Manufacturer Response to the ACD - dabigatran etexilate for stroke prevention in atrial fibrillation

Please consider this document as Boehringer Ingelheim's formal response to the Appraisal Consultation Document (ACD) resulting from the 1st Appraisal Committee meeting for the Single Technology Appraisal (STA) of dabigatran etexilate for the prevention of stroke in atrial fibrillation.

This response is split into three sections.

Firstly, in **Table 1** we list the instances in the ACD that we believe to be either typographical error, factually inaccurate or potentially misleading to the reader. These comments are generally limited to Sections 2 and 3 of the ACD since Section 4 is a reflection of the Committee's deliberations, and therefore cannot by definition be factually inaccurate. We would be extremely grateful if these comments could be given serious consideration during the formulation of the Final Appraisal Determination (FAD).

Secondly, we provide further clarification and detail regarding the sequence dosing regimen. The purpose of this section is to state for the record the process, as seen from our perspective, that led to the confusion surrounding this issue at the 1st Committee Meeting.

Thirdly, we include for completeness our previously submitted response to the request for further information as laid out in the ACD.

Therefore this document in its totality can be regarded as our full response to the ACD. We welcome the opportunity to submit this response and look forward to the ensuing discussions at the next Committee meeting on September 20th.

ACD "Fact Check"

Table 1 presents the instances in the ACD that we believe to be either typographical error, factually inaccurate or potentially misleading to the reader. We would be grateful if these comments could be reflected in the FAD.

Boehringer Ingelheim

Table 1 "Fact Check" Comments on the ACD

Comment	Page number	Section	Text in question	Proposed correction	Rationale/other information
1	4	2.1	"…is an orally administered anticoagulant that inhibits the formation of the thrombin enzyme."	"…is an orally administered anticoagulant that inhibits the ~~formation of the~~ thrombin enzyme."	
2	5	2.3	"The most frequently observed adverse events…"	"The most common ~~frequently observed~~ adverse events…"	
3	5	2.3	"…and comes in packs of 10, 30, 60 and 180 capsules."	"…and comes in packs of ~~10, 30,~~ 60 ~~and 180~~ capsules."	Whilst all these pack sizes are licenced in Europe, in the UK only 60 x 110mg and 60 x 150mg packs are currently planned to be available for this indication.
4	5	2.3	"…a pack of 60 tablets…"	"…a pack of 60 capsules ~~tablets~~…"	
5	6	3.2	"…left atrial ejection fraction…"	"…left ventricular ~~atrial~~ ejection fraction…"	
6	8	3.5	"[…] and dabigatran 110 mg twice daily failed to show non-inferiority for ischaemic stroke at the lower margin of 1.38."	This statement is invalid and should be deleted.	The FDA non-inferiority margin was set for the primary endpoint (composite of stroke and systemic embolism) only and does not apply to ischemic stroke as a single endpoint, as power is clearly lower for this endpoint. This renders the statement invalid.
7	8	3.5	"HR = 1.27, 95 % CI 0.96 to 1.75 [150 mg twice daily])."	"HR = 1.27, 95 % CI 0.94 to 1.71 [150 mg twice daily])."	Typographical error.
8	12	3.13	"Therefore, the sequential regimen model resulted in two sets of outputs: a sequential regimen model for people under 80 years and a sequential regimen model for those 80 years or older. "	"Therefore, the sequential regimen model resulted in two sets of outputs: a sequential regimen model for people starting under 80 years (incorporating a life-time horizon including the switch to 110 mg bid at age 80) and a sequential regimen model for those starting at 80 years or older."	It is important that the sequential analysis is correctly described. As it stands the reader could interpret that the first set of outputs is truncated at age 80 years. This is not the case.
9	13	3.17	"The incremental cost-effectiveness ratios (ICERs) for the dabigatran sequential regimen in people under 80 years and the sequential regimen in people over 80 years compared with warfarin were £7314 and £7873 per QALY gained respectively."	"The incremental cost-effectiveness ratios (ICERs) for the dabigatran sequential regimen in which people started under 80 years and continued life-long, and the sequential regimen in people ~~over~~ starting at age 80 years compared with warfarin were £7314 and £7873 per QALY gained respectively."	As comment 8 above.

