NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Denosumab for the Prevention of Osteoporotic Fractures in Postmenopausal Women

Manufacturer Response to Clarification Questions Received 4 March 2010

Amgen UK Ltd.

Submitted 10 March 2010

Section A Clarification on effectiveness data

A.1 Please clarify why studies with open label design were excluded from the meta-analysis (figure B2). The usual reason for such exclusion is the possibility of bias by observers aware of allocation, but that should not be a problem if clinical fractures such as hip or wrist are used, or if outcomes are assessed by a reporter unaware of the allocation.

In order to ensure consistency with the approach previously taken by the Institute, our study selection replicated that of the National Collaborating Centre for Nursing and Supportive Care (NCCNSC) review (October 2008) prepared for