nausea, vomiting)		£217	
Hepatic events		£919	
Hyperthyroidism		£552	
Hypothyroidism		£542	
Neurological events (tremor, sleep disorder)		£441	
Pulmonary (dyspnea)		£1,011	
Skin events (photosensitivity, rash etc)		£178	
Event costs	**Source**	**Cost 1 off or Daily**	
Ablation	UK ref costs (HRG: EA04z)	£3,137	
ACS	Palmer er al.	£4,568	
AF hospitalisation	UK ref costs (HRG: EA04z)	£1,154	
CHF (female acute)	Stewart et al. EJHF 2002	£4,765	
CHF (female ongoing)	Stewart et al. EJHF 2002	£5	
CHF (male acute)	Stewart et al. EJHF	£3,938	

	2002		
CHF (male ongoing)	Stewart et al. EJHF 2002	£4	
Cardioversion	Boodhoo et al, 2004	£373	
Stroke (acute cost)	Youman et al. Pharmacoeconomics 2003	£8,803	
Stroke (ongoing daily cost)	Youman et al. Pharmacoeconomics 2003	£10	
6 Months monitoring costs	**Treatment**	**Monitoring Costs**	
Dronedarone	Dronedarone	£0.00	
Amiodarone	Amiodarone	£51.92	
Sotalol	Sotalol	£75.71	
Class 1c*	Class 1c*	£75.71	
Treatment Initiation Costs			
Dronedarone	Dronedarone	£213	
Amiodarone	Amiodarone	£249	
Sotalol	Sotalol	£249	
Class 1c*	Class 1c*	£249	
Utility Scores			
Utility Base constant	Mean	1.061	0.045
Health state/disease condition			
Age		[redacted]	0.001
Gender		[redacted]	0.008
Stroke		[redacted]	0.036
CHF		[redacted]	0.014
ACS		[redacted]	0.047
Symptomatic AF		[redacted]	0.009
T*reatment related adverse event utility detriment*			
Paroxysmal patients			
Circulatory issues		0.010	

Dizziness		0.010	
Rash		0.030	
Liver deposits		0.030	
Sleep disturbances		0.040	
Fatigue		0.040	
Nausea		0.060	
Dermatological changes		0.060	
Hyperthyroidism		0.080	
Neuropathy		0.080	
Diarrhoea		0.080	
Optical issues		0.080	
Hypothyroidism		0.100	
Pulmonary issues		0.170	
Permanent			
Circulatory issues		0.020	
Dizziness		0.030	
Rash		0.030	
Liver deposits		0.030	
Sleep disturbances		0.040	
Fatigue		0.050	
Nausea		0.050	
Dermatological changes		0.090	
Hyperthyroidism		0.060	
Neuropathy		0.070	
Diarrhoea		0.080	
Optical issues		0.080	
Hypothyroidism		0.100	
Pulmonary issues		0.150	

Addendum: Updated Results 7th October 2009

Base-case analysis

The following results used the fixed random number seed 1, therefore it should be possible to replicate the results exactly if the appropriate functionality is used within the revised model.

Paroxysmal patient with no structural heart disease

The treatment pathway for these patients is for baseline therapy followed by either sotalol or class 1c 1st line anti-arrhythmic when an AAD is deemed needed and then amiodarone as 2nd line anti-arrhythmic.

Table 7.18: Cost effectiveness results for paroxysmal patients with no structural heart disease (dronedarone priced at £2.30 per day)

Pathway	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs	Cost per QALY gained
Position 1: – on top of standard baseline therapy ($CHADS_2 \geq 4$)					
Without Dronedarone	£3,445	4.18			
With Dronedarone	£6,891	4.62	£3,446	0.44	**£7,885**
Position 2: – Replacing Sotalol as 1st line AAD					
Without Dronedarone	£2,268	2.33			
With Dronedarone	£6,358	4.39	£4,091	2.07	**£1,980**
Position 3: – Replacing Class 1c as 1st line AAD					
Without Dronedarone	£4,085	4.17			
With Dronedarone	£6,166	4.27	£2,081	0.10	**£21,026**

Paroxysmal patient with coronary artery disease

The treatment pathway for these patients is for baseline therapy followed by either sotalol when an AAD is deemed needed and then amiodarone as 2nd line anti-arrhythmic.