10	13-14	3.17	"An incremental analysis presented by the manufacturer showed that dabigatran 110 mg twice daily and the dabigatran sequential regimen were both dominated by the 150 mg twice daily dose because they had the same cost but lower efficacy than the 150 mg twice daily dose"	This statement is not accurate nor placed in context. It should be corrected to this effect.	This analysis was only provided at the request of the ERG and in our response we stated: "*These comparisons can not and should not be made in the sequence model as the clinical data used is specific to dose and age*". Therefore, either the full context should be included or the statement excluded as it is misleading because it implies that we regard this to be a legitimate analysis, which we do not. It is also factually incorrect that the total costs for all three regimens were the same.
11	15	3.20	"In the probabilistic sensitivity analysis, the ICERs for the dabigatran sequential regimen in people under 80 years and the sequential regimen in people over 80 years compared with warfarin were £7811 and £11,912 per QALY gained respectively."	"In the probabilistic sensitivity analysis, the ICERs for the dabigatran sequential regimen in people starting under 80 years and the sequential regimen in people starting at ~~over~~ 80 years compared with warfarin were £7811 and £11,912 per QALY gained respectively."	As comment 8 above.
12	15	3.20	"…110 mg twice daily twice daily…"	Remove duplication.	Typographical error.
13	16-17	3.23	"The ERG commented that the population in the manufacturer's submission seemed to be at higher risk of stroke because the definition of moderate risk included those aged 75 years and over with no additional risk factors, whereas NICE clinical guideline 36 defines moderate risk as people aged 65 years and over with no additional risk factors. The ERG commented that including the potentially large subgroup of people over 65 years with atrial fibrillation but with no other risk factors for stroke would have been useful, and would reflect NICE clinical guideline 36 more closely and reduce the overall risk level of the population. The clinical specialists advising the ERG noted that the threshold for treatment with warfarin seems to be decreasing, therefore decreasing the risk of stroke in the eligible atrial fibrillation population, making the	This whole passage is irrelevant to the decision problem and should be deleted.	It is extremely important to note that we have included the patient population that is eligible for treatment <u>according to our licensed indication</u>. This is the stated requirement of the final scope. Inclusion of patients at age 65 without additional risk factors as suggested by the ERG would be <u>off-label</u>, therefore this criticism is not appropriate and should be removed. The relevant section of the indication from the final label reads: *"Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension."*

			population in the RE-LY trial less representative of clinical practice over time."		
14		3.24	"The ERG commented that excluding pulmonary embolism is potentially an optimistic approach in favour of dabigatran because dabigatran is associated with higher rates of pulmonary embolism than warfarin."	The exclusion of pulmonary embolism (PE) from the economic model has a negligible effect on the overall results and this should be contextualised.	The absolute rates of PE in RE-LY are extremely low and differences between the treatment arms are not clinically or statistically significant. The annual rate of PE was 0.12%, 0.15% and 0.10% for dabigatran 110mg bid, dabigatran 150mg bid and warfarin respectively (p-values 0.71 and 0.30). These rates would translate into Numbers Needed to Harm of approximately 5,000 for dabigatran 110mg bid and 2,000 dabigatran 150mg bid. The ACD statement therefore places far more weight on this issue than the evidence suggests it merits.
15	18	3.27	"The ERG was concerned that the magnitude of this difference may have been incorrectly extrapolated into the future, possibly biasing the results of the model."	This statement is unsubstantiated and should be deleted.	As we applied the ITT results from RE-LY to the economic model, we cannot see where any such potential bias could have been introduced.
16	18	3.28	"…and that people with well-controlled INR will have much lower costs than people with uncontrolled INR."	This statement is unsubstantiated and should be deleted.	This statement, based on expert opinion, is at odds with published peer-reviewed evidence that demonstrates good INR control to be associated with higher, not lower, costs (Dolan et al 2008). We note that under the NICE reference case we would be expected to account for hierarchy of evidence and request that the ERG is held to the same standard.
17	18-19	3.29	"The ERG carried out an analysis that suggested that warfarin was the most cost-effective intervention for people with good INR control. In this group the ICER for dabigatran 150 mg twice daily compared with warfarin was £60,895 per QALY gained;[…]".	"The ERG carried out an analysis that suggested that warfarin was the most cost-effective intervention for people with ~~good~~ "perfect" INR control (i.e. 100% time in target range). In this group the ICER for dabigatran 150 mg twice daily compared with warfarin was £60,895 per QALY gained."	As already stated in our response to the ERG some months ago, this analysis categorically does not represent "good" INR control, but "perfect" INR control (meaning 100% of INR time in range). As noted in our earlier response: We expand on this issue in our response to the request for further information later in the document. We request that this paragraph be reworded as suggested in order to be factually accurate.
18	19	3.30	"Dabigatran 110 mg twice daily and the sequential regimen model were associated with increased costs and decreased health benefits when compared with dabigatran 150 mg twice daily."	This analysis is invalid and should be removed from the ACD.	As agreed by the NICE project team, this analysis forms part of the invalid comparison made by the ERG where outcomes from the different models were inappropriately compared. This statement must be removed or contextualised to the effect that NICE recognises that

					these results are not valid with respect to the decision problem. This error is repeated in 3.35 and 4.11
19	20	3.33	"The ERG considered this assumption to be unsubstantiated by the evidence provided."	On the contrary, we did provide evidence to substantiate this assumption, therefore this statement should be deleted.	Please refer to the main publication of the RE-LY trial (reference 43 of our main submission) which has subsequently been superceded by the updated letter to the NEJM and associated appendix (Connolly *et al*., 2010). These sources show that dabigatran 150mg bid demonstrated a statistically significant improvement comapred to warfarin with respect to disabling or fatal stroke (HR: 0.66; CI: 0.50 – 0.87; p = 0.004). We note that the ERG does not present any evidence to support its assertion.
20	21	3.35	"Dabigatran 110 mg twice daily and the sequential regimen model were associated with increased costs and lower health benefits compared with dabigatran 150 mg twice daily."	This analysis is invalid and should be removed from the ACD.	See comment 18 above.
21	26	4.11	"The Committee noted that the ICERs for dabigatran in the sequential regimen model for people under 80 years and people over 80 years, respectively, were £7314 and £7873 per QALY gained compared with warfarin."	"The Committee noted that the ICERs for dabigatran in the sequential regimen model for people started under 80 years and people started at age ~~over~~ 80 years, respectively, were £7314 and £7873 per QALY gained compared with warfarin."	See comment 8 above.
22	26	4.11	"…and that dabigatran 110 mg twice daily and the sequential regimen model were dominated by the higher dabigatran dose because they had the same cost but lower efficacy."	This analysis is invalid and should be removed from the ACD. It is also inaccurate to state that the three regimens had the same cost.	See comments 10 and 18 above.

