Key Matters for Clarification

Clinical effectiveness

A1. (incorporating B2 and B3)

A full list of the 15 excluded studies is provided below in **Table 1**, complete with reasons for exclusion.

Table 1 Papers excluded from the effectiveness evaluation

	Reference	Reason for exclusion
1	Caprini JA. 21st Cong of the International Society on Thrombosis and Haemostasis (ISTH), Geneva, 6 - 12 Jul 2007 J Thromb Haemost 5 (Suppl 2), (2007)	Abstract of pooled analysis of RE-MODEL, RE-NOVATE and RE-MOBILIZE. More detailed information from the pooled analysis is included Section 5.5 of the main submission and later in this document.
2	Eriksson BI. 21st Cong of the International Society on Thrombosis and Haemostasis (ISTH), Geneva, 6 - 12 Jul 2007 J Thromb Haemost 5 (Suppl 2), (2007)	Abstract - conference presentation of RE-NOVATE.
3	Kurth AA. 8th Cong of the European Federation of National Associations of Orthopaedics and Traumatology (EFORT), Florence, 11 - 15 May 2007 (CD), (2007)	Abstract - conference presentation of RE-MODEL.
4	Troconiz IF. J Clin Pharmacol 47 (3), 371-382 (2007)	Not an RCT (pharmacokinetic study).
5	Eriksson BI. 48th Ann Mtg of the American Society of Hematology (ASH), Orlando, 9 - 12 Dec 2006 Blood 108, (2006)	Abstract - conference presentation of RE-MODEL.
6	Eriksson BI. 17th Int Cong on Thrombosis, Bologna, 26 - 30 Oct 2002 Pathophysiol Haemost Thromb 32 (Suppl 2), 69 (2002)	Not an RCT (dose-escalating study).
7	Stangier J. 18th Int Cong on Thrombosis, Ljubljana, 20 - 21 Jun 2004 Pathophysiol Haemost Thromb 33 (Suppl 2), 76-77 (2003)	Abstract of BISTRO-II - pharmacokinetic/pharmacodynamic data only, no clinical data presented.
8	Dahl OE. 18th Int Cong on Thrombosis, Ljubljana, 20 - 21 Jun 2004 Pathophysiol Haemost Thromb 33 (Suppl 2), 38-39 (2003)	Abstract – conference presentation of BISTRO-II (timing of initiation).
9	Eriksson BI. 18 Int Cong on Thrombosis, Ljubljana, 20 - 24 Jun 2004 J Thromb Haemost 3, 103-111 (2005)	Abstract – conference presentation of BISTRO-II (dose-response).
10	Eriksson BI. 17th Int Cong on Thrombosis, Bologna, 26 - 30 Oct 2002 J Thromb Haemost 2, 1573-1580 (2004)	Abstract of BISTRO-I (not an RCT).
11	Stangier J. Clin Pharmacokinet 47 (1), 47-59 (2008)	Not an RCT (pharmacokinetic study).
12	Stangier J. J Clin Pharmacol 45 (5), 555-563 (2005)	Not an RCT (pharmacokinetic study).
13	Pechlaner C. Lancet. 2007;370(9604):2002	Comment on RE-NOVATE.
14	National Horizon Scanning Centre, Year: 2006	Horizon scanning review.
15	N Ivanovic Centre for Reviews and Dissemination Year: 2007	Review.

The abstracts of the above records (where available) are provided in a separate document accompanying this written response.

The 7 conference abstracts referred to in point B2 of the clarification list are references 1, 2, 3, 5, 7, 8 and 9 in **Table 1**. We can confirm that these references

report on clinical trials subsequently published in full (RE-NOVATE, RE-MODEL and BISTRO-II) with the exception of reference 1, which reports on the pre-specified pooled analysis of the phase-III trials detailed in section 5.5 of the main submission (and discussed later in this document).

A full list of the BILIT and pre-BILIT citations is provided in a separate document accompanying this written response. We can confirm that the 9 further unique citations referred to in point B3 of the clarification list were identified via this search, including the RE-MOBILIZE abstract.

A2. (incorporating B1 and B4)

In the main submission, it is stated that the RE-NOVATE and RE-MODEL clinical trials represent the pivotal evidence base for dabigatran etexilate (DBG) in the submission for regulatory approval in the EU. Further, the RE-MOBILIZE study provides supportive, as opposed to pivotal evidence. The differences between the designs of the studies, principally the different dosing regimens and treatment durations employed in the RE-MOBILIZE study, make it less applicable to the European/UK setting than the other two trials.

In the economic evaluation, we have attempted to ensure that the most appropriate evidence base is used for the UK setting, which clearly is the RE-NOVATE and RE-MODEL clinical trials.

Nevertheless, the submission template does not have the same criteria for study inclusion between the clinical effectiveness and cost-effectiveness sections. In the preamble to section 5 of the template, the instructions state the following:

"*The systematic review is not required to be exhaustive (that is, it is not necessary to include all evidence relating to the use of the technology), but justification needs to be provided for the exclusion of any evidence… The Institute has a strong preference for evidence from 'head-to-head' randomised controlled trials (RCTs) that directly compare the technology and the appropriate comparator(s).*"

Whilst the RE-MOBILIZE clinical trial is not a pivotal study, it is an active comparator phase-III RCT similar to RE-NOVATE and RE-MODEL. That is, the RE-MOBILIZE study provides additional evidence on the relative efficacy and safety of DBG, albeit under different study conditions. Although we believe the efficacy comparison in RE-MOBILIZE to be inappropriate for the UK setting, we would be reticent to exclude any data on the safety of DBG, irrespective of setting. In our opinion it is not for us to decide whether this evidence is appropriate and we believe it would be difficult to justify exclusion of the RE-MOBILIZE study from a general review of the clinical data on DBG. To do so would likely arouse suspicion. We would prefer to be transparent and present the data, allowing the reviewer to have access to all the evidence and draw their own conclusions.

However, importantly, this does not preclude the exclusion of RE-MOBILIZE from an economic evaluation applicable to a particular setting.

The RE-MOBILIZE study has been submitted and accepted for publication as a full manuscript but at the time of writing the timelines for publication are unknown. Consequently it is only currently available as an abstract as cited in the main submission.

A3. (incorporating B5-7)

Baseline demographics and clinical characteristics

Please find the baseline demographic and clinical characteristics for the three trials, stratified by treatment group presented in **Table 2** to **Table 4**.

Table 2 RE-NOVATE baseline demographics and clinical characteristics

	Dabigatran 220 mg	Dabigatran 150 mg	Enoxaparin	Total
Treated	1146 (100.0)	1163 (100.0)	1154 (100.0)	3463 (100.0)
Age [years]				
Mean (SD)	64.6 (10.4)	63.4 (11.1)	63.8 (10.8)	63.9 (10.8)
Median	65.0	65.0	65.0	65.0
Range	24 to 91	19 to 89	20 to 88	19 to 91
<65	536 (46.8)	578 (49.7)	572 (49.6)	1686 (48.7)
65-75	448 (39.1)	437 (37.6)	425 (36.8)	1310 (37.8)
>75	162 (14.1)	148 (12.7)	157 (13.6)	467 (13.5)
<70	770 (67.2)	785 (67.5)	777 (67.3)	2332 (67.3)
≥70	376 (32.8)	378 (32.5)	377 (32.7)	1131 (32.7)
Gender				
Male	510 (44.5)	496 (42.6)	503(43.6)	1509 (43.6)
Female	636 (55.5)	667 (57.4)	651(56.4)	1954 (56.4)
Race [N (%)]				
White	1137 (99.2)	1158 (99.6)	1146(99.3)	3441 (99.4)
Black	4 (0.3)	2 (0.2)	8 (0.7)	14 (0.4)
Asian	5 (0.4)	3 (0.3)	0 (0.0)	8 (0.2)
Height [cm]				
N	1146	1163	1151	3460
Mean (SD)	168 (9)	168 (9)	168 (10)	168 (9)
Median	168.0	168.0	168.0	168.0
Range	135 to 196	146 to 195	140 to 213	135 to 213
Weight [kg]				
Mean (SD)	78.6 (14.9)	79.1 (15.4)	77.8 (14.9)	78.5 (15.1)
Median	78.0	78.0	77.0	78.0
Range	36.5 to 140.0	44.0 to 142.0	40.0 to 142.0	36.5 to 142.0
Body Mass Index [kg/m²]				
N	1146	1163	1151	3460
Mean (SD)	27.7 (4.6)	27.8 (4.6)	27.5 (4.3)	27.7 (4.5)
Median	27.3	27.3	27.1	27.3
Range	16.4 to 50.8	17.1 to 48.2	16.2 to 48.9	16.2 to 50.8
CrCl at screening [mL/min]				
Missing	25 (2.2)	29 (2.5)	30 (2.6)	84 (2.4)
<30	4 (0.3)	0 (0.0)	7 (0.6)	11 (0.3)
30-50	76 (6.6)	60 (5.2)	71 (6.2)	207 (6.0)
50-80	384 (33.5)	402 (34.6)	395 (34.2)	1181 (34.1)
≥80	657 (57.3)	672 (57.8)	651 (56.4)	1980 (57.2)
Mean	88.6 (28.7)	90.3 (31.0)	88.9 (30.0)	89.3 (29.9)
Median	85.9	86.4	85.5	85.9
Range	26.4 to 231.0	30.2 to 295.7	22.4 to 238.7	22.4 to 295.7

In the RE-NOVATE trial, the demographic and baseline characteristics of the treated patients were similar in the three treatment groups. The median age was 65.0 years in all treatment groups; the percentages of patients in the age categories ≥70 years and >75 years were also similar in all treatment groups. The majority of patients were female in all treatment groups (55.5% for DBG 220 mg, 57.4% for DBG 150 mg and 56.4% for enoxaparin). Almost all patients were white (99.4%).

The median height was 168 cm in all treatment groups; median weight was 78.0 kg for both DBG groups and 77.0 kg in the enoxaparin group. The median BMI was 27.3 kg/m² in both DBG groups and 27.1 kg/m² in the enoxaparin group. The proportion of obese patients, i.e. with a BMI >35kg/m², was 6.6% in the DBG 220 mg group, 7.8% in the DBG 150 mg group, and 4.4% in the enoxaparin group.

Creatinine clearance was determined at screening and was calculated using the Cockroft-Gault formula. The investigator was requested to calculate creatinine clearance only in cases where he suspected renal insufficiency. The median creatinine clearance was 85.9 mL/min in the DBG 220 mg group, 86.4 mL/min in the DBG 150 mg group, and 85.5 mL/min in the enoxaparin group. Four patients (0.3%) randomised to the DBG 220 mg group and 7 patients (0.6%) randomised to the enoxaparin group had a creatinine clearance below 30 mL/min. Overall 6.0% of patients had moderately impaired renal function (CrCl 30-50 mL/min) and 34.1% of all patients had mildly impaired renal function (CrCl 50-80 mL/min). However, the majority of patients (overall 57.2%) had normal kidney function (≥80 mL/min).