Table 7.19: Cost effectiveness results for paroxysmal patients with coronary artery disease (dronedarone priced at £2.30 per day)

Pathway	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs	Cost per QALY gained
Position 1: – on top of standard baseline therapy ($CHADS_2 \geq 4$)					
Without Dronedarone	£4,619	4.12			
With Dronedarone	£8,031	4.54	£3,412	0.42	**£8,142**
Position 2: – Replacing Sotalol as 1st line AAD					
Without Dronedarone	£2,947	2.34			
With Dronedarone	£7,429	4.33	£4,482	2.00	**£2,246**

Paroxysmal patients with Left Ventricular Dysfunction.

The treatment pathway for these patients is for baseline therapy followed by amiodarone when an AAD is deemed needed. Patients in this scenario have better overall survival that the previous scenarios because they do not receive sotalol.

Table 7.20: Cost effectiveness results for paroxysmal patients with LVD (dronedarone priced at £2.30 per day)

Pathway	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs	Cost per QALY gained
Position 1: – on top of standard baseline therapy (CHADS$_2$≥ 4)					
Without Dronedarone	£3,321	4.23			
With Dronedarone	£6,745	4.66	£3,424	0.44	**£7,865**
Position 2: – Replacing Amiodarone as 1st line AAD					
Without Dronedarone	£2,618	3.14			
With Dronedarone	£6,251	4.47	£3,633	1.33	**£2,724**

Persistent patient with no structural heart disease.

The treatment pathway for these patients is for baseline therapy followed by sotalol or class 1c when AAD is deemed needed and then amiodarone as 2nd line anti-arrhythmic.

Table 7.20: Cost effectiveness results for persistent patients without SHD – (dronedarone priced at £2.30 per day)

Pathway	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs	Cost per QALY gained
Position 1: –on top of standard baseline therapy ($CHADS_2 \geq 4$)					
Without Dronedarone	£4,261	4.19			
With Dronedarone	£7,427	4.64	£3,167	0.45	**£7,007**
Position 2: – Replacing sotalol as 1st line AAD					
Without Dronedarone	£2,538	2.32			
With Dronedarone	£6,861	4.40	£4,324	2.08	**£2,082**
Position 3: – Replacing class 1c as 1st line AAD					
Without Dronedarone	£4,492	4.17			
With Dronedarone	£6,661	4.27	£2,169	0.10	**£21,770**

Persistent patients with structural heart disease.

The treatment pathway for these patients is for baseline therapy followed by amiodarone when an AAD is deemed needed.

Table 7.22: Cost effectiveness results for persistent patients with SHD (dronedarone priced at £2.30 per day)

Pathway	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs	Cost per QALY gained
Position 1: – on top of standard baseline therapy (CHADS$_2$ ≥ 4)					
Without Dronedarone	£4,660	4.16			
With Dronedarone	£7,680	4.58	£3,020	0.42	**£7,163**
Position 2: – Replacing amiodarone as 1st line AAD					
Without Dronedarone	£3,230	3.14			
With Dronedarone	£7,308	4.42	£4,078	1.28	**£3,185**

Addendum: Updated Results 20th November 2009

Base-case analysis: Dronedarone price of £2.25 per day

The following results use the revised Simul8 model and excel spreadsheet submitted to NICE on the 7th October 2009. The model uses the fixed random number seed 1, therefore it should be possible to replicate the results exactly if the appropriate functionality is used within the revised model.

Please note that the ERG made a couple of further revisions to the model as noted in their report on page 101 – 103. These have not been incorporated within the results presented below. However it is worth noting that with the confirmed price of £2.25, if the ERG reran the analysis based on their revised model the ICERs would be more favourable to dronedarone than those presented below. This is especially apparent given the technical error spotted by the ERG which means the results previously presented by sanofi-aventis and the results below only assume a two-year mortality benefit rather than a lifetime mortality benefit. When the ERG group revised the model to take this into account their resulting ICERs were even more in favour of dronedarone.