Discussion of the process leading to confusion at the 1st Committee Meeting

We note that the main reason for the preliminary decision of "minded not to recommend" is uncertainty surrounding the sequential dosing regimen of dabigatran etexilate (DBG) as per the approved EU label. We would like to take the opportunity to fully clarify how and why this regimen was presented in our original submission, and how the uncertainty surrounding this issue subsequently persisted up to and during the 1st Committee Meeting.

We made our original submission on October 5th 2010. As this date was well in advance of our expected date for the receipt of positive CHMP opinion from the EMA, it was necessary to present the economic evaluation according to the most likely product label that would be received in the UK.

Based on discussions with the EMA prior to our submission to NICE, it was clear that an EU label mirroring that issued in Canada on October 28th 2010 was the most likely scenario. In Canada, DBG 150mg bid is licensed for use in all eligible patients up to the age of 80 years. DBG 110mg bid is licensed for use in all eligible patients aged 80 years and over. Therefore, under the final scope, it was necessary for us to assess the cost-effectiveness of DBG used according to this posology in accordance with the expected label.

Therefore we decided to present BOTH the sequential dosing regimen, and the regimens as studied in the RE-LY trial to provide not only the cost-effectiveness according to the expected label with its underlying clinical rationale, but also to provide cost-effectiveness information in patient cohorts as randomised in the RE-LY trial. It was never intended that these regimens should be compared with one another.

As stated in our original submission:

"*Interventions 1 [150mg b.i.d in all patients] and 2 [110mg b.i.d in all patients] follow the original design of the RE-LY trial and will provide cost-effectiveness estimates for each DBG dose in a general, eligible AF population. However, given the clear dose-response demonstrated in Sections 3 and 4, it is clear that one or other of the doses may be more appropriate in patients of differing risk profiles. Therefore intervention 3 [sequence] targets each dose within a specific patient population as per the current proposed SPC, thereby increasing the overall capacity to benefit.*" (Section 6.2.1, page 151 of our original submission)

We attempted twice more to reinforce this principle with the ERG. Firstly, in the ERG's clarification letter (sent 28th October 2010) we were asked to provide:

"…the results of the cost-effectiveness analysis using simultaneous comparisons between dabigatran (150mg and 110mg) and all comparators…" (Question B5, page 384 of the full ACD information package)

Our response (dated 11th November 2010) stated:

"*It is … not reflective of the expected posology according to the draft SPC currently under EMA review and already approved in Canada… These comparisons can not and should not be*

made in the sequence model as the clinical data used is specific to dose and age." (Response to Question B5, page 397 of the full ACD information package)

Nevertheless, on receiving their full report (9th February 2011) it was clear that the ERG had continued to incorrectly compare all alternatives with one another across all patients and had concluded that 150mg bid (extendedly) dominated 110mg bid. We were asked only to check for factual inaccuracies in the ERG report, of which we firmly believed this was such an instance. Therefore, in our response (dated 16th February 2011) we reinforced this principle for the second time:

"*The final scope states that DBG is to be appraised within its licensed indication. Throughout the report the ERG's own analyses repeatedly compare DBG 110mg bid directly with DBG 150mg bid. It is inappropriate to continually make this comparison without providing the context that the proposed licensed indication for DBG is for the two doses to be used in different patient groups*." (Issue 8, page 631-2 of the full ACD information package)

The ERG did respond to this issue, but unfortunately we were not immediately privy to their response and our first sight of it was on receiving the full ACD documentation on August 10th 2011, only after the 1st Committee meeting. In their response the ERG stated:

"*The manufacturer has not presented a factual inaccuracy. The ERG has undertaken a full incremental analysis by comparing all available treatments for each sub-group. The manufacturer's proposed licensed indication is not a treatment option in the RE-LY trial but a post-hoc subgroup analysis and has not been recommended by the FDA. However, it was included to determine whether it was a cost-effective option.*" (Response to issue 8, page 631-2 of the full ACD information package)

This is extremely disappointing because the resulting confusion at the 1st Committee meeting could have been easily avoided.

