sanofi aventis
Because health matters

Meindert Boysen,
The National Institute for Health and Clinical Excellence,
MidCity Place,
71 High Holborn,
London,
WC1V 6NA.

5th November 2009.

Dear Meindert,

Single Technology Appraisal of dronedarone: factual inaccuracies within the ERG report

Please find attached a document that outlines the factual inaccuracies contained within the ERG report for dronedarone.

Sanofi-aventis believe the ERG have done a thorough job in reviewing the evidence and have highlighted the key issue that dronedarone spares patients from mortality risk and risk of stroke, especially as the safety profile of currently available antiarrhythmic drugs is not optimal, with some actually increasing the risk of mortality. Sanofi-aventis would also like to point out the extension of the sensitivity analysis within the ERG report, around the mortality benefits, reinforces our own conclusion that the results of the economic analysis are robust.

Sanofi-aventis would also like to explain the reason for there being no distinction between Atrial Fibrillation and Atrial Flutter (AF/AFL) is that our submission was made prior to CHMP opinion and as such we are only now in a position to confirm our indication as per the SpC:
"MULTAQ is indicated in adult clinically stable patients with a history of, or current non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate."

Should you require anything further please do not hesitate to contact me.

Yours sincerely,

Philip Booth
Head of Health Outcomes
sanofi-aventis UK

National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Dronedarone for the treatment of atrial fibrillation and atrial flutter

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from *Centre for Reviews and Dissemination (CRD), Centre for Health Economics (CHE)* to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 5pm, 5th November 2009 using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

29th October 2009

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment
Page 10, paragraph 4, line 3 (also p26, paragraph 3) – notes 39 studies eligible for inclusion with reference to meta-analysis.	"A total of **72** studies were considered eligible for inclusion from the systematic review, however the number of studies included for subsequent analyses were dictated by the specific outcome of interest."	From the systematic review a total of 72 studies were identified as eligible for inclusion in subsequent analyses however the actual number included did depend on the specific outcome of interest which was noted in the associated appendices to support each outcome (appendices 5 – 9).

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment
Page 11, paragraph 3, line 3 – Factually inaccurate comparator named.	"Only limited data from 4 studies was available for stroke, including 2 RCTs of dronedarone versus control, 1 RCT of dronedarone versus amiodarone and 1 RCT comparing sotalol versus **amiodarone versus control**."	This should read 1 RCT comparing sotalol versus amiodarone versus control as this refers to the 3-arm SAFE-T study.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment
Page 11, paragraph 2 – sanofi-aventis feel this sentence is open to misinterpretation.	"..**this was not statistically significant in the moderate to high risk ATHENA population.**"	If the ERG report is referring to the full ATHENA population then it would be more appropriate to state ".this was not statistically significant in the moderate to high risk ATHENA population." If the high risk population is the CHADS2≥ 4 sub-population then there was a statistically significant difference in all-cause mortality.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment
Page 13, 1.4.2, line 2 – The inclusion/exclusion criteria were not explicitly stated, this comment is not factually correct.	"The systematic review produced by the manufacturer appeared comprehensive; the inclusion/exclusion criteria applied to studies to be included in direct and indirect analysis were not fully explicit in the submission but were provided in subsequent reports."	Within the main submission information was provided on inclusion criteria (page 51) and additional information providing full clarity was provided on the 8th September (Protocol v4.doc).

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment
Page 14, paragraph 1 – "Finally, there was inconsistent use of continuity corrected data and inconsistency in the use of time points. " This is incorrect following information submitted.	When appropriate a continuity correction was used and data provided on different time-points.	Sanofi-aventis believe that when possible the continuity corrected data and all appropriate time-point data was provided in supporting appendices (appendices 5 – 9; for example, please see appendix 6, Table 7, 9, 11, 13 etc which provide the Peto Odds Ratio, the Peto OR with continuity correction and the random effects OR for different time periods when data allowed).