Paroxysmal patient with no structural heart disease

The treatment pathway for these patients is for baseline therapy followed by either sotalol or class 1c 1st line anti-arrhythmic when an AAD is deemed needed and then amiodarone as 2nd line anti-arrhythmic.

Table 7.18: Cost effectiveness results for paroxysmal patients with no structural heart disease (dronedarone priced at £2.25 per day)

Pathway	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs	Cost per QALY gained
Position 1: – on top of standard baseline therapy ($CHADS_2 \geq 4$)					
Without Dronedarone	£3,445	4.18			
With Dronedarone	£6,777	4.62	£3,332	0.44	**£7,625**
Position 2: – Replacing Sotalol as 1st line AAD					
Without Dronedarone	£2,268	2.33			
With Dronedarone	£6,253	4.39	£3,986	2.07	**£1,929**
Position 3: – Replacing Class 1c as 1st line AAD					
Without Dronedarone	£4,085	4.17			
With Dronedarone	£6,065	4.27	£1,980	0.10	**£20,003**

Paroxysmal patient with coronary artery disease

The treatment pathway for these patients is for baseline therapy followed by either sotalol when an AAD is deemed needed and then amiodarone as 2nd line anti-arrhythmic.

Table 7.19: Cost effectiveness results for paroxysmal patients with coronary artery disease (dronedarone priced at £2.25 per day)

Pathway	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs	Cost per QALY gained
Position 1: – on top of standard baseline therapy ($CHADS_2 \geq 4$)					
Without Dronedarone	£4,619	4.12			
With Dronedarone	£7,926	4.54	£3,307	0.42	**£7,890**
Position 2: – Replacing Sotalol as 1st line AAD					
Without Dronedarone	£2,947	2.34			
With Dronedarone	£7,331	4.33	£4,384	2.00	**£2,197**

Paroxysmal patients with Left Ventricular Dysfunction.

The treatment pathway for these patients is for baseline therapy followed by amiodarone when an AAD is deemed needed. Patients in this scenario have better overall survival that the previous scenarios because they do not receive sotalol.

Table 7.20: Cost effectiveness results for paroxysmal patients with LVD (dronedarone priced at £2.25 per day)

Pathway	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs	Cost per QALY gained
Position 1: – on top of standard baseline therapy (CHADS$_2$≥ 4)					
Without Dronedarone	£3,321	4.23			
With Dronedarone	£6,632	4.66	£3,310	0.44	**£7,604**
Position 2: – Replacing Amiodarone as 1st line AAD					
Without Dronedarone	£2,618	3.14			
With Dronedarone	£6,146	4.47	£3,528	1.33	**£2,645**

Persistent patient with no structural heart disease.

The treatment pathway for these patients is for baseline therapy followed by sotalol or class 1c when AAD is deemed needed and then amiodarone as 2nd line anti-arrhythmic.

Table 7.20: Cost effectiveness results for persistent patients without SHD – (dronedarone priced at £2.25 per day)

Pathway	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs	Cost per QALY gained
Position 1: –on top of standard baseline therapy ($CHADS_2 \geq 4$)					
Without Dronedarone	£4,261	4.19			
With Dronedarone	£7,314	4.64	£3,053	0.45	**£6,757**
Position 2: – Replacing sotalol as 1st line AAD					
Without Dronedarone	£2,538	2.32			
With Dronedarone	£6,757	4.40	£4,219	2.08	**£2,031**
Position 3: – Replacing class 1c as 1st line AAD					
Without Dronedarone	£4,492	4.17			
With Dronedarone	£6,561	4.27	£2,069	0.10	**£20,761**

Persistent patients with structural heart disease.

The treatment pathway for these patients is for baseline therapy followed by amiodarone when an AAD is deemed needed.

Table 7.22: Cost effectiveness results for persistent patients with SHD (dronedarone priced at £2.25 per day)

Pathway	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs	Cost per QALY gained
Position 1: – on top of standard baseline therapy ($CHADS_2 \geq 4$)					
Without Dronedarone	£4,660	4.16			
With Dronedarone	£7581	4.58	£2,921	0.42	**£7,163**
Position 2: – Replacing amiodarone as 1st line AAD					
Without Dronedarone	£3,230	3.14			
With Dronedarone	£7,216	4.42	£3,986	1.28	**£3,113**