The cost-effectiveness presentation given at the meeting continued with the ERG's flawed comparison. However, the Committee quickly accepted Boehringer Ingelheim's explanation that the sequence regimen model was the only one appropriate for decision making in light of the approved label, and that it cannot be compared with the single dose regimen model. This conflict led to the ERG making an impromptu, manual calculation during the meeting itself that should not have been performed as it was methodologically erroneous. NICE have since agreed that this calculation was invalid. Had we had sight of the above response prior to the 1st Committee meeting we would surely have made strong representations to ensure that the correct analyses were prepared by the ERG for the meeting.

It is difficult to understand why the ERG consistently chose to disregard our clear and continual provision of the most likely product label. The ERG was wrong to state that this issue was not a factual inaccuracy. The final scope states that cost-effectiveness is to be examined within the product's licensed indication and we have always provided the most accurate information regarding our likely licensed indication to the best of our knowledge. We assume that the Committee would concur that the most up-to-date information on the likely licensed indication during ongoing regulatory review could only come from the manufacturer. Further, given the fact that this was already the approved indication in

Canada, and that we had made explicit reference to this in our commentary on November 11th 2010, we remain puzzled by the ERG's obvious reticence to accept the likelihood of this label. We also do not understand the relevance of any recommendation or otherwise by the FDA to this appraisal.

Finally, although the EPAR was not available prior to the 1st Committee Meeting, we informed NICE on 15th April 2011 that CHMP positive opinion had been received and provided the draft SPC on 19th April 2011, which confirmed the sequence dosing regimen. Clearly the ERG either did not have access to this information before the 1st Committee Meeting, or it was not accounted for.

In light of these complicated circumstances we are grateful to the Committee for choosing the pragmatic option of "minded not to recommend". We welcome the opportunity to provide further clarification and information directly to the Committee and look forward to a productive discussion at the 2nd Committee Meeting.

New Information Requested by the Committee

As outlined in Section 1.2 of the ACD, the Committee has made the following request:

The Committee requests further information about the licensed regimen, in which people under 80 years begin treatment with dabigatran etexilate 150 mg twice daily, and at 80 years switch to dabigatran etexilate 110 mg twice daily. The manufacturer of dabigatran etexilate should provide the following for the second Appraisal Committee meeting:

- *A cost-effectiveness analysis of the sequential regimen outlined above, comparing dabigatran etexilate with warfarin using relative risks from the whole RE-LY trial population rather than from the post hoc subgroup analysis. The analysis should include sensitivity analyses using a range of assumptions of international normalised ratio (INR) monitoring costs such as those used by the Evidence Review Group (ERG) (£279.36, £241.54 and £115.14) in addition to the cost stated in the manufacturer's submission (£414.90).*

- *A cost-effectiveness analysis of the sequential regimen outlined above, comparing dabigatran etexilate with warfarin and including sensitivity analyses using a range of assumptions of INR monitoring costs and the assumptions suggested by the ERG:*
    - *a patient cohort representing people with atrial fibrillation in the UK, using the data reported by Gallagher et al. (2008)*
    - *a variable (per patient) cost of £115.14 for anticoagulant monitoring*
    - *people have dyspepsia throughout dabigatran etexilate treatment, not just in the first 3 months of treatment*
    - *disability and mortality risks after stroke are treatment-independent*
    - *disutility associated with dabigatran etexilate during the first 12 months of treatment as used in the RE-LY quality of life sub-study (the details are academic-in-confidence).*

The following sections outline the necessary changes made to the economic model and associated results according to the above specifications.

Changes made to the economic model

In order to comply with the above requests, a number of changes were made to the "sequence model" that was originally submitted. The updated model has been attached to the covering email of this response. These changes are outlined below.

The principal change was to replace the clinical data inputs from the age-dependant sub-group analysis with that from the entire ITT population in RE-LY. That is, the modelled cohort is now subject to the baseline and relative risks for the whole 150mg b.i.d RE-LY population at ages under 80 years, and subject to the baseline and relative risks for the whole 110mg b.i.d RE-LY population at ages of 80 years and over. These changes are marked in orange in the model worksheets 'Clinical Inputs' and 'Clinical Input Store'.

A further adaptation to the model was made to enable different levels of disutility to be applied to patients receiving dabigatran etexilate (DBG) 150mg b.i.d and 110mg b.i.d (model worksheets 'Model Steps - Dabigatran 80+', 'Model Steps - Untreated 80+', 'Model Steps - Dabigatran -80', 'Model Steps - Untreated -80' and 'Utility and Costs'). The cost of INR monitoring was also modified, however this is a simple adjustment (worksheet 'Utility and Costs').

These adaptations to the model were made by the original developers (United BioSource Corporation, Bethesda MD, USA) and verified by Boehringer Ingelheim's in-house health economists.

Results

Using this revised model, a "new base case" (hereafter called "base case") was formulated with the INR monitoring costs set at the ERG's second-lowest suggested level (£241.54). The base case, alongside the various permutations relating to the above set of requests, is presented in **Table 1**. Results are presented both for the full sequence where patients start on 150mg b.i.d and switch to 110mg b.i.d at age 80 years, and for the alternative scenario considering patients who are already aged 80 years or over at initiation who would only ever receive 110mg b.i.d.