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment
Page 14, paragraph 2, last sentence – sanofi-aventis consider that the lower risk and younger AF population have been considered in the submission.	"Exchangeability of this study with lower risk and younger AF populations has been considered within the submission.	Sanofi-aventis feel the lower risk and younger AF population have been considered. The ATHENA sub-group analysis (page 38 of the submission, Figure 6.1) considers this within the specific trial population, while the univariate sensitivity analysis for the economic model detailed in Appendix 20

		considered CHADS2 scores 0 – 6 and age of 65 therefore considering the lower risk and younger AF population

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment
Page 16, paragraph 1 – sanofi-aventis consider that the ERG has not been clear what they define as efficacy within this first statement. The third sentence is also incomplete.	Quantification of "relative efficacy". Completion of third sentence required	This will allow further understanding as to the ERG's thoughts regarding the relative efficacy of dronedarone compared to other AAD's.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment
Page 18, paragraph 2, last sentence – monitoring costs have been defined.	"…monitoring costs assumed for dronedarone are **defined in the draft SpC for dronedarone were it is specified that there are no monitoring requirements post initiation follow-up**."	Within the manufacturer submission (page 90) it is stated that there are no requirements for monitoring with dronedarone outside of the initiation follow-up as per the draft SpC. Sanofi-aventis feel it is therefore incorrect to assume uncertainty around the monitoring of dronedarone.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment
Page 23, paragraph 2, last line – this	"…Class 1c anti-arrhythmic agents (flecainide **and**	This is factually incorrect and current only

sentence is factually incorrect.	**propafenone**); **amiodarone** and sotalol.”	notes flecainide and sotalol.

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment
Page 27, paragraph 1, last sentence – point of accuracy.	“Outcomes of interest included mortality, stroke, AF recurrence, treatment withdrawals (**due to any cause and due to AE’s)** and serious adverse effects (SAEs).”	For accuracy this should identify that there were 2 aspects of treatment withdrawal considered – due to any cause and specifically due to AE’s.

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment
Page 27, paragraph 1, this sentence could be misleading.	….in adult participants with any type of AF, **and where patients had had cardiac surgery that was more than 3 months prior to inclusion.**	Current wording might suggest that all patients had to have had cardiac surgery which is misleading.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment
Page 28, paragraph 2, line 7 states there is no equivalent table of the smaller number of trials that are actually considered in the submission.	**“Supplementary information was provided within appendices and additional submitted reports.”**	Within the appendices of the submission (appendices 5-9), tables did list the specific trials that were used for each outcome considered. Additional data was also provided on treatment arms, patient numbers etc to supplement this information (MA_MTC Tables 22Sept09.doc, submitted with initial clarification questions).

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment
Page 31, paragraph 1, last sentence – However, data provided to the ERG would indicate …. Not factually accurate	**"…would indicate that most patients had asymptomatic (or at least no troublesome) non-permanent AF."**	Based on the submitted abstract from Page et al. this post-hoc analysis was only able to make a distinction between non-permanent and permanent patients (those with AF/AFL at every baseline ECG). It is not possible from this information to infer that most patients had asymptomatic paroxysmal AF as it is impossible to identify paroxysmal or persistent patients

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment
Page 31, paragraph 4, last sentence – support the suggestion that dronedarone may be used in moderate to high-risk elderly AF patients who may not benefit from other AADs.	**"…dronedarone may be used for patients with multiple CV risk factors (corresponding to a CHADS2 ≥4) on top of standard baseline therapy."**	It has never been suggested that dronedarone may be used in moderate to high risk elderly AF patients who may not benefit from other AADs. Our suggestion is that in patients with a higher CV risk profile as indicated by a CHADS2≥ 4, the addition of dronedarone to standard therapy at an early stage might bring benefit.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment
Page 36, all-cause mortality, line 7 – data was provided to allow for interpretation.	"**The data provided in the supporting appendix provided information on the available time-points for each individual trial considered and also the time criteria used for each presentation of results"**	The time point for the analysis is available within the associated appendix (appendix 6). For example for sotalol versus non-active control, the time-point for all studies plus

		number of events are listed in Table 8 and of the 3 meeting the 12 month criteria plus events, the results are shown in Figure 2 (pages 6 – 8).