Table 3 RE-MODEL baseline demographics and clinical characteristics

	Dabigatran 220 mg	Dabigatran 150 mg	Enoxaparin	Total
Treated	679 (100.0)	703 (100.0)	694 (100.0)	2076 (100.0)
Age [years]				
Mean (SD)	67.3 (9.0)	67.5 (8.8)	68.3 (8.8)	67.7 (8.9)
Median	68.0	68.0	69.0	68.0
Age categories [years]				
<65	242 (35.6)	257 (36.6)	208 (30.0)	707 (34.1)
65-75	304 (44.8)	312 (44.4)	337 (48.6)	953 (45.9)
>75	133 (19.6)	134 (19.1)	149 (21.5)	416 (20.0)
<70	373 (54.9)	388 (55.2)	354 (51.0)	1115 (53.7)
≥70	306 (45.1)	315 (44.8)	340 (49.0)	961 (46.3)
Gender				
Male	238 (35.1)	252 (35.8)	216 (31.1)	706 (34.0)
Female	441 (64.9)	451 (64.2)	478 (68.9)	1370 (66.0)
Race				
White	671 (98.8)	690 (98.2)	689 (99.3)	2050 (98.7)
Black	5 (0.7)	8 (1.1)	4 (0.6)	17 (0.8)
Asian	3 (0.4)	5 (0.7)	1 (0.1)	9 (0.4)
Smoking history				
Missing	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Never smoked	488 (71.9)	502 (71.4)	518 (74.6)	1508 (72.6)
Ex-smoker	125 (18.4)	131 (18.6)	120 (17.3)	376 (18.1)
Smoker	65 (9.6)	70 (10.0)	56 (8.1)	191 (9.2)
Height, N	677	702	693	2072
Missing, N	2	1	1	4
Mean, (SD), [cm]	166 (10)	166 (10)	166 (10)	166 (10)
Median	165.0	165.0	165.0	165.0
Weight, N	679	703	693	2075
Missing, N	0	0	1	1
Mean (SD), [kg]	82.4 (14.6)	83.3 (15.0)	82.0 (15.3)	82.6 (15.0)
Median	81.0	82.0	80.0	81.0
Body Mass Index, N	677	702	692	2071
Missing, N	2	1	2	5
Mean (SD) [kg/m²]	29.9 (4.9)	30.1 (5.0)	29.8 (4.9)	29.9 (4.9)
Median	29.3	29.4	29.4	29.4
CrCl at screening [mL/min]				
N	653	677	677	2007
Missing	26	26	17	69
<30	1 (0.1)	1 (0.1)	2 (0.3)	4 (0.2)
30-50	37 (5.4)	36 (5.1)	57 (8.2)	130 (6.3)
50-80	234 (34.5)	235 (33.4)	256 (36.9)	725 (34.9)
≥80	381 (56.1)	405 (57.6)	362 (52.2)	1148 (55.3)
Mean (SD)	89.4 (28.7)	89.6 (28.1)	86.2 (28.5)	88.4 (28.4)
Median	86.6	87.2	82.4	85.1

In the RE-MODEL trial, the demographic characteristics were similar in all three treatment groups. The median age was 68.0 years (DBG 220 mg), 68.0 years (DBG 150 mg), and 69.0 years (enoxaparin); the percentage of patients of 70 years and older was 45.1% (DBG 220 mg), 44.8% (DBG 150 mg), and slightly higher at 49.0% in the enoxaparin group. The proportion of female patients was slightly lower in the DBG groups with 64.9% (DBG 220 mg), 64.2% (DBG 150 mg) than in the enoxaparin group with 68.9%. The mean BMI was also similar in all three treatment groups with 29.9, 30.1, and 29.8 kg/m^2, respectively. The vast majority of all patients were of white ethnic origin (overall 98.7%) with little differences between the three treatment groups. The majority of patients never smoked, and the proportion of non-smokers was slightly lower in the DBG groups (71.9% and 71.4%) than in the enoxaparin group (74.6%).

Only 4 patients, 1 patient in the DBG 220 mg group, 1 patient in the DBG 150 mg group, and 2 patients in the enoxaparin group had severely impaired renal function (creatinine clearance <30 mL/min). Moderately impaired kidney function (creatinine clearance 30 to 50 mL/min) was present in 5.4% (DBG 220 mg), 5.1% (DBG 150 mg), and 8.2% (enoxaparin) of patients. However, the majority of patients in all treatment groups had normal kidney function with creatinine clearance ≥80 mL/min (DBG 220 mg: 56.1%, DBG 150 mg: 57.6%, enoxaparin: 52.2%).

Table 4 RE-MOBILIZE baseline demographics and clinical characteristics

	Dabigatran 220 mg	Dabigatran 150 mg	Enoxaparin	Total
Treated	857 (100.0)	871 (100.0)	868 (100.0)	2596 (100.0)
Age [years]				
Mean (SD)	66.2 (9.5)	65.9 (9.5)	66.3 (9.6)	66.1 (9.5)
Median	67.0	66.0	67.0	67.0
Age categories [years]				
<65	350 (40.8)	358 (41.1)	340 (39.2)	1048 (40.4)
65-75	353 (41.2)	367 (42.1)	373 (43.0)	1093 (42.1)
>75	154 (18.0)	146 (16.8)	155 (17.9)	455 (17.5)
<70	526 (61.4)	535 (61.4)	519 (59.8)	1580 (60.9)
≥70	331 (38.6)	336 (38.6)	349 (40.2)	1016 (39.1)
Gender				
Male	371 (43.3)	364 (41.8)	364 (41.9)	1099 (42.3)
Female	486 (56.7)	507 (58.2)	504 (58.1)	1497 (57.7)
Race				
White	745 (86.9)	740 (85.0)	757 (87.2)	2242 (86.4)
Black	34 (4.0)	38 (4.4)	28 (3.2)	100 (3.9)
Asian	78 (9.1)	93 (10.7)	83 (9.6)	254 (9.8)
Height, N	857	871	868	2596
Mean, (SD), [cm]	167.2 (10.5)	166.8 (10.8)	167.3 (10.8)	167.1 (10.7)
Median	166.0	165.0	168.0	166.5.0
Weight				
Mean (SD), [kg]	88.4 (19.1)	87.6 (20.0)	88.0 (19.2)	88.0 (19.4)
Median	86.0	85.7	86.2	86.0
Body Mass Index				
Mean (SD) [kg/m²]	31.6 (6.0)	31.4 (6.1)	31.4 (6.0)	31.5 (6.0)
Median	30.6	30.3	30.5	30.5
CrCl at screening [mL/min]				
N	857	871	868	2596
Missing	13	15	9	37
<30	5 (0.6)	6 (0.7)	5 (0.6)	16 (0.6)
30-50	86 (10.0)	89 (10.2)	91 (10.5)	266 (10.2)
50-80	327 (38.2)	374 (42.9)	349 (40.2)	1050 (40.4)
≥80	426 (49.7)	387 (44.4)	414 (47.7)	1227 (47.3)
Mean (SD)	83.6 (30.1)	82.3 (30.0)	82.9 (29.5)	82.9 (29.9)
Median	80.3	77.3	78.6	78.3

In the RE-MOBILIZE trial, the demographic characteristics at baseline were similar for all treatment groups. The median age was 67.0 years (DBG 220 mg), 66.0 years (DBG 150 mg), and 67.0 years (enoxaparin); the percentage of patients 70 years and older was 38.6% (DBG 220 mg), 38.6% (DBG 150 mg), and 40.2% (enoxaparin). The proportion of female patients was 56.7% (DBG 220 mg), 58.2% (DBG 150 mg), and 58.1% (enoxaparin). The mean BMI was similar in all 3 treatment groups with 31.6, 31.4, and 31.4 kg/m^2 for DBG 220 mg, 150 mg and enoxaparin, respectively. Most patients were of white ethnic origin; 86.9% (DBG 220 mg), 85.0% (DBG 150 mg), and 87.2% (enoxaparin). Approximately half the patients from each treatment group had never smoked: 49.9% (DBG 220 mg), 50.2% (DBG 150 mg), and 52.9% (enoxaparin). The majority of the patients were from North America with 91.2%,

91.0% and 91.2% in the DBG 220 mg, DBG 150 mg, and enoxaparin treatment group, respectively.

A total of 16 patients (5 patients in the DBG 220 mg group, 6 in the DBG 150 mg group, and 5 in the enoxaparin group) had severely impaired renal function (creatinine clearance <30 mL/min) at baseline. Moderately impaired kidney function (creatinine clearance 30 to 50 mL/min) was present in 10.0% (DBG 220 mg), 10.2% (DBG 150 mg), and 10.5% (enoxaparin) of patients. The median creatinine clearance at baseline was 80.3 mL/min (DBG 220 mg), 77.3 mL/min (DBG 150 mg), and 78.6 mL/min (enoxaparin).

Participant involvement

In the RE-NOVATE study 3,613 patients were enrolled. One hundred and nineteen patients were not randomised since these patients did not meet some inclusion or exclusion criteria, withdrew informed consent, or experienced an adverse event prior to randomisation.

Therefore, 3,494 patients were randomised. Thirty-one randomised patients (DBG 220 mg: 12; DBG 150 mg: 11; enoxaparin: 8 patients) were not treated. Three patients did not receive any trial medication because of adverse events related to the surgery, 4 patients were not treated due to protocol violations, and 14 patients withdrew informed consent. Additionally, 10 patients were not treated because of "other reasons" including pre-dominantly re-scheduled surgery or patient's unsuitable medical conditions.

Overall, 3,463 patients were treated (DBG 220 mg: 1,146; DBG 150 mg: 1,163; enoxaparin: 1,154). This group formed the largest analysis dataset (safety set/treated set) which comprised all treated patients (3,463). A patient was regarded as treated if he or she received at least 1 dose of trial medication, i.e. DBG, enoxaparin, or placebo.

The treated and operated population (FAS-op, n=3,435; DBG 220 mg: 1,137; DBG 150 mg: 1,156; enoxaparin: 1,142) was smaller than the treated population (n=3,463) since for most patients study drug (enoxaparin or matching placebo) was initiated the night before the planned surgery. Some patients received study drug, but then did not undergo the planned surgery. This analysis set was the basis for the analysis of bleeding events and symptomatic efficacy events.

Baseline diagnostic testing for the presence of VTEs by routine venography in patients scheduled for elective total hip replacement is neither feasible nor practical. Therefore, the trial protocol as well as the statistical analysis plan specified that the analysis populations for each efficacy endpoint be established on the basis of the inclusion of patients evaluable for that particular endpoint. To be included in the analyses of efficacy endpoints, the patients had to be randomised, had to receive treatement with study drug, had to undergo surgery, and had to have an evaluable venogram or an event that qualified for the primary endpoint (i.e. symptomatic VTE or death).

The largest analysis set for the analysis of efficacy endpoints was the treated and operated set (FAS-op). All other efficacy analysis sets were sub-sets of this population but were not necessarily nested within each other. The full analysis set (FAS) was defined as all patients who were treated, operated, and had venograms evaluable for distal and proximal DVT, or a symptomatic DVT, or pulmonary embolism confirmed by the central adjudication committee, or had died during the treatment period. The FAS consisted in total of 2651 patients overall (dabigatran 220 mg: 880 patients [77.4%], dabigatran 150 mg: 874 patients [75.6%], and enoxaparin: 897 patients [78.5%]); overall these were 77.2% of the patients belonging to the treated and operated set. Hence, the percentages of patients excluded from the FAS were similar in all treatment groups. In the trial protocol it was assumed that 35% of the patients would have non-evaluable venographies and hence only 65% of patients would have evaluable venographies. In fact, in this study, overall 76.5% of the treated and operated patients had an evaluable venography and were included in the FAS, further evidence that this study was conducted to a high standard.

In the RE-MODEL study a total of 2,183 patients were enrolled after informed consent. Of these 82 patients were not randomised to treatment, as either these patients did not meet the inclusion or exclusion criteria.

Overall, 2,101 patients were randomised to treatment, 25 patients were not treated because patients did not undergo surgery (n=19) and/or withdrew consent (n=9). Over all groups, 2,076 patients received treatment, 679 patients in the DBG 220 mg group, 703 patients in the DBG 150 mg group, and 694 patients in the enoxaparin group.

The largest analysis set was the safety set which comprised all patients who were randomised and received at least one oral dose or one subcutaneous injection (n=2,076). Of these, 4 patients (DBG 220 mg), 7 patients (DBG 150 mg), and 9 patients (enoxaparin) were not operated leaving 675 patients (DBG 220 mg), 696 patients (DBG 150 mg), and 685 patients (enoxaparin) who received treatment and underwent surgery; this population constituted the FAS-op analysis set.