The base case INR monitoring cost was selected based on the comments from the Committee in section 4.11 of the ACD: "*First, the Committee noted that the ERG's analysis assumed lower anticoagulant monitoring costs of £115.14 per patient (per annum) instead of £414.90 estimated by the manufacturer. […] It also heard that INR monitoring costs varied in different settings and could not be quantified precisely, and that the real cost of INR monitoring was most likely to fall between the values estimated by the manufacturer and ERG.*"

Analyses 1 to 4 relate to the first bullet of the Committee's request above, incorporating the change in clinical data informing baseline and relative risks with varying costs of INR monitoring. Analysis 1 is the base case; analysis 2 is analogous to our originally submitted base case (also provided alongside for ease of comparison). Analyses 3 and 4 utilise the other suggested INR monitoring cost levels.

Analysis 2 shows that the change in clinical data inputs had a limited effect on the full sequence (ICER rose by approximately £1,000 per QALY gained). The alternative scenario considering only those 80 and over was more sensitive to this change, mainly due to the difference in relative risk for ischaemic stroke between the subgroup analysis for this age group and whole 110mg b.i.d population. Nevertheless, the ICER for this group (£12,671) remains cost-effective.

Analysis 1 (base case) is identical to analysis 2 except for the revised cost of INR monitoring. Unsurprisingly, the ICERs for both groups rise due to the reduced level of cost-offsets but remain below £20,000 per QALY gained.

Analysis 3 is not greatly different to analysis 1 and moves the ICERs slightly in favour of DBG due to increased cost offsets. Analysis 4 shows that even when INR monitoring

costs are set at unrealistically low levels, the ICER for the full sequence remains below £20,000 per QALY gained, with the 80+ group ICER only slightly higher.

In summary, analyses 1 to 4 show that DBG remains cost effective both under the base case according to the Committee's requested changes and under associated sensitivity analyses around the cost of INR monitoring.

In addition, a probabilistic sensitivity analysis (PSA) on the full sequence group for the base case was performed (**Figure 1**). The results from this analysis showed that approximately 70.1% of simulations were below £20,000 per QALY gained and approximately 92.0% of simulations were below £30,000 per QALY gained, confirming the robustness of the base case result.

Figure 1 Probabilistic sensitivity analysis of the base case (full sequence group)

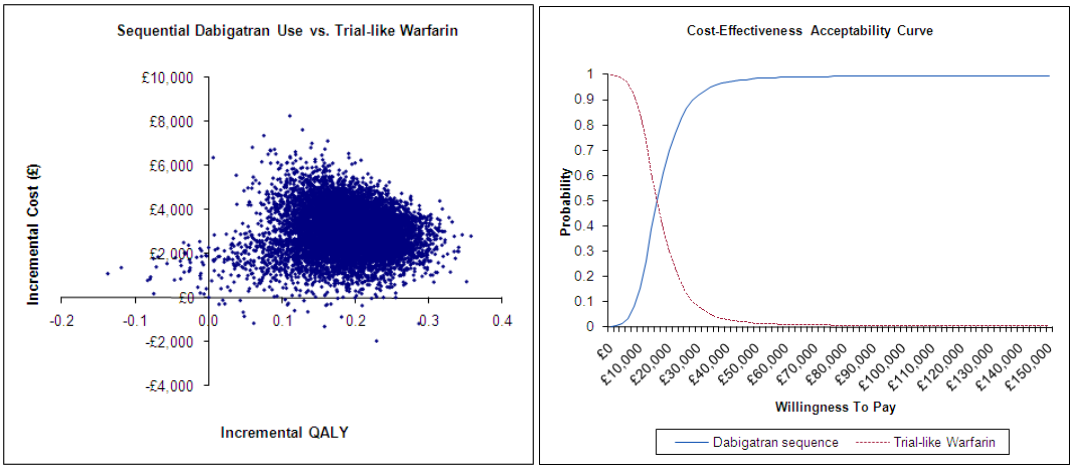

Table 2 New sequence regimen analyses as per the Committee's request

Analysis	Category	Parameter changes	New sequence model (ALL RE-LY)		Original sequence model	
			Full sequence	80+ only	Full sequence	80+ only
1	Variation in annual cost of INR monitoring	£241.54 (base case)	£14,518	£18,269		
2		£414.90 (BI's original value)	£8,388	£12,671	£7,314	£7,873
3		£279.36 (ERG upper suggestion)	£13,181	£17,048		
4		£115.14 (ERG lowest suggestion)	£18,987	£22,350		
5	Variation in baseline population (relative to analysis 1)	Baseline demographics and stroke risk based on GPRD analysis	£17,373	£19,680		
6	Other ERG suggestions (relative to analysis 1)	Dyspepsia management costs applied to whole duration of DBG treatment	£14,957	£18,711		
7		Disability and mortality risks after stroke are treatment-independent	£14,071	£14,454		
8		DBG disutility applied for 12 months	£15,578	£20,648		
9	Worst-case scenario*	Analysis 4 combined with analyses 5 to 8	£22,593	£22,487		
10	Conservative base case	Analysis 1 combined with analyses 5 to 8	£17,660	£18,392		

*Section 4.12 of ACD: "Based on these factors, the Committee concluded that the ERG's alternative base-case ICER was likely to represent a worst-case estimate of the cost effectiveness of dabigatran compared with warfarin […]"

Analyses 5 to 8 perform further sensitivity tests on the base case (analysis 1) according to the Committee's requests in the second bullet above.