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment
Page 37, paragraph 1, line 3 – point of correction regarding the studies in which there were zero events of mortality in both study arms.	**"Furthermore, having specified in their methods that such trials would be included, studies in which there were zero events of mortality in both study arms were excluded from the MTC analysis. However, the meta-analyses and indirect comparisons present the results both excluding these trials and including them using the continuity correction."**	Studies in which there were zero events of mortality in both study arms were excluded from the MTC analysis however both meta-analyses and indirect comparisons present the results both excluding these trials or including them using the continuity correction (please see appendix 6, e.g. Table 7, 9, 13 etc).

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment
Page 41, MTC, paragraph 3, line 8 – factual correction regarding "either with an untreated control group or an alternative target pharmaceutical with at least 100 subjects".	"…either with an untreated control group or an alternative target pharmaceutical with at least 100 subjects **with a stepwise approach.**"	Sanofi-aventis consider it to be factually correct to include "with stepwise approach".

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment
Page 42, paragraph 2, 1st sentence – factual correction regarding "Details of the	"Details of the complete data set (before any studies were lost due to convergence problems) together with the *a priori*	Full descriptive information for each outcome was provided in the appendices (appendices

complete data set (before any studies were lost due to convergence problems) together with the *a priori* inclusion criteria were not provided to the ERG".	inclusion criteria were provided to the ERG **within appendices 5-9.**"	5 – 9).

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment
Page 50, paragraph 2, line 4 – factual correction regarding "appears to have the smallest effect size"	"appears to have the smallest effect size **and smallest confidence intervals**"	Point of factual correction.

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment
Page 51, third bullet – factual correction regarding "use of continuity corrected data was inconsistently applied in the submission".	"Use of continuity corrected data was **consistently** applied in the submission."	Sanofi-aventis consider that each direct and indirect analysis presents all the results with and without continuity correction for each outcome (appendices 5 – 9) therefore the continuity correction was consistently used for direct and indirect comparison.

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment
Page 56, paragraph 1, line 2 – factual correction regarding "Withdrawals are very important in determining the efficacy of dronedarone compared to other drugs. This is because dronedarone is less effective	"Withdrawals, **including a combination of lack of efficacy and adverse events,** are very important in determining the efficacy of dronedarone compared to other drugs. This is because dronedarone is less effective than amiodarone, sotalol or class 1 c agents at reducing AF recurrence. However	Sanofi-aventis consider that to make this comment factual accurate it would be appropriate to note that withdrawals include a combination of lack of efficacy and adverse events.

than amiodarone, sotalol or class 1 c agents at reducing AF recurrence. However this might be counterbalanced by a better tolerability profile".	this might be counterbalanced by a better tolerability profile".	

Issue 22

Description of problem	Description of proposed amendment	Justification for amendment
Page 61, 1st bullet point – factual correction regarding "The main concern with regard to the synthesis of SAEs was the omission of EURIDIS/ADONIS serious adverse event data from the analysis"	There is no published information on the SAEs within the EURIDIA/ADONIS trial which is unfortunate when considering the serious adverse event data available.	The SAE data from EURIDIS/ADONIS was not omitted from the meta-analysis as it was not reported in the publication.

Issue 23

Description of problem	Description of proposed amendment	Justification for amendment
Page 61, paragraph 2 – factual correction regarding "However, the omission of data from the EURIDIS/ADONIS trial, which was a large good quality RCT with a population that reflects that of the licensed indication, means that there is uncertainty in this conclusion".	"However**,** SAEs were not reported in the EURIDIS/ADONIS trial publication. While this was a large good quality RCT with a population that reflects that of the licensed indication, this lack of reporting means that there may be some uncertainty in this conclusion".	See Issue 21

Issue 24

Description of problem	Description of proposed amendment	Justification for amendment
Page 63 – factual correction regarding "unspecified study inclusion/.exclusion criteria for direct and indirect".	"Study inclusion/.exclusion criteria for direct and indirect analyses used in the submission **were partially specified in the manufacturer's submission and more fully explained**	The inclusion criteria were specified in the full submission page 51, Table 6.8 and within additional documentation provided to the

	with additional documentation provided upon request".	ERG upon request (Protocol v4.doc provided 8th September 2009).