The full-analysis set (FAS) was defined as all patients who received treatment and underwent surgery, had an evaluable venogram for distal and proximal DVT, or confirmed symptomatic DVT, PE, or had died. Overall, this population comprised 1,541 patients (75.0%) of all patients treated and operated. In all treatment groups, similar proportions of patients (DBG 220 mg: 25.5%, DBG 150 mg: 24.4%, enoxaparin: 25.3%) were excluded from the FAS-op to form the FAS. For almost all of these patients, the reason for the exclusion from FAS was the lack of an evaluable venogram. Only 2 patients in the DBG 150 mg group and 1 patient in the enoxaparin group had either a PE or had died prior to the venography. In the calculation of the sample size in the study protocol, a rate of 25% of non-evaluable venograms was assumed and hence the observed rate was very similar to the expected rate.

For the analysis of major VTE and VTE-related mortality, the FAS-major population was used that comprised 1,544 patients (75.1%). For the analysis of proximal DVT, FAS-pDVT was used comprising 1,541 (75.0%) patients; for the analysis of the total DVT, i.e. proximal and distal DVTs, the FAS-tDVT population was used (n=1,538, 74.8%). Finally the per-protocol set (PPS) comprised 1,439 (70.0%) patients without important protocol violations.

In the RE-MOBILIZE study a total of 3,016 patients were screened after informed consent. Of these 401 patients were not randomised to treatment as the patients did not meet the inclusion or exclusion criteria. It is not surprising that this number is much higher in RE-MOBILIZE than either RE-NOVATE or RE-MODEL. In RE-MOBILIZE, patients were randomised to treatment post-surgery, whereas randomisation took place pre-surgery in RE-NOVATE and RE-MODEL. Therefore any patient experiencing complications or events, either during surgery or in the immediate post-operative period, would be excluded. Overall, 2,615 patients were randomised to treatment, 19 patients were not treated. Over all groups, 2,596 patients received treatment, 857 patients in the DBG 220 mg group, 871 patients in the DBG 150 mg group, and 868 patients in the enoxaparin group.

This group formed the largest analysis set for this study (safety set). The full analysis set (FAS) was defined as all patients who had surgery and were randomised, received treatment, had an evaluable venogram for distal and proximal DVT, or had confirmed symptomatic DVT, PE, or had died. Overall, this population comprised 1,896 (73.0%) treated patients. Similar proportions of treated patients in the three arms were included in the FAS (DBG 220 mg: 70.5%, DBG150 mg: 74.5%, enoxaparin: 74.1%). The majority of patients who were excluded from the FAS did not have an evaluable venogram. A 25% non-evaluable venogram rate was assumed for calculating the sample size of the study; the observed rate of non-evaluable venograms was not unexpected. Four patients in the DBG 220 mg group, 1 in the DBg 150 mg group and 4 in the enoxaparin group had either a PE or died prior to the venography.

The FAS-major population was used for the analysis of major VTE and VTE-related mortality that comprised 1,942 patients (74.8%). The FAS-pDVT was used for the analysis of proximal DVT, including 1,934 (74.5%) patients. The FAS-tDVT population was used for the analysis of total DVT (proximal and distal DVTs; n=1,887, 72.7%). The PPS consisted of 1,811 (69.8%) patients without important protocol violations.

The analysis sets for each trial are summarised in **Table 5** to **Table 7**.

Table 5 RE-NOVATE analysis sets

	Dabigatran 220 mg N (%)	Dabigatran 150 mg N (%)	Enoxaparin N (%)	Total
Treated	1146	1163	1154	3463
Treated and operated	1137 (100.0)	1156 (100.0)	1142 (100.0)	3435 (100.0)
Total VTE and all-cause mortality (FAS)	880 (77.4)	874 (75.6)	897 (78.5)	2651 (77.2)
Major VTE and VTE related mortality (FAS-major)	909 (79.9)	888 (76.8)	917 (80.3)	2714 (79.0)
Proximal DVT (FAS-pDVT)	905 (79.6)	885 (76.6)	914 (80.0)	2704 (78.7)
Total DVT (FAS-tDVT)	874 (76.9)	871 (75.3)	894 (78.3)	2639 (76.8)
Symptomatic DVT (FAS-op)	1137 (100.0)	1156 (100.0)	1142 (100.0)	3435 (100.0)
PE (FAS-op)	1137 (100.0)	1156 (100.0)	1142 (100.0)	3435 (100.0)
Death (FAS-op)	1137 (100.0)	1156 (100.0)	1142 (100.0)	3435 (100.0)
Total VTE and all-cause mortality without major protocol violation (PPS)	816 (71.8)	812 (70.2)	824 (72.1)	2452 (71.4)

Table 6 RE-MODEL analysis sets

Analysis set *(criteria for inclusion)*	Dabigatran 220 mg	Dabigatran 150 mg	Enoxaparin	Total
Randomised, N	693**	708	699	2101
Safety set, N *(Randomised and treated*)*	679	703	694	2076
FAS-op, N (%) *(Treated and operated)*	675 (100.0)	696 (100.0)	685 (100.0)	2056 (100.0)
Full analysis set (FAS), N (%) *(evaluable venogram for distal and proximal DVT, or symptomatic DVT, PE, death)*	503 (74.5)	526 (75.6)	512 (74.7)	1541 (75.0)
FAS-major, N (%) *(evaluable venogram for proximal DVT, or confirmed symptomatic proximal DVT, PE, VTE-related death)*	506 (75.0)	527 (75.7)	511 (74.6)	1544 (75.1)
FAS-pDVT, N (%) *(evaluable venogram for proximal DVT or confirmed symptomatic proximal DVT)*	506 (75.0)	525 (75.4)	510 (74.5)	1541 (75.0)
FAS-tDVT, N (%) *(evaluable venogram for total VTE or confirmed symptomatic DVT)*	503 (74.5)	524 (75.3)	511 (74.6)	1538 (74.8)
Per-protocol set, N (%) *(Patients in FAS without relevant protocol deviations)*	475 (70.4)	494 (71.0)	470 (68.6)	1439 (70.0)

* Received at least one dose of oral study medication or at least one subcutaneous injection
** Patient 3693 was randomized to Dabigatran 220 mg (kit no 1915) but never received any treatment. The investigator reassigned the kit to patient 3689. Thus, 694 patients underwent randomisation to the dabigatran 220 mg group.

Table 7 RE-MOBILIZE analysis sets

Analysis set *(criteria for inclusion)*	Dabigatran 220 mg	Dabigatran 150 mg	Enoxaparin	Total
Randomised, N	862	877	876	2615
Safety set, N *(Randomised and treated*)*	857	871	868	2596
FAS-op, N (%) *(Treated and operated)*	857 (100.0)	871 (100.0)	868 (100.0)	2596 (100.0)
Full analysis set (FAS), N (%) *(evaluable venogram for distal and proximal DVT, or symptomatic DVT, PE, death)*	604 (70.5)	649 (74.5)	643 (74.1)	1896 (73.0)
FAS-major, N (%) *(evaluable venogram for proximal DVT, or confirmed symptomatic proximal DVT, PE, VTE-related death)*	618 (72.1)	656 (75.3)	668 (77.0)	1942 (74.8)
FAS-pDVT, N (%) *(evaluable venogram for proximal DVT or confirmed symptomatic proximal DVT)*	614 (71.6)	656 (75.3)	664 (76.5)	1934 (74.5)
FAS-tDVT, N (%) *(evaluable venogram or confirmed symptomatic DVT)*	600 (70.0)	648 (74.4)	639 (73.6)	1887 (72.7)
Per-protocol set, N (%) *(Patients in FAS without relevant protocol deviations)*	580 (67.7)	621 (71.4)	610 (70.3)	1811 (69.8)

* Received at least one dose of oral study medication or at least one subcutaneous injection

Critical appraisal of trials

Table 8 Critical appraisal of included clinical trials

Trial aspect	RE-NOVATE	RE-MODEL	RE-MOBILIZE
How was allocation concealed?	Each phase-III trial had a double blind, double dummy design. Randomisation was blinded to both investigators and patients. All patients received double-blind clinical supplies with double-dummy matching placebo to ensure complete blinding during the conduct of the trial. Each patient received one capsule on the day of surgery, and two capsules on each day of treatment thereafter (i.e., DBG or matching placebo). Each patient also received twice daily subcutaneous injections (i.e., enoxaparin or matching placebo). All members of the Clinical Project Team remained blinded to the randomisation schedule until after the final database was locked. Prior to database lock, procedures were in place to ensure that individuals associated with the conduct of the studies remained blinded to the PK/PD data to preserve blinding of individual patient treatment assignments. The results of the independent analysis of the PK/PD data were not made available until after database lock. The results were not released to the trial teams nor were they entered into the trial databases until after database lock.		
What randomisation technique was used?	Patients were randomly assigned to treatment groups with equal probability of assignment to each treatment. Randomisation was stratified by study centre and performed in blocks to prevent unequal treatment allocation. The randomisation schedule was generated using validated software and verified by an internal statistician not involved in the planning or analysis of the trials.		
Was a justification of the sample size provided?	Depending on the assumed incidences, sample sizes were to be calculated to achieve 95% power to declare non-inferiority with a margin of 7.7% difference for total VTE and all-cause mortality. Preservation of 2/3 of the benefit of enoxaparin compared to placebo was acceptable to the FDA as an appropriate non-inferiority margin based on historical data.	Depending on the assumed incidence rates, sample sizes were calculated to achieve 90% power to state non-inferiority with a margin of 9.2% difference for total VTE and all-cause mortality. Preservation of 2/3 of the benefit of enoxaparin compared to placebo was acceptable to the FDA as an appropriate non-inferiority margin based on historical data.	Depending on the assumed incidence rates, sample sizes were calculated to achieve 90% power to state non-inferiority with a margin of 9.2% difference for total VTE and all-cause mortality. Preservation of 2/3 of the benefit of enoxaparin compared to placebo was acceptable to the FDA as an appropriate non-inferiority margin based on historical data.
Was follow-up adequate?	Yes. Follow up to 3 months. Mean duration of study 94 days. Haematology & clinical chemistry tests performed at 2 & 3months with focus on LFTs.	Yes. Follow up for 3 months. Haematology & clinical chemistry tests performed at 3 months with focus on LFTs.	Yes. Patients were followed up for 12-14 weeks.
Were the individuals undertaking the outcomes assessment aware of allocation	No. The independent VTE endpoint adjudication committees performed their work blinded to randomised treatment assignments, as did the independent Bleeding Adjudication Committee, which was responsible for adjudicating all bleeding		

	events. The same was true for the activities of the Hepatology Panel, which was charged with reviewing and evaluating all hepatic adverse events and laboratory abnormalities and the Cardiac Safety Panel, which reviewed all cases involving cardiac events to determine an ischaemic cardiac aetiology.		
Was the design parallel-group or crossover?	Parallel	Parallel	Parallel
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	Multinational. No UK centres. European, Australian & S African populations. Similar to recommended UK practice, refer to NICE clinical guideline (reference 1 of the main submission).	Multinational. No UK centres. European, Australian & S African populations. Similar to recommended UK practice, refer to NICE clinical guideline (reference 1 of the main submission).	No, conducted in North America (with the exception of three UK patients). Dose regimens of enoxaparin differ from those used in UK, and timing of the DBG dose differ from that proposed in the UK. See below for detail Higher proportion of general (rather than localised) anaesthesia
How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	Population similar to UK population based on UK census data (please refer to tables 46 to 48 and accompanying text in the main submission).	Population similar to UK population (please refer to tables 46 to 48 and accompanying text in the main submission).	Broadly similar, though with a higher proportion of black patients, and slightly older age group (please refer to tables 46 to 48 and accompanying text in the main submission).
What dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	DBG: 220mg or 150mg od, starting with a half dose 1-4 hours after surgery Enoxaparin: 40mg od, starting the day before surgery. Both are in line with UK SPCs.	DBG: 220mg or 150mg od, starting with a half dose 1-4 hours after surgery Enoxaparin: 40mg od, starting the day before surgery Both are in line with UK SPCs.	DBG: 220mg or 150 mg od, starting 6-12 hours after surgery This is the same dose as UK SPC, but initiation is outside marketing authorisation. Enoxaparin: 30mg bd, starting 12-24 hours after surgery. This is a higher dose and later initiation than the UK SPC (but complies with the American label). Duration was 12-15 days for both treatments, which is outside the UK SPCs.