Analysis 5 reflects the base case using baseline demographics and stroke risk (according to the $CHADS_2$ risk score) of a UK atrial fibrillation (AF) population. The Committee suggested using the data presented in Gallagher *et al*. (2008) however there are severe limitations to this approach. Firstly, to populate the sequence model, data is required specific to the age groups below and above 80 years. These values are not immediately derivable from the Gallagher study. Secondly, many of the patients included in the Gallagher analysis would be "off-label" for treatment with DBG with regards to the required risk profile in the product licensed indication. This is particularly evident with respect to the relative proportions of patients with a $CHADS_2$ score of zero.

To remedy this situation, and to be able to fully comply with the Committee's request to use population-based data representative of the UK, Boehringer Ingelheim's epidemiology department has performed an analysis of the GRPD database (patient records as at 31st December 2010 covering 48,526 AF patients) to derive the data as required for the model and according to the product's label. The analysis calculates the age, gender and $CHADS_2$ score mix for UK AF patients who would be eligible for treatment with DBG according to the licensed indication (known in the analysis as "Pradaxa Score" of greater than or equal to 1). The analysis also presents the corresponding data for the wider UK AF population for comparison. Our full GPRD analysis is attached to the covering email of this response and is provided Academic-in-Confidence. The data used for the economic model is presented in **Table 2** alongside the data from Gallagher for comparison.

Table 3 Baseline demographics and stroke risk

	GPRD analysis ("Pradaxa score" of at least 1)		Gallagher *et al*. (2008)
	Aged under 80 years	Aged 80 years or over	
Average age of cohort	[redacted]	[redacted]	77
% Male	[redacted]	[redacted]	55.1
$CHADS_2$=0	[redacted]	[redacted]	12.6%
$CHADS_2$=1	[redacted]	[redacted]	30.6%
$CHADS_2$=2	[redacted]	[redacted]	30.7%
$CHADS_2$=3	[redacted]	[redacted]	14.9%
$CHADS_2$=4	[redacted]	[redacted]	8.1%
$CHADS_2$=5	[redacted]	[redacted]	2.8%
$CHADS_2$=6	[redacted]	[redacted]	0.4%
$CHADS_2$ = 2 and previous stroke	[redacted]	[redacted]	-
$CHADS_2$ = 3 and previous stroke	[redacted]	[redacted]	-
$CHADS_2$ = 4 and previous stroke	[redacted]	[redacted]	-

Analysis 5 therefore presents the base case with baseline demographics and stroke risk changed to reflect those from the outlined GPRD analysis (**Table 2**). This change raises

the ICER slightly for both the full sequence and the 80+ group. This is intuitive given that the starting age of both analyses has increased from our original base case (which used values derived from the RE-LY trial), serving to effectively reduce the model time horizon. Nevertheless, the ICERs for both analyses remain below £20,000 per QALY gained.

Analyses 6 to 8 vary the base case with respect to the further requests relating to dyspepsia costs, treatment-independent stroke disability/mortality (rates assumed same as warfarin) and DBG disutility. As can be clearly seen, these changes, individually, have in general a minimal effect on the base case ICER. Although it is worth noting that the assumption of treatment-independent stroke disability/mortality reduces the ICER for both groups, and in the 80+ group by almost £4,000 per QALY gained.

Analysis 9 can be regarded as a worst-case analysis (as noted by the Committee in the ACD Section 4.12) in that it reflects the ERG's preferred base case scenario. That is, analysis 4 (base case but with the ERG's lowest suggested INR monitoring cost) combined with analyses 5 through 8. This ultra-conservative analysis results in ICERs for both the full sequence and the 80+ group that are above £20,000 per QALY gained but still well below £30,000 per QALY gained (£22,593 and £22,487 per QALY gained for the two groups respectively). Comparing the full sequence result (£22,593) to the analogous result from the ERG's preferred base case (£24,173) presented in the ACD (Section 3.35), the moderate difference in favour of DBG can be explained by the lower starting age in our analysis (i.e. GPRD analysis reflecting the DBG label vs. Gallagher study). This analysis provides a high level of comfort regarding the robustness of the results.

For comparison, we have provided a further analysis (10) which could be termed as a "conservative base case". It mirrors the worst-case analysis above but uses analysis 1 (base case) rather than analysis 4 as the foundation. In this case, both ICERs are below £20,000 per QALY gained, providing further reassurance.

<u>Further discussion regarding INR control</u>

The Committee also requested the following (section 1.2 of the ACD):

- *Further comment and consideration of the cost effectiveness of dabigatran etexilate in the subgroup of people who are already well controlled on warfarin*.