Issue 25

Description of problem	Description of proposed amendment	Justification for amendment
Page 63 – factual correction regarding – "Lack of exploration … inconsistent use of continuity corrected … inconsistent use of time point".	A lack of full clarity on the exploration of clinical and statistical heterogeneity etc. A lack of full clarity on the use of continuity corrected data A lack of full clarity on the use of time points	Given the volume of information from the systematic review, meta-analysis and MTC there may be an issue of clarity but sanofi-aventis feel that all of the issues raised have been addressed but are perhaps not obvious in the submitted documentation (for example please see issue 5 on continuity correction and time-points).

Issue 26

Description of problem	Description of proposed amendment	Justification for amendment
Page 89, 5.2.4 Adverse events, line 4 – factual correction regarding "the rationale for this is not clear".	"The rationale for this **has been explained by the manufacturer, individual adverse events data were not available from the meta-analysis and MTC analysis hence the use of alternative sources to populate the economic model for adverse events**."	In the manufacturer submission section 7.2.7.4, page 93 it clearly states that the individual adverse events data were not available from the meta-analysis and MTC analysis hence the use of alternative sources to populate the economic model for adverse events.

National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

ERG responses to 'Factual Errors' in ERG report 12th November 2009

Dronedarone for the treatment of atrial fibrillation and atrial flutter

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10, paragraph 4, line 3 (also p26, paragraph 3) – notes 39 studies eligible for inclusion with reference to meta-analysis.	"A total of **72** studies were considered eligible for inclusion from the systematic review, however the number of studies included for subsequent analyses were dictated by the specific outcome of interest."	From the systematic review a total of 72 studies were identified as eligible for inclusion in subsequent analyses however the actual number included did depend on the specific outcome of interest which was noted in the associated appendices to support each outcome (appendices 5 – 9).	We do not accept this. The ERG checked all 72 studies against those included in analyses presented in the submission and appendices 5-9. Of the 72 studies only 39 were eligible for the analyses presented in the submission or in appendices 5-9.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11, paragraph 3, line 3 – Factually inaccurate comparator named.	"Only limited data from 4 studies was available for stroke, including 2 RCTs of dronedarone versus control, 1 RCT of dronedarone versus amiodarone and 1 RCT comparing sotalol versus **amiodarone versus control**."	This should read 1 RCT comparing sotalol versus amiodarone versus control as this refers to the 3-arm SAFE-T study.	Agree

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 11, paragraph 2 – sanofi-aventis feel this sentence is open to misinterpretation.	"..**this was not statistically significant in the moderate to high risk ATHENA population.**"	If the ERG report is referring to the full ATHENA population then it would be more appropriate to state ".this was not statistically significant in the moderate to high risk ATHENA population." If the high risk population is the CHADS2≥ 4 sub-population then there was a statistically significant difference in all-cause mortality.	Agree

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13, 1.4.2, line 2 – The inclusion/exclusion criteria were not explicitly stated, this comment is not factually correct.	"The systematic review produced by the manufacturer appeared comprehensive; the inclusion/exclusion criteria applied to studies to be included in direct and indirect analysis were not fully explicit in the submission but were provided in subsequent reports."	Within the main submission information was provided on inclusion criteria (page 51) and additional information providing full clarity was provided on the 8th September (Protocol v4.doc).	We do not accept this. Whilst the inclusion and exclusion criteria are explicitly stated in the protocol they are for the broader Abacus systematic review, and not for the analyses presented in the submission or appendices 5 to 9.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14, paragraph 1 – "Finally, there was inconsistent use of continuity corrected data and inconsistency in the use of time points. " This is incorrect following information submitted.	When appropriate a continuity correction was used and data provided on different time-points.	Sanofi-aventis believe that when possible the continuity corrected data and all appropriate time-point data was provided in supporting appendices (appendices 5 – 9; for example, please see appendix 6, Table 7, 9, 11, 13 etc which provide the Peto Odds Ratio, the Peto OR with continuity correction and the random effects OR for different time periods when data allowed).	There was inconsistency, sometimes across analyses, sometimes regarding which result was presented in the body of the submission