Were the study groups comparable?	Yes. Demographic and surgical characteristics were similar across treatment groups within each study.	
Were the statistical analyses used appropriate?	Yes. The endpoints considered and the non-inferiority design complies with the EMEA guideline for study development in this therapeutic area (reference 29 in the main submission).	
Was an intention-to-treat analysis undertaken?	The primary analysis was based on the Full Analysis Set (FAS) that was comprised of those patients who were randomised, received at least one subcutaneous injection or one oral dose of study medication, and had an evaluable venogram or confirmed symptomatic DVT, PE, or death. This set is regarded as a modified intention to treat population in this type of study.	
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	The inclusion criteria were selected to allow entry of a representative yet homogeneous sample of patients undergoing primary elective total hip or knee replacement surgery. The exclusion criteria prevented entry of patients with significant co-morbidities or those whose participation might have represented a health risk for the patient. There is debate around the use of venographically confirmed VTE as the primary endpoint. It can be argued that symptomatic VTE and VTE-related mortality is a more clinically relevant outcome. However the problems associated with the use of this endpoint are well documented (i.e. the rarity of the event) and the primary endpoint adheres with the EMEA guideline for study development in this therapeutic area (reference 29 in the main submission).	The inclusion criteria were selected to allow entry of a representative yet homogeneous sample of patients undergoing primary elective total knee replacement surgery. The exclusion criteria prevented entry of patients with significant co-morbidities or those whose participation might have represented a health risk for the patient. There is debate around the use of venographically confirmed VTE as the primary endpoint. It can be argued that symptomatic VTE and VTE-related mortality is a more clinically relevant outcome. However the problems associated with the use of this endpoint are well documented (i.e. the rarity of the event) and the primary endpoint adheres with the EMEA guideline for study development in this therapeutic area (reference 29 in the main submission). As discussed, the dosing regimens, points of initiation and treatment durations in this study confound the results with respect to the UK setting.

DBG, dabigatran etexilate; DVT, deep vein thrombosis; LFT, liver function test; PE, pulmonary embolism; PK/PD, pharmacokinetic/pharmacodynamic; od, once daily dosing; SPC, summary of product characteristics; VTE, venous thromboembolism.

A4. (incorporating B9-13 and B16)

The full set of meta-analyses to cover all doses, endpoints and combination of trials is extensive. In the main submission, our intention was to present sufficient analyses to illustrate the trends in the results without overburdening the document. However, we acknowledge that the reasons for exclusion of the remaining analyses could have been made clearer.

The remaining analyses (for relative risk) are presented at the end of this document in **Figure 1** through **Figure 30**. The full set of analyses for risk difference is presented in a separate document accompanying this written response.

A5. (incorporating B14)

As stated in the main submission, the purpose of the pre-specified pooled analysis was to examine the secondary efficacy endpoint using a larger population than a single trial could permit. The EMEA guideline for development of studies in this therapeutic area (reference 29 in the main submission) advocates the use of the primary endpoint from the three DBG trials. It may be argued that the secondary endpoint (major VTE and VTE-related death) is more clinically relevant, however these events are rare and single trials powered to study this endpoint would need to be extremely large. This analysis was pre-specified for this particular purpose and should not be confused with a standard set of meta-analyses covering several endpoints.

Accordingly, no further analyses were performed as part of this study on other endpoints and therefore there is nothing additional for us to present.

This was a pooled analysis based on the summary statistics calculated for the three individual phase-III trials. The analysis used the overall absolute risk difference across the three studies and the 95% confidence interval for incidence of major VTE and VTE-related mortality during the treatment period, using a fixed effects model. As stated in the main submission, no confirmatory statistical hypothesis test was pre-specified. All analyses were exploratory and presented confidence intervals and descriptive *p*-values to compare each test therapy to enoxaparin.

A6. (incorporating B8)

We apologise for any confusion caused by the use of the term “modified intention to treat analysis” (mITT) in the main submission. As presented in the response to A3, the analysis set used depends on the endpoint under consideration. In the main submission, we have used mITT as a catch-all term to represent the appropriate analysis set for each endpoint.

A7 and A8. (incorporating B15)

It is necessary to clarify the background and the rationale behind the choice of mixed treatment comparison (MTC).

In preparation for the potential submissions for health technology appraisal of DBG, it is not feasible to wait for a final scope to be issued by NICE before performing an indirect comparison that would exactly isolate a comparison of DBG with whichever indirect comparator is deemed appropriate. Such therapies (other than LMWH) differ significantly between countries, even within the UK (aspirin is an appropriate comparator for Scotland), and therefore a comprehensive MTC that compared DBG with the full range of possible comparators was most desirable. Nevertheless, such an analysis must also be robust in terms of methodology and included studies.

Crucially, it must be clearly pointed out that the MTC presented in the main submission is based on that presented by the NCC-AC (reference 41 in the main submission), which formed the basis for the economic evaluation within the NICE clinical guideline on VTE prevention in surgical patients (reference 1 in the main submission). This analysis was selected following a systematic review of meta-analyses in this indication as the most robust and up-to-date study on which to base our MTC.

The methods and results of this study are outlined concisely in Section 12 of the NCC-AC report. The analysis included data from all relevant RCTs identified by the NCC-AC's clinical review. Full evidence tables for included studies are listed in Appendix D to the NCC-AC report.

In order to draw indirect comparisons between DBG and prophylactic interventions other than LMWH (including fondaparinux), the relative risks (RRs) for DBG versus enoxaparin were combined with RRs for LMWH versus Nil (estimated by the NCC-AC MTC), in order to estimate the RR for dabigatran versus Nil. Relative risks were combined using the adjusted indirect comparison method of Bucher *et al.*, (1997) (reference 69 in the main submission) as follows:

> If DBG is represented as D; the comparator as C and the common agent (LMWH) as A; and
>
> Estimates of RR are represented as follows:
>
> - dabigatran vs the common agent: RR_{DA} and
> - the comparator vs the common agent: RR_{CA} (available from the NCC-AC meta-analysis).
>
> Then, using the method of Bucher, the RR for dabigatran vs the comparator (RR_{DC}) is given by:
>
> $$\ln RR_{DC} = \ln RR_{DA} - \ln RR_{CA}$$
>
> and the variance of RR_{DC} is given by:
>
> $$\text{Var}(\ln RR_{DC}) = \text{Var}(\ln RR_{DA}) + \text{Var}(\ln RR_{CA})$$
>
> Assuming that lnRR is normally distributed, then the upper 95% confidence interval (UCI) and lower 95% confidence interval (LCI) may be estimated as:

$$\ln UCI_{DC} = \ln RR_{DC} + 1.96 \times Var(\ln RR_{DC})$$
$$\ln LCI_{DC} = \ln RR_{DC} - 1.96 \times Var(\ln RR_{DC})$$

In reply to point 1c) of B15: This refers to the methods employed in the meta-analyses for accounting for the differing durations of treatment in the three DBG trials. In essence, it is assumed that the treatment effect is independent of the duration of treatment provided that the durations are the same for both agents. In this way, the meta-analyses give a measure of treatment effect for DBG versus enoxaparin that is not specific to any duration of treatment.

However, the RE-NOVATE study compared extended duration DBG with extended duration enoxaparin (28-35 days). Therefore the statement "No adjustment of meta-analysed RRs was possible for the extended regimen in trial 1160.48 (RE-NOVATE)" indicates that although RE-NOVATE data were included in the meta-analysis, no adjustment for the extended duration of treatment was made. In the analyses under question, all the RRs for DBG represent standard duration of treatment with the exception of the RR for RE-NOVATE only.

In reply to point B15, 2a):

We would like to make clear that we have made a similar assumption to that of NCC-AC that relative treatment effect of the various thromboprophylactic alternatives is independent of surgery type. Whilst developing this analysis, we contacted the authors of the NCC-AC report with the aim of confirming the quality of the analysis and, in particular, investigating the heterogeneity they may have discovered in their analysis. In their personal communication to us, the authors ("The NCC-AC Team", personal communication, February 2007) confirmed the following:

"Question: Section 3.10 mentions sub-group analysis by surgery type but I couldn't see any mention of this in the results section. Were analyses performed for individual surgery types, or sub-sets of surgery types?

Response: The subgroups were for each surgical speciality (i.e. general, gynaecological, orthopaedic, neurosurgery, cardiac, thoracic, neurosurgery, urology, vascular and mixed).

Question: To your knowledge, is there evidence that treatment effect varies by surgery type?

Response: We tested for heterogeneity within the subgroup analyses and found no convincing evidence of a difference between surgery types."

As such, we regard the MTC presented in the main submission as a robust analysis utilising all the available evidence and based on sound assumptions.

In your request, we are unsure whether you are asking us to (A) perform an indirect comparison within the meta-analysis (e.g. a meta-regression of the fondaparinux and DBG clinical trials) or (B) just a meta-analysis of the fondaparinux trials. If the analysis is to include the DBG trials, it is not clear which trials should be included.

If B is the request, the second analysis requested (US dose) has already been presented in Appendix E (Figure 147-150) to the NCC-AC report. In terms of the first analysis requested, this request seems to contradict point B10 which states: "*there is a case for combining the two knee trials as they concern the same population.*" Rather than mix the THR and TKR populations the NCC-AC included a sub-analysis of the 5 fondaparinux trials with a different approach, focussing on timing of initiation and different doses:

1) vs Pre-op LMWH: Agnelli (dalteparin, abdominal surgery); Eriksson (40mg enoxaparin, femoral fracture); Lassen (40mg enoxaparin, THR)
2) vs Post-op LMWH: Bauer (30mg enoxaparin, TKR); Turpie (30mg enoxaparin, THR)

It is likely that this choice of approach was a result of their findings relating to lack of evidence of differences between treatment effects across types of surgery.

Unfortunately there has been insufficient time to perform the extra analyses requested in point B15 2a). If these are absolutely required then they can be performed if extra time can be granted. However we believe that the analyses outlined above should be sufficient to address the concerns that have been raised.

In response to point B15 2b): We would like to express our concerns as to the validity of this request. Given that this submission concerns a single technology appraisal of dabigatran etexilate, we do not believe that it is required of us to complete full literature searches on clinical evidence for comparator medications. Nevertheless, a full literature search of both LMWH and fondaparinux was completed by the NCC-AC and we are confident that this search was of sufficient quality to satisfy the requirements of the indirect comparison.

We would also like to emphasise a general point regarding the indirect comparison with fondaparinux. We remain to be convinced that the comparison of DBG with fondaparinux is appropriate to practice in England and Wales. Whilst we acknowledge that fondaparinux is recommended as an alternative to LMWH in the NICE clinical guideline, this agent is very rarely used in standard practice as demonstrated by data from the National Joint Registry (reference 16 in the main submission). We would urge reviewers to place this comparison in context when critically assessing its methods and results.

A9.

We are concerned by this request which asks us to speculate on possible discounts or contract prices offered by competitors to hospitals, whilst ignoring any discounts that may be offered by ourselves. We have used the published NHS list prices of all the medications in our economic evaluation as recommended by the NICE Guide to Methods of Technology Appraisals. We acknowledge that the Methods Guide also states that any variations between public list price and actual price should be assessed in sensitivity analysis. However such prices that may be offered by our competitors are not in the public domain, and we have no evidence to suggest that any such discounts are of greater or lesser magnitude to discounts that we may offer following the launch of DBG.

Further, it should be noted that we have already reduced the price of LMWH in the base case from the list price of enoxaparin to a notional weighted average including the less expensive LMWH alternatives.