This issue is referred to specifically in other parts of the ACD, firstly:

Section 3.22
The ERG noted that a submission from the manufacturer to the FDA indicated that dabigatran 150 mg twice daily reduced the risk of stroke or systemic embolism compared with warfarin in people with good INR control (HR = 0.68, 95% CI 0.50 to 0.92 for time in therapeutic INR range 65% or above; HR = 0.70, 95% CI 0.51 to 0.96 for time in therapeutic INR range 68% or above). The ERG also highlighted that an analysis in the submission produced for the FDA showed a greater benefit of dabigatran in people with poor INR control than in those who were well controlled (the threshold being the centre-level median of 67%). The report concluded that, although the results showed efficacy of

dabigatran in people who had INR control above the centre-level median, the results did not show superiority over warfarin. The submission further subdivided people by INR control (less than 58.5%, 58.5% or above, less than 66.8%, 66.8% or above, and less than 74.2%). This demonstrated that the greatest benefit of dabigatran was in the lowest quartile of INR control and that, in people with good INR control with warfarin, little or no additional benefit in terms of effectiveness would be gained with dabigatran.

The results of the INR control analyses submitted to the FDA referred to above, stratified by individual time in therapeutic range (iTTR), should be interpreted with caution. Stratification for this analysis occurs only in the warfarin arm of RE-LY, introducing potential bias. While such an analysis can be performed as a *sensitivity analysis* to assess the overall robustness of study findings, it would be completely inappropriate to use it as a basis for decision making. The superiority of DBG 150mg b.i.d and the non-inferiority of DBG 110mg b.i.d are maintained even against warfarin ≥65% TTR, reinforcing the consistent results of RE-LY. Nevertheless we maintain that these sensitivity analyses are an unsuitable basis on which to formulate definite assessments of the relative efficacy and safety of DBG.

The analyses stratified on centre TTR (cTTR) – a method that maintains randomisation within a centre (Wallentin *et al*., 2010) - should carry more weight, if such an analysis is to be considered at all. This publication states: "*In the absence of any indicator of anticoagulation status in the dabigatran groups, the average TTR each centre achieved in its patients treated with warfarin was used as an approximation of quality of INR control for all its patients (centre's mean TTR [cTTR]) receiving warfarin*." Overall, the cTTR analysis will be associated with considerably less bias than the analysis based on iTTR.

Results of the cTTR analysis clearly confirm the overall results of RE-LY. There was no interaction between cTTR and the primary endpoint, thus supporting the robustness of the RE-LY findings across all INR values achieved for warfarin. The study authors note that "*…there were no significant interactions between cTTR and stroke and systemic embolism with either dose of dabigatran versus warfarin*" (please see Table 2 and Figure 2 in the Wallentin publication).

Finally, the authors state the following in the discussion section: "*Thus, these findings support the superiority of 150 mg dabigatran twice daily and the noninferiority of 110 mg dabigatran twice daily versus warfarin for protection against stroke in atrial fibrillation irrespective of the quality of INR control that a centre can achieve*." It is also important to note that the risk of intracranial haemorrhage (ICH) observed with warfarin was not affected (i.e., did not decrease) by improved TTR and was substantially reduced by both doses of DBG, irrespective of the quality of INR control.

Importantly, we note that the Committee has requested that the full population RE-LY clinical data to be used in the economic model, as opposed to our original analysis which utilised the post-hoc subgroup analysis of RE-LY, which was deemed inappropriate. It would then follow that the same principle must be applied when considering the results of subgroup analyses relating to INR control, i.e. decision making must be based on results of the full trial population not the results of under-powered subgroup analyses.

Moreover, age is a baseline covariate whereas INR control is only known at study end. This leads to potential bias as described because patient subgroups by INR control have very different baseline characteristics (such as $CHADS_2$ scores).

The ACD also reports the following:

Section 3.29
The ERG carried out an analysis that suggested that warfarin was the most cost-effective intervention for people with good INR control. In this group, the ICER for dabigatran 150 mg twice daily compared with warfarin was £60,895 per QALY gained; dabigatran 110 mg twice daily and the sequential regimen model were dominated by warfarin because they were associated with greater costs but lower health benefits. The group of people with poor INR control was also evaluated by the ERG. The ICER for dabigatran 150 mg twice daily compared with warfarin for people with an INR below 2 was £740 per QALY gained. For people with an INR above 3, warfarin was dominated by dabigatran 150 mg twice daily. Dabigatran 110 mg twice daily, either in the single-dose model or in the sequential regimen model, was associated with higher costs and lower health benefits than dabigatran 150 mg twice daily in both the group with good INR control and in the group with poor INR control. The ERG concluded that INR control is a key parameter in the economic evaluation.

As already stated in our response to the ERG some months ago, this analysis categorically does not represent "good" INR control, but rather "perfect" INR control (meaning 100% of time in target INR range for the entire duration of treatment). It is extremely important that this hypothetical analysis is not given a disproportionate and misleading level of significance.

Firstly, "perfect" INR control, i.e. 100% time in target range (TTR) as used in the ERG's analysis, is very rare. For example in RE-LY (which has median follow-up of 2 years), only 50 patients of over 18,000 (0.8%) achieved 100% TTR, of which only 1 was a UK patient (0.9% of the UK cohort). Importantly, INR control in a clinical trial such as RE-LY is known to be superior to real-world practice (see for example van Walraven *et al*., 2006), making real-world observation of 100% TTR even less likely. For further discussion on this topic we also refer to Sorensen *et al*. (2009), attached to the covering email.