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14, paragraph 2, last sentence – sanofi-aventis consider that the lower risk and younger AF population have been considered in the submission.	"Exchangeability of this study with lower risk and younger AF populations has been considered within the submission.	Sanofi-aventis feel the lower risk and younger AF population have been considered. The ATHENA sub-group analysis (page 38 of the submission, Figure 6.1) considers this within the specific trial population, while the univariate sensitivity analysis for the economic model detailed in Appendix 20 considered CHADS2 scores 0 – 6 and age of 65 therefore considering the lower risk and younger AF population	While we acknowledge that the manufacturer has partially considered this issue, we do not consider that these analyses are sufficient. The subgroup analysis referred to is for the primary 'composite' outcome from ATHENA not the individual endpoints which were used in the economic model. Similarly, the univariate sensitivity analyses employed only considered variation in the baseline risk (primarily using the ATHENA study) and not in the relative effect estimates.

			ERG proposed amendment: "Exchangeability of this study with lower risk and younger AF populations has not been fully considered within the submission."

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16, paragraph 1 – sanofi-aventis consider that the ERG has not been clear what they define as efficacy within this first statement. The third sentence is also incomplete.	Quantification of "relative efficacy". Completion of third sentence required	This will allow further understanding as to the ERG's thoughts regarding the relative efficacy of dronedarone compared to other AAD's.	This was a general statement across all outcomes to capture the findings that dronedarone is less efficacious in preventing AF recurrence, that it is unclear how it compares with other drugs regarding rate control, cv hospitalisation, mortality and withdrawals. The third sentence of the paragraph has been deleted.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 18, paragraph 2, last sentence – monitoring costs have been defined.	"…monitoring costs assumed for dronedarone are **defined in the draft SpC for dronedarone were it is specified that there are no**	Within the manufacturer submission (page 90) it is stated that there are no requirements for monitoring with	There may not be uncertainty around the monitoring costs of dronedarone as specified in the

	monitoring requirements post initiation follow-up."	dronedarone outside of the initiation follow-up as per the draft SpC. Sanofi-aventis feel it is therefore incorrect to assume uncertainty around the monitoring of dronedarone.	draft SpC but there remains uncertainty about the differential monitoring costs between treatments. ERG proposed amendment: "Finally, the lower initiation costs assumed for dronedarone and differential monitoring costs between treatments are uncertain, although these do not appear to have a significant impact on the final ICER results."

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23, paragraph 2, last line – this sentence is factually incorrect.	"…Class 1c anti-arrhythmic agents (flecainide **and propafenone**); **amiodarone** and sotalol."	This is factually incorrect and current only notes flecainide and sotalol.	Agree

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 27, paragraph 1, last sentence – point of accuracy.	"Outcomes of interest included mortality, stroke, AF recurrence, treatment withdrawals (**due to any cause and due to AE's)** and serious adverse effects (SAEs)."	For accuracy this should identify that there were 2 aspects of treatment withdrawal considered – due to any cause and specifically due to AE's.	Agree

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 27, paragraph 1, this sentence could be misleading.	….in adult participants with any type of AF, **and where patients had had cardiac surgery that was more than 3 months prior to inclusion.**	Current wording might suggest that all patients had to have had cardiac surgery which is misleading.	Agree