Cost-effectiveness

A10. (incorporating B17)

In the clinical effectiveness section, the bleeding rates from the DBG trials are presented in as disaggregated a form as possible with regards to definition of event. However in the economic evaluation, it was necessary to use a set of definitions that were as consistent as possible across all comparators. In our analyses, as it was feasible for a patient to have both a major and clinically relevant bleed, the categories "Major", "Clinically Relevant" and "Minor" were based on the "worst" event data, and were therefore mutually exclusive. As an example, the data for the DBG 220mg treatment group of RE-MODEL were:

1. Major; 10/679
2. Clinically Relevant: 40/679
3. Clinically relevant and Minor combined: 100/679

Category 1 (Major) and 3 (Clinically relevant and Minor combined) were used in the economic evaluation. In our analysis of the NCC-AC trials for the minor bleed endpoint, minor bleed was defined as any bleed reported in the study that was not categorised as a major bleed (as defined in each individual study - there was no option but to rely on original study endpoint definitions). Unfortunately this was the closest we could get to equivalent definitions of major and minor bleed for the various possible interventions in the economic evaluation.

In the direct comparison, any difference between DBG and enoxaparin created by adjusting the definition of major and minor bleeding is unlikely to affect the overall results. In the indirect comparison, by categorising clinically relevant bleeding as minor bleed (which in the economic evaluation has minimal cost and quality of life impact), this approach is likely to favour fondaparinux which has a less favourable bleeding profile than DBG.

A11-12. (incorporating B18-19)

Table 9 and Table 10 present the overall results of the model utilising further meta-analysed estimates for the primary efficacy endpoint, major and minor bleed.

As would be expected, inclusion of the RE-MOBILZE data to the analysis shifts the results against DBG. However we would like to reiterate that we believe these analyses to be inappropriate to the England and Wales setting. Whilst the populations in RE-MODEL and RE-MOBILIZE may be similar, RE-MOBILIZE considers dosing regimens, treatment initiation and durations outside the UK marketing authorisations for both DBG and enoxaparin.

Table 9 Overall results utilising expanded set of meta-analyses (DBG 220mg)

	Description of sensitivity analysis	Original value	New value	ICER (THR)	ICER (TKR)	Probability of CE (THR)	Probability of CE (TKR)
	Base case	**-**	**-**	**DOMINANT**	**DOMINANT**	**99%**	**82%**
	Treatment effects						
B	RE-NOVATE + RE-MODEL (random)	VTE: 0.90 (THR) 0.97 (TKR) MJB: 1.29 (THR) 1.14 (TKR) MNB: 1.04 (THR) 0.96 (TKR)	VTE: 0.95 MJB: 1.24 MNB: 1.00	DOMINANT	DOMINANT	100%	88%
C	RE-MOBILIZE + RE-MODEL (fixed)	VTE: 0.90 (THR) 0.97 (TKR) MJB: 1.29 (THR) 1.14 (TKR) MNB: 1.04 (THR) 0.96 (TKR)	VTE: 1.08 MJB: 0.73 MNB: 0.97	N/A	DOMINATED	N/A	35%
D	RE-MOBILIZE + RE-MODEL (random)	VTE: 0.90 (THR) 0.97 (TKR) MJB: 1.29 (THR) 1.14 (TKR) MNB: 1.04 (THR) 0.96 (TKR)	VTE: 1.09 MJB: 0.72 MNB: 0.97	N/A	DOMINATED	N/A	40%

CE, cost-effectiveness; DBG, dabigatran etexilate; ICER, incremental cost-effectiveness ratio; MJB, major bleeding; MNB, minor bleeding; N/A, not applicable; QALY, quality-adjusted life year; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism

Table 10 Overall results utilising expanded set of meta-analyses (DBG 150mg)

	Description of sensitivity analysis	Original value	New value	ICER (THR)	ICER (TKR)	Probability of CE (THR)	Probability of CE (TKR)
	Base case	**-**	**-**	**DOMINANT**	**DOMINATED**	**76%**	**38%**
	Treatment effects						
E	RE-NOVATE + RE-MODEL (fixed)	VTE: 1.28 (THR) 1.07 (TKR) MJB: 0.83 (THR) 0.99 (TKR) MNB: 1.11 (THR) 1.00 (TKR)	VTE: 1.12 MJB: 0.88 MNB: 1.05	DOMINANT	DOMINATED	99%	20%
F	RE-NOVATE + RE-MODEL (random)	VTE: 1.28 (THR) 1.07 (TKR) MJB: 0.83 (THR) 0.99 (TKR) MNB: 1.11 (THR) 1.00 (TKR)	VTE: 1.11 MJB: 0.88 MNB: 1.05	DOMINANT	DOMINATED	99%	22%
G	RE-MOBILIZE + RE-MODEL (fixed)	VTE: 1.07 MJB: 0.99 MNB: 1.00	VTE: 1.19 MJB: 0.66 MNB: 0.97	N/A	DOMINATED	N/A	4%
H	RE-MOBILIZE + RE-MODEL (random)	VTE: 1.07 MJB: 0.99 MNB: 1.00	VTE: 1.19 MJB: 0.66 MNB: 0.97	N/A	DOMINATED	N/A	11%

CE, cost-effectiveness; DBG, dabigatran etexilate; ICER, incremental cost-effectiveness ratio; MJB, major bleeding; MNB, minor bleeding; N/A, not applicable; QALY, quality-adjusted life year; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism

Requested meta-analyses:

Primary efficacy endpoint

Figure 1 RE-NOVATE plus RE-MODEL (random effects) – 220mg

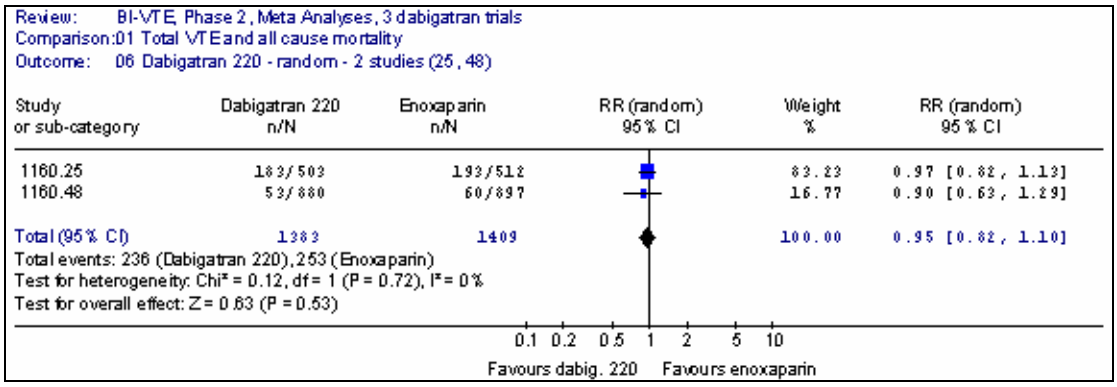


Figure 2 RE-MOBILIZE plus RE-MODEL (random effects) – 220mg

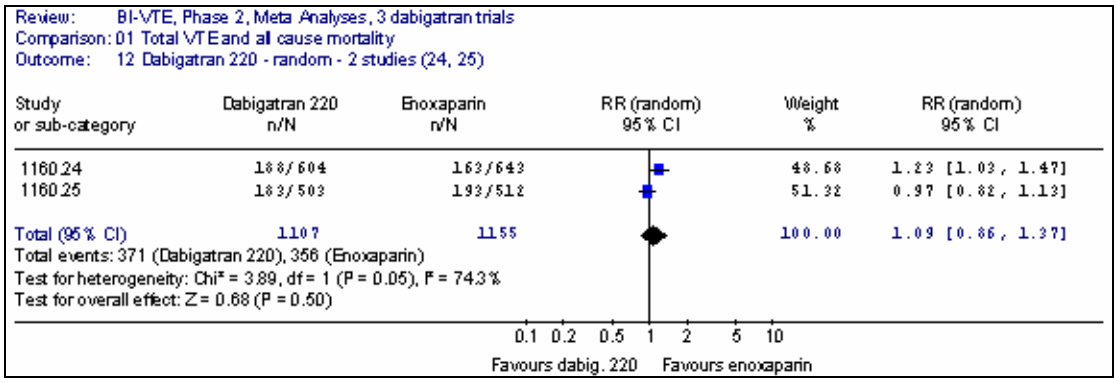


Figure 3 RE-MOBILIZE plus RE-MODEL (fixed effects) – 220mg

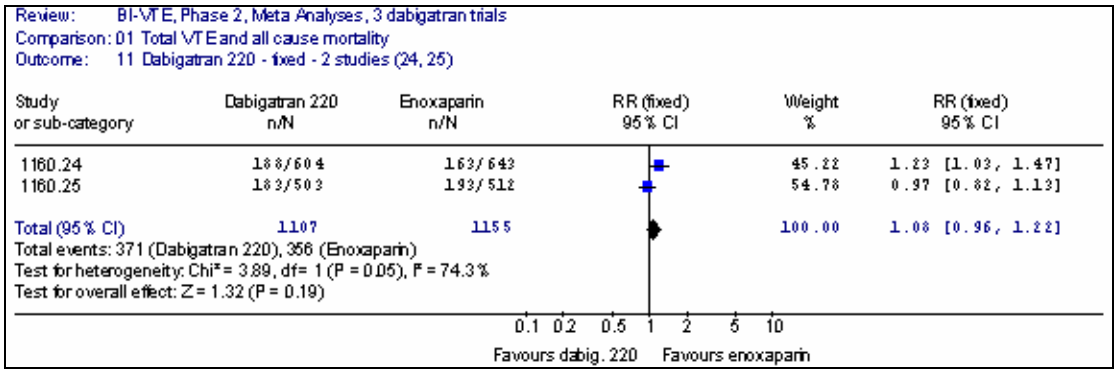


Figure 4 **RE-NOVATE plus RE-MODEL (random effects) – 150mg**

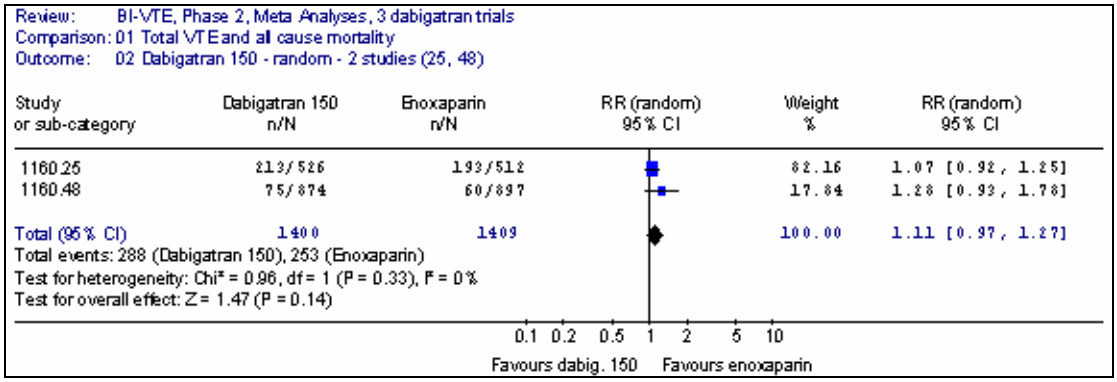


Figure 5 **RE-MOBILIZE plus RE-MODEL (random effects) – 150mg**

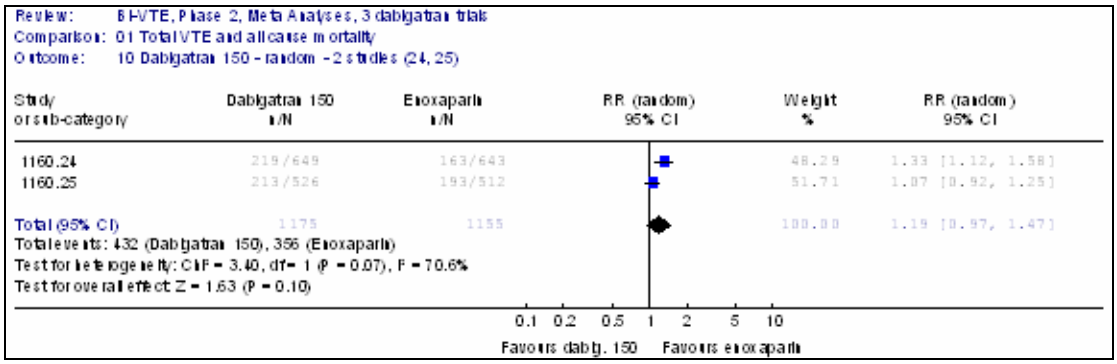
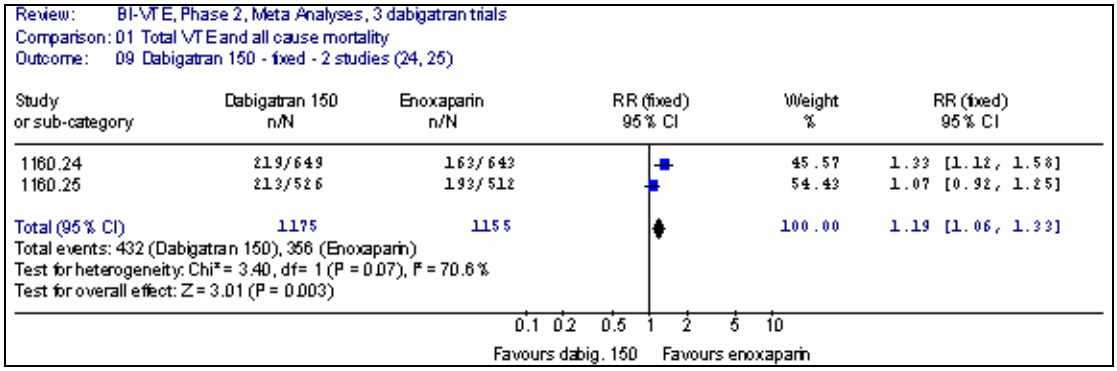