Secondly, 100% TTR could only ever apply on an individual-patient basis, and even then for an undetermined time period. This presents several problems with respect to our economic model:

- Our economic model considers a patient cohort, not individual patients.
- The ERG's analysis therefore implies that a cohort of patients can be pre-defined whose INR will be perfectly controlled for an indefinite period, which is clearly impossible.
- Even if it were possible, this analysis assumes that such pre-definition is costless and without consequence, which is also clearly unrealistic given that a warfarin "test-period" would be the minimum requirement. Nevertheless, the ethics, costs and consequences of such a test period are not considered in the ERG analysis.

- As such, our economic model has been constructed to analyse a cohort of warfarin patients with variable TTR. The economic model will allow the user to define the average TTR (using the "real-world warfarin" option) for the cohort as a whole and has been populated with data according to this principle, i.e. the values should represent the average proportion of time spent within, under and over the target range by the whole cohort. With this in mind, and the factors outlined above, the ERG's analysis is an improper use of the economic model.

Whilst we concede that the quality of INR control is an important consideration in the cost-effectiveness discussion, we object to this analysis and outline below what we consider to be the correct approach to the issue.

Section 4.15
Finally, the Committee noted the ERG's comments that the cost-effectiveness of dabigatran compared with warfarin varied substantially according to level of INR control in those already being treated with warfarin.

As noted above, the economic model is constructed to analyse variable INR control in a cohort of patients. As such, the correct way to analyse the sensitivity of the ICERs to INR control is to vary the TTR using the "real-world warfarin" comparator in the economic model within plausible population-level ranges. To this end we have used analysis 1 (the base case from **Table 1**) and assessed the threshold levels of TTR that would be required in order to raise the ICERs for both treatment groups above £30,000 per QALY gained.

For both the full sequence and 80+ cohorts, it is estimated that INR would need to be within the target range an average of approximately 83-85% of the time across each cohort for the ICERs to be above £30,000 per QALY gained. Whilst such high levels of INR control may be expected in some individual patients, this could not realistically be expected on any population basis, howsoever defined. Of note, the TTR in RE-LY was 72% for the UK centres (Wallentin *et al*., 2010), albeit in a limited number of patients, and 64% for the overall RE-LY population (Connolly *et al*., 2009). Thus, in routine practice, average INR control achieved would need to be significantly higher than in investigator centres of RE-LY to result in ICERs that are not cost-effective.

Therefore our conclusion is that whilst the ICER of DBG compared to warfarin is sensitive to the quality of INR control, in the base case the quality of INR control must be raised to unachievable population levels in order for cost-effectiveness not to be demonstrated.

It should be noted that we consider these analyses to be conservative since they assume that costs for INR monitoring are independent of the resultant INR control. However, there is evidence that good INR control is typically resource intensive and costly (c.f. Dolan *et al.*, 2008). Thus it could reasonably be argued that increasing the level of INR control should be accompanied by an associated increase in the cost of INR monitoring.

Rationale for sequence dosing regimen

In addition to the requests in the ACD, in a briefing teleconference NICE instructed Boehringer Ingelheim to provide the Committee with a summary of the regulatory

rationale for the "sequence" regimen. We cite here from the EPAR (page 61), which was uploaded to the EMA website on August 23, 2011:

"*For patients ≥ 80 years the HRs for both dosages of DE [dabigatran etexilate] vs. warfarin on NCB [net clinical benefit] were similar and in favour of warfarin (DE110 bid = 1.12 (95% CI: 0.93, 1.36); DE150 bid = 1.13 (95% CI: 0.94, 1.35)). The rates of MBE [major bleeding event] in DE treated patients≥ 80 accounted for the unfavourable effect on NCB (DE 110 5.25%, DE150 6.24% and warfarin 4.70%/year). The increased rate of MBE was however not due to an increased rate of devastating ICHs (DE110 bid 0.32%, DE150 bid 0.69% and warfarin 1.31%/year). Based on almost comparable NCB between DE 150 and 110 and a maintained favourable effect on Stroke/SEE (1.88%, 1.78% and 2.72% for DE110 bid, DE150 bid and warfarin) and ICH (0.32%, 0.69% and 1.31% for DE110 bid, DE150 bid and warfarin) the lower dose of DE seems most appropriate for the elderly≥ 80 years of age in order to bring down the risk of MBEs: 10 additional stroke/SEE would be experienced compared to DE 150bid however, 99 MBE and 37 ICH would be avoided with DE 110bid compared to DE 150bid.*"

Thus, the sequence model originally submitted by Boehringer Ingelheim aimed to reflect this risk-benefit assessment by using only the efficacy and safety data from patients aged 80 and above in the DBG 110 mg bid treatment arm of RE-LY for this age group in the model (and vice versa for the younger age group). This was considered to be the most appropriate approach to support the decision problem regarding cost-effectiveness since it closely reflected the underlying clinical rationale.