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 28, paragraph 2, line 7 states there is no equivalent table of the smaller number of trials that are actually considered in the submission.	**"Supplementary information was provided within appendices and additional submitted reports."**	Within the appendices of the submission (appendices 5-9), tables did list the specific trials that were used for each outcome considered. Additional data was also provided on treatment arms, patient numbers etc to supplement this information (MA_MTC Tables 22Sept09.doc, submitted with initial clarification questions).	We reject this correction. No equivalent table was provided and if the pertinent information was provided it was very hard to find.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 31, paragraph 1, last sentence – However, data provided to the ERG would indicate …. Not factually accurate	**"…would indicate that most patients had asymptomatic (or at least no troublesome) non-permanent AF."**	Based on the submitted abstract from Page et al. this post-hoc analysis was only able to make a distinction between non-permanent and permanent patients (those with AF/AFL at every baseline ECG). It is not possible from this information	Agree

		to infer that most patients had asymptomatic paroxysmal AF as it is impossible to identify paroxysmal or persistent patients	

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 31, paragraph 4, last sentence – support the suggestion that dronedarone may be used in moderate to high-risk elderly AF patients who may not benefit from other AADs.	**"…dronedarone may be used for patients with multiple CV risk factors (corresponding to a CHADS2 ≥4) on top of standard baseline therapy."**	It has never been suggested that dronedarone may be used in moderate to high risk elderly AF patients who may not benefit from other AADs. Our suggestion is that in patients with a higher CV risk profile as indicated by a CHADS2≥ 4, the addition of dronedarone to standard therapy at an early stage might bring benefit.	Agree

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 36, all-cause mortality, line 7 – data was provided to allow for interpretation.	"**The data provided in the supporting appendix provided information on the available time-points for each individual trial considered and also the time criteria used for each presentation of results"**	The time point for the analysis is available within the associated appendix (appendix 6). For example for sotalol versus non-active control, the time-point for all studies plus number of events are listed in Table 8 and of the 3 meeting the 12 month criteria plus events, the results are shown in Figure 2 (pages 6 – 8).	It was not clear if the criterion referred to the 12 month time point only or at least 12 months and there was some inconsistency across analyses.

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 37, paragraph 1, line 3 – point of correction regarding the studies in which there were zero events of mortality in both study arms.	**"Furthermore, having specified in their methods that such trials would be included, studies in which there were zero events of mortality in both study arms were excluded from the MTC analysis. However, the meta-analyses and indirect comparisons present the results both excluding these trials and including them using the continuity correction."**	Studies in which there were zero events of mortality in both study arms were excluded from the MTC analysis however both meta-analyses and indirect comparisons present the results both excluding these trials or including them using the continuity correction (please see appendix 6, e.g. Table 7, 9, 13 etc).	Agree

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 41, MTC, paragraph 3, line 8 – factual correction regarding "either with an untreated control group or an alternative target pharmaceutical with at least 100 subjects".	"…either with an untreated control group or an alternative target pharmaceutical with at least 100 subjects **with a stepwise approach.**"	Sanofi-aventis consider it to be factually correct to include "with stepwise approach".	Agree

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 42, paragraph 2, 1st sentence – factual correction regarding "Details of the complete data set (before any studies were	"Details of the complete data set (before any studies were lost due to convergence problems) together with the *a priori* inclusion criteria were provided to the ERG **within**	Full descriptive information for each outcome was provided in the appendices (appendices 5 – 9).	We do not accept this correction. The MTC data sets appeared to include trials that were not included in the direct

lost due to convergence problems) together with the *a priori* inclusion criteria were not provided to the ERG".	**appendices 5-9.**"		and indirect analyses.

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 50, paragraph 2, line 4 – factual correction regarding "appears to have the smallest effect size"	"appears to have the smallest effect size **and smallest confidence intervals**"	Point of factual correction.	Accept this with a small amendment "appears to have the smallest effect size ***albeit with the*** smallest confidence intervals"

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 51, third bullet – factual correction regarding "use of continuity corrected data was inconsistently applied in the submission".	"Use of continuity corrected data was **consistently** applied in the submission."	Sanofi-aventis consider that each direct and indirect analysis presents all the results with and without continuity correction for each outcome (appendices 5 – 9) therefore the continuity correction was consistently used for direct and indirect comparison.	We do not agree. The continuity correction was not used in the MTC. Furthermore, even though in the direct and indirect analysis results in the appendices were presented with and without the continuity correction which of these was presented in the body of the submission was not consistent nor was it specified.