Figure 6 **RE-MOBILIZE plus RE-MODEL (fixed effects) – 150mg**



Secondary efficacy endpoint

Figure 7 RE-NOVATE plus RE-MODEL (random effects) – 220mg

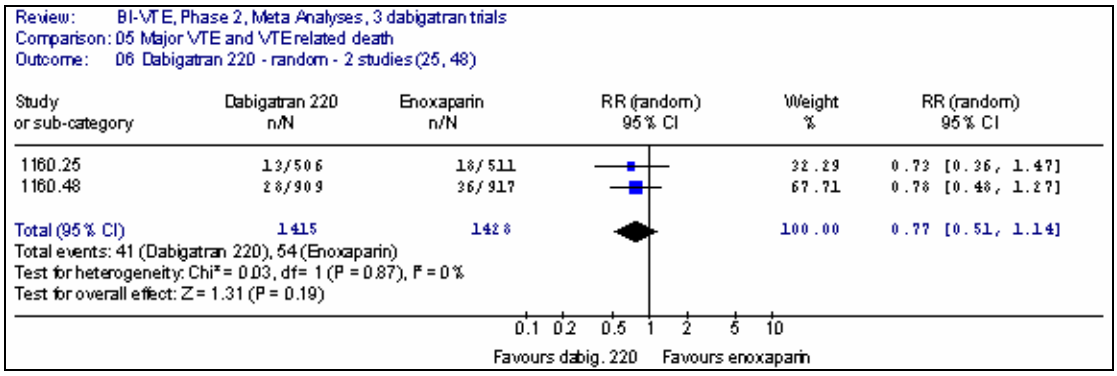


Figure 8 RE-MOBILIZE plus RE-MODEL (random effects) – 220mg

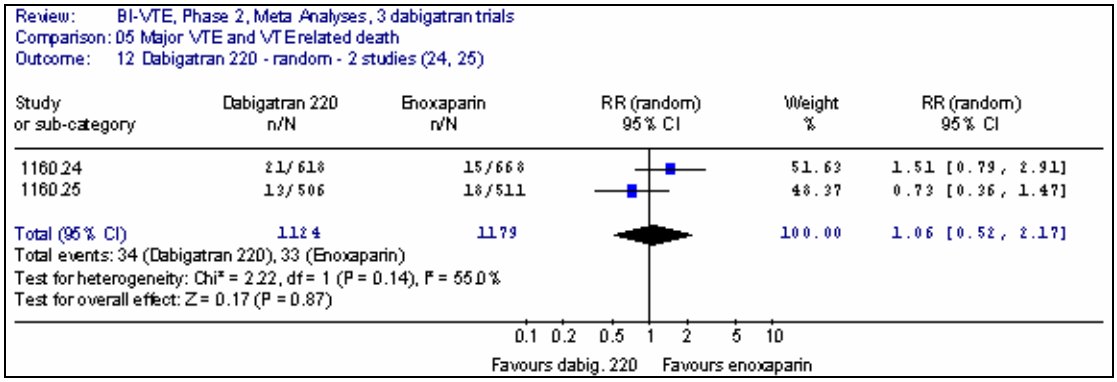


Figure 9 RE-MOBILIZE plus RE-MODEL (fixed effects) – 220mg

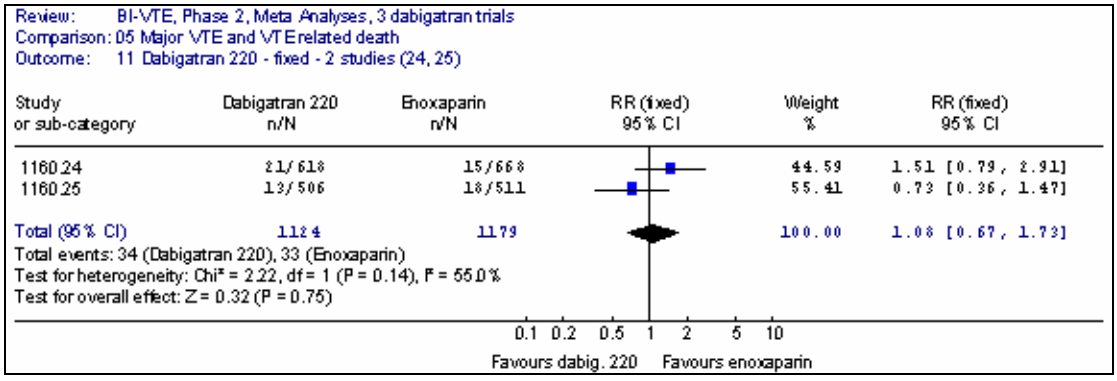


Figure 10 **RE-NOVATE plus RE-MODEL (random effects) – 150mg**

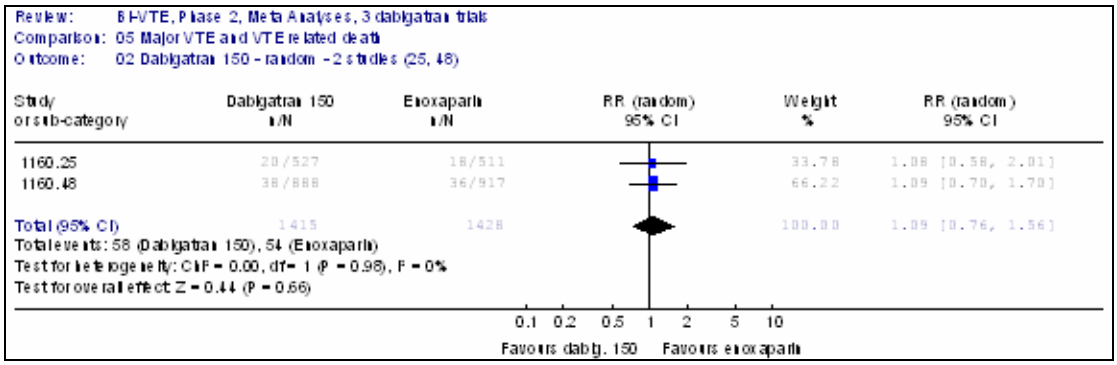


Figure 11 **RE-MOBILIZE plus RE-MODEL (random effects) – 150mg**

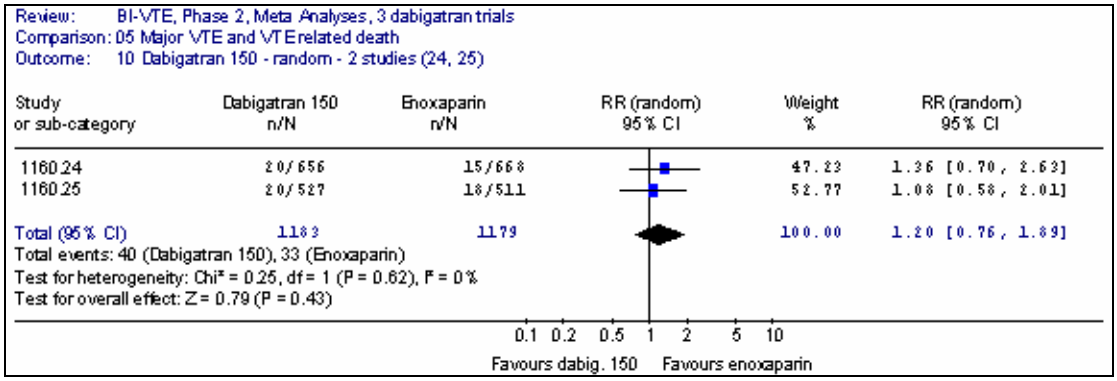
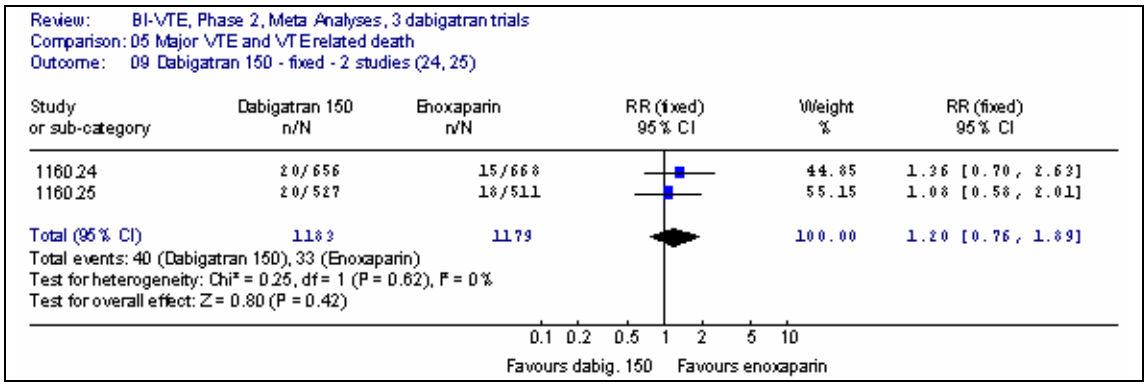