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 56, paragraph 1, line 2 – factual correction regarding "Withdrawals are very important in determining the efficacy of dronedarone compared to other drugs. This is because dronedarone is less effective than amiodarone, sotalol or class 1 c agents at reducing AF recurrence. However this might be counterbalanced by a better tolerability profile".	"Withdrawals, **including a combination of lack of efficacy and adverse events,** are very important in determining the efficacy of dronedarone compared to other drugs. This is because dronedarone is less effective than amiodarone, sotalol or class 1 c agents at reducing AF recurrence. However this might be counterbalanced by a better tolerability profile".	Sanofi-aventis consider that to make this comment factual accurate it would be appropriate to note that withdrawals include a combination of lack of efficacy and adverse events.	Agree

Issue 22

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 61, 1st bullet point – factual correction regarding "The main concern with regard to the synthesis of SAEs was the omission of EURIDIS/ADONIS serious adverse event data from the analysis"	There is no published information on the SAEs within the EURIDIA/ADONIS trial which is unfortunate when considering the serious adverse event data available.	The SAE data from EURIDIS/ADONIS was not omitted from the meta-analysis as it was not reported in the publication.	The ERG questions the requirement for published data. Why were they not used and included as CIC?

Issue 23

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 61, paragraph 2 – factual correction regarding "However, the	"However**,** SAEs were not reported in the EURIDIS/ADONIS trial publication. While this	See Issue 21	The ERG questions the requirement for published

omission of data from the EURIDIS/ADONIS trial, which was a large good quality RCT with a population that reflects that of the licensed indication, means that there is uncertainty in this conclusion".	was a large good quality RCT with a population that reflects that of the licensed indication, this lack of reporting means that there may be some uncertainty in this conclusion".		data. Why were they not used and included as CIC?

Issue 24

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 63 – factual correction regarding "unspecified study inclusion/.exclusion criteria for direct and indirect".	"Study inclusion/.exclusion criteria for direct and indirect analyses used in the submission **were partially specified in the manufacturer's submission and more fully explained with additional documentation provided upon request".**	The inclusion criteria were specified in the full submission page 51, Table 6.8 and within additional documentation provided to the ERG upon request (Protocol v4.doc provided 8th September 2009).	See ERG response to issue 4

Issue 25

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 63 – factual correction regarding – "Lack of exploration … inconsistent use of continuity corrected … inconsistent use of time point".	A lack of full clarity on the exploration of clinical and statistical heterogeneity etc. A lack of full clarity on the use of continuity corrected data A lack of full clarity on the use of time points	Given the volume of information from the systematic review, meta-analysis and MTC there may be an issue of clarity but sanofi-aventis feel that all of the issues raised have been addressed but are perhaps not obvious in the submitted documentation (for example please see issue 5 on continuity correction and time-	We reject these corrections. There was no exploration of statistical heterogeneity in any analysis. We believe the use of time points and the continuity correction was inconsistent.

		points).	

Issue 26

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 89, 5.2.4 Adverse events, line 4 – factual correction regarding "the rationale for this is not clear".	"The rationale for this **has been explained by the manufacturer, individual adverse events data were not available from the meta-analysis and MTC analysis hence the use of alternative sources to populate the economic model for adverse events**."	In the manufacturer submission section 7.2.7.4, page 93 it clearly states that the individual adverse events data were not available from the meta-analysis and MTC analysis hence the use of alternative sources to populate the economic model for adverse events.	We agree that justification was provided for why data from the MTC were not used, however, justification was not provided for the approach which was subsequently employed by the manufacturer and the different sources used for the alternative comparators. ERG proposed amendment: "Although the rationale for this has been explained by the manufacturer (i.e. individual adverse events data were not available from the meta-analysis and MTC analysis), adequate justification for the different approaches and sources subsequently used to populate the economic model for adverse events were not provided."