Figure 12 **RE-MOBILIZE plus RE-MODEL (fixed effects) – 150mg**



Major bleed

Figure 13 RE-NOVATE plus RE-MODEL (random effects) – 220mg

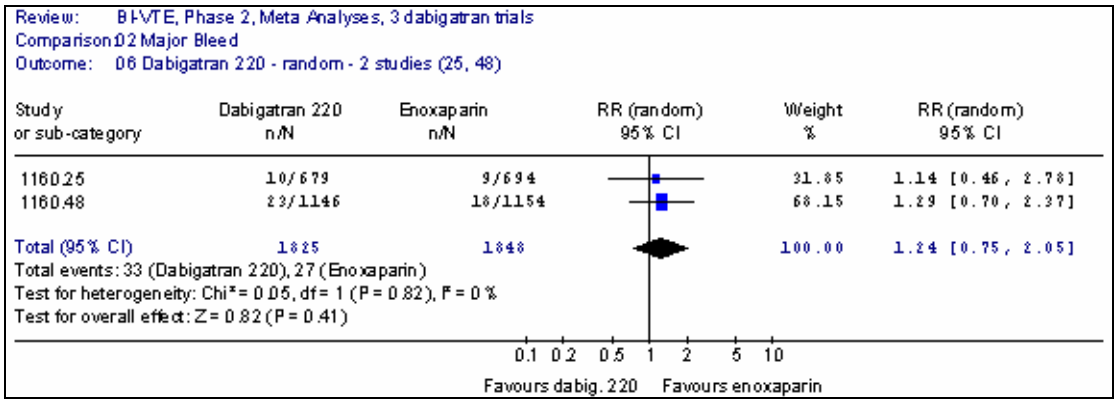


Figure 14 RE-MOBILIZE plus RE-MODEL (random effects) – 220mg

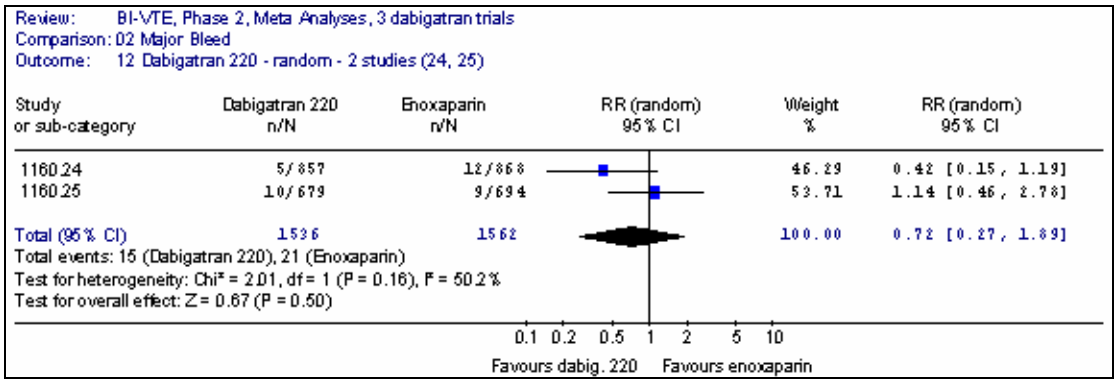


Figure 15 RE-MOBILIZE plus RE-MODEL (fixed effects) – 220mg

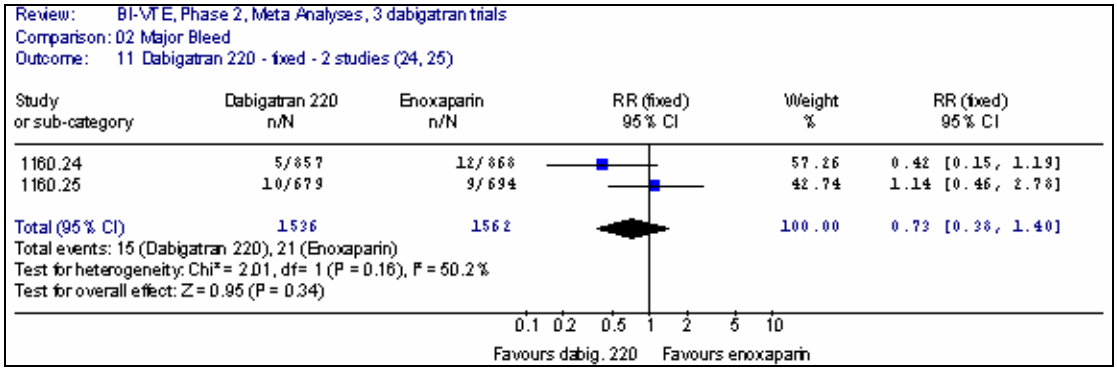


Figure 16 RE-NOVATE plus RE-MODEL (random effects) – 150mg

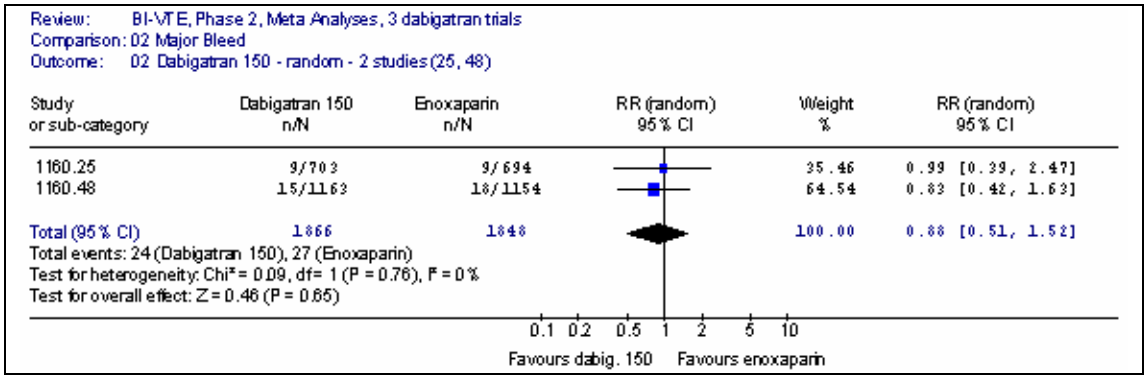


Figure 17 RE-MOBILIZE plus RE-MODEL (random effects) – 150mg

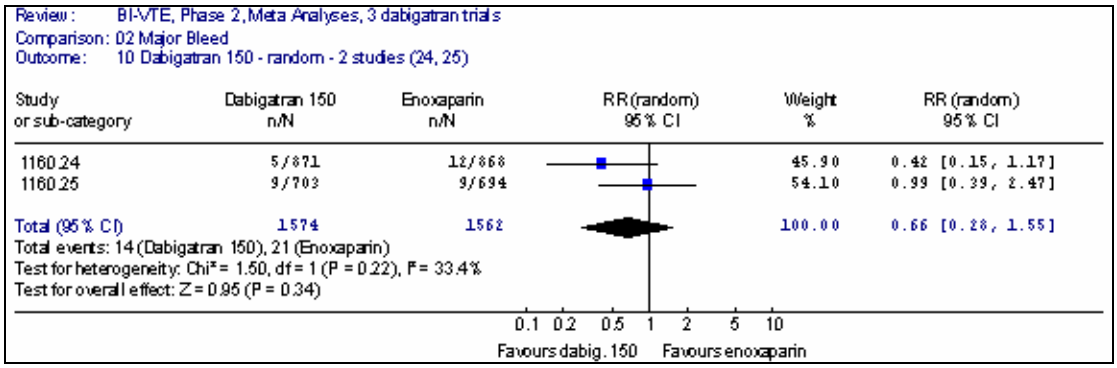
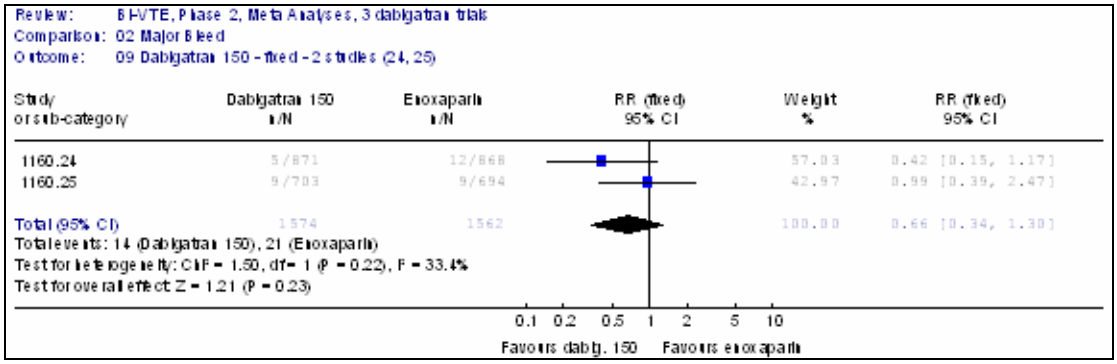


Figure 18 RE-MOBILIZE plus RE-MODEL (fixed effects) – 150mg



Clinically relevant bleed

Figure 19 RE-NOVATE plus RE-MODEL (random effects) – 220mg

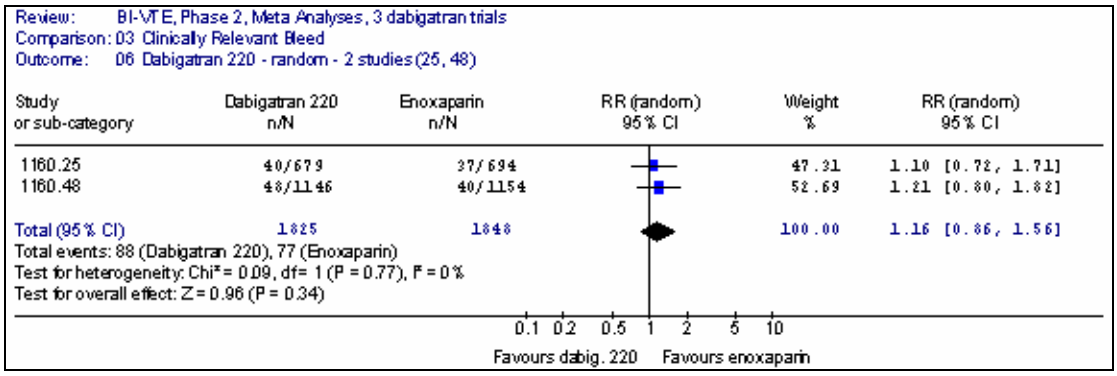


Figure 20 RE-MOBILIZE plus RE-MODEL (random effects) – 220mg

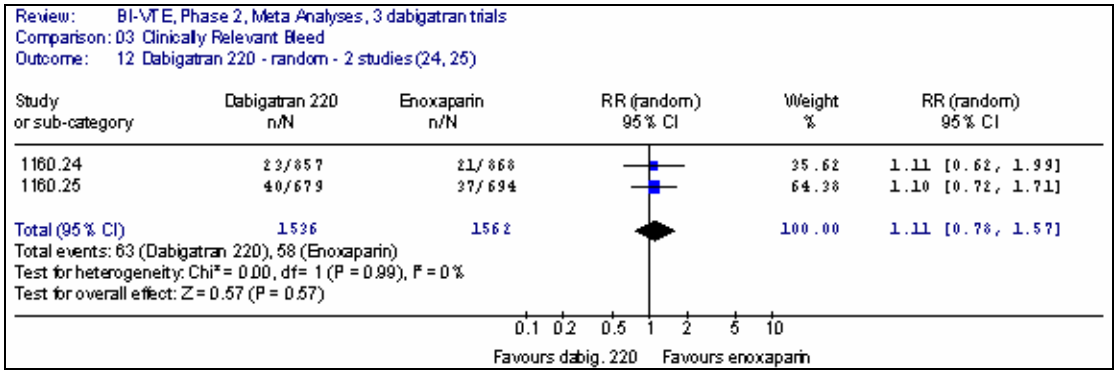


Figure 21 RE-MOBILIZE plus RE-MODEL (fixed effects) – 220mg

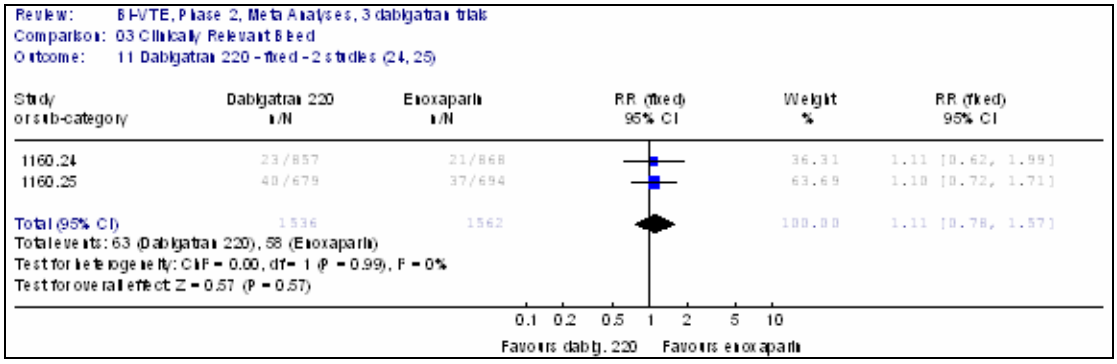


Figure 22 RE-NOVATE plus RE-MODEL (random effects) – 150mg

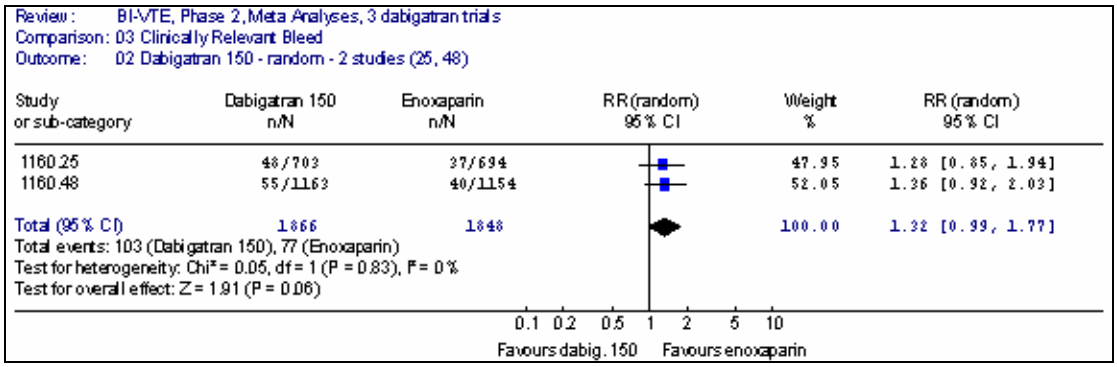


Figure 23 RE-MOBILIZE plus RE-MODEL (random effects) – 150mg

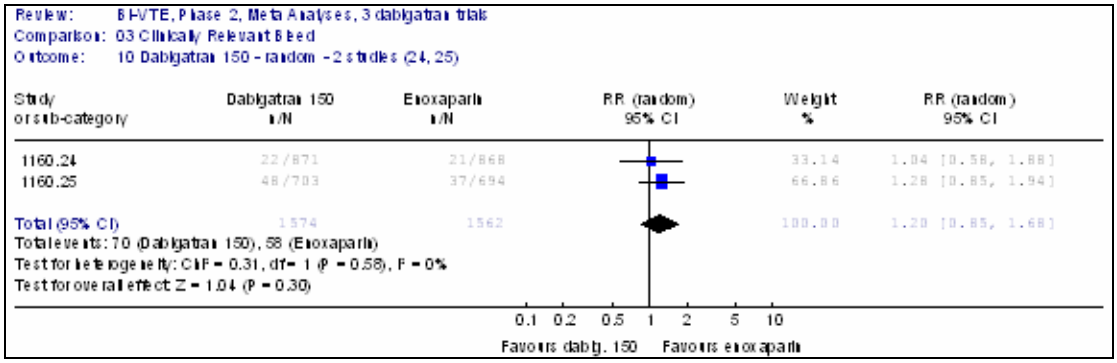
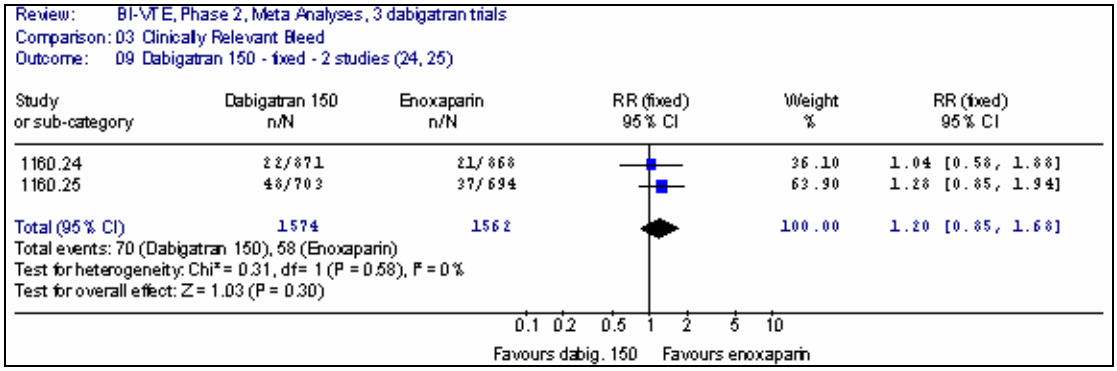


Figure 24 RE-MOBILIZE plus RE-MODEL (fixed effects) – 150mg



Clinically relevant/minor bleed

Figure 25 RE-NOVATE plus RE-MODEL (random effects) – 220mg

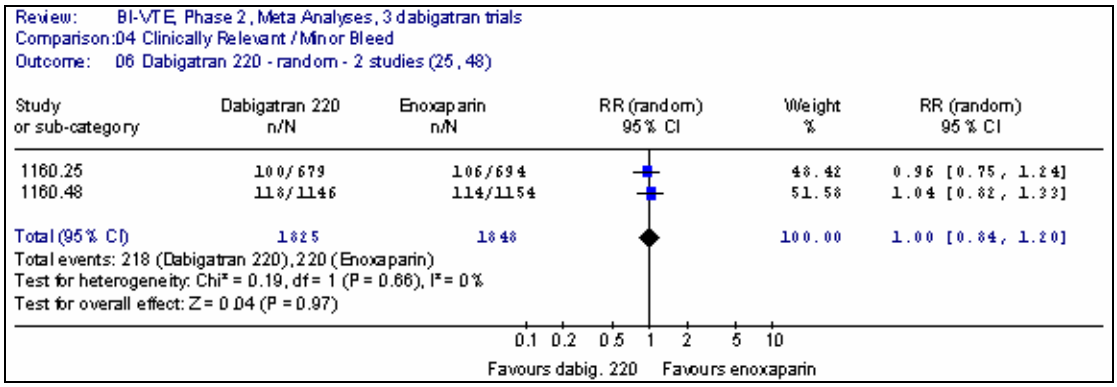


Figure 26 RE-MOBILIZE plus RE-MODEL (random effects) – 220mg

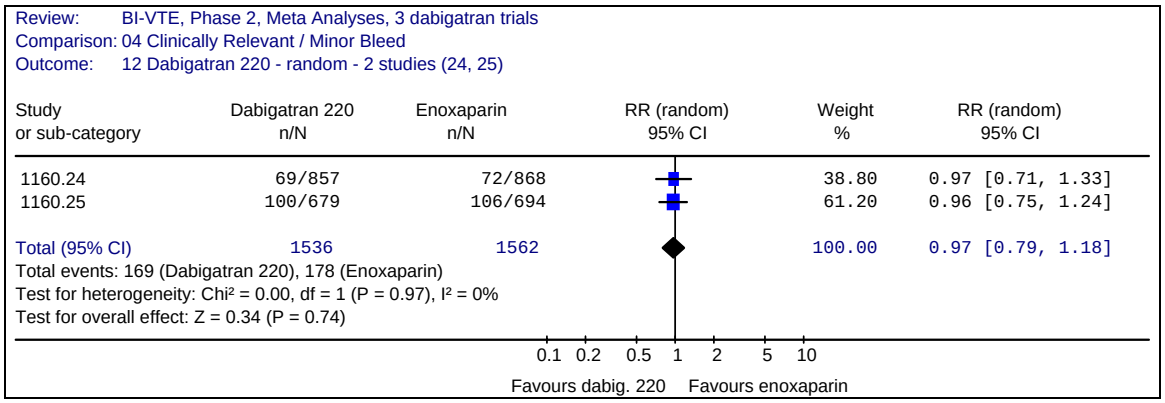


Figure 27 RE-MOBILIZE plus RE-MODEL (fixed effects) – 220mg

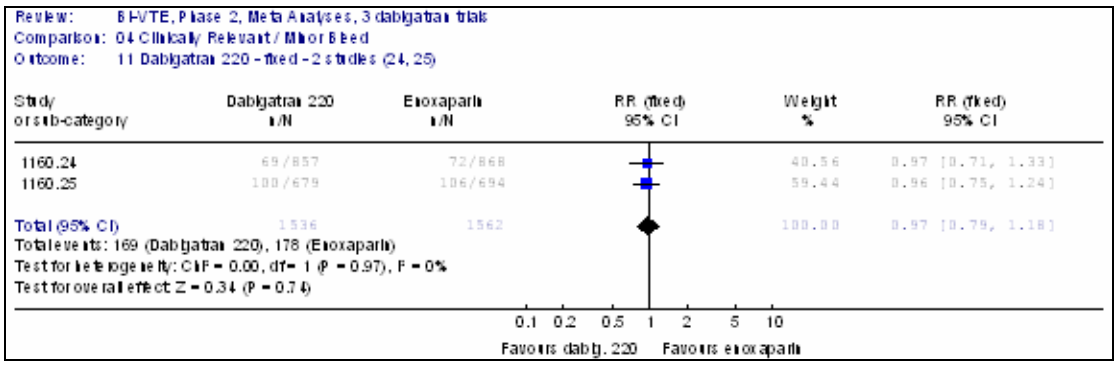


Figure 28 RE-NOVATE plus RE-MODEL (random effects) – 150mg

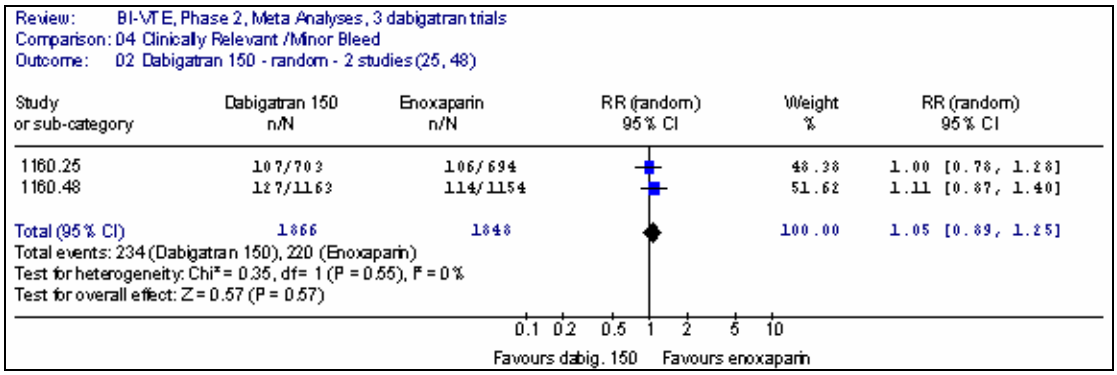


Figure 29 RE-MOBILIZE plus RE-MODEL (random effects) – 150mg

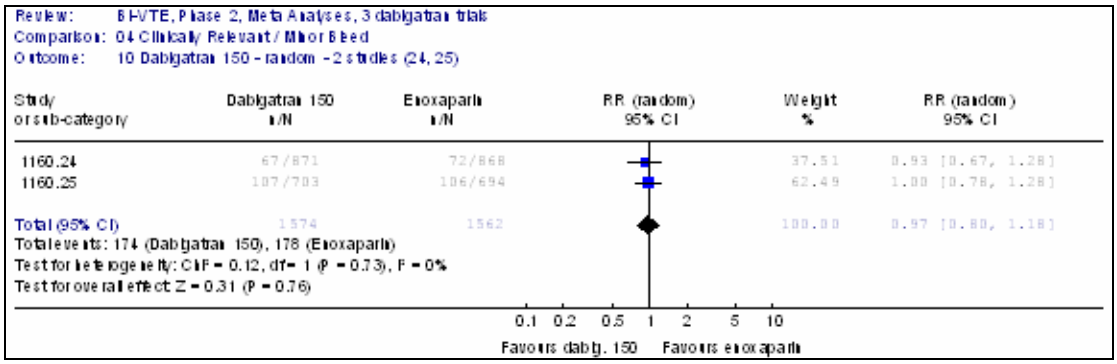


Figure 30 RE-MOBILIZE plus RE-MODEL (fixed effects) – 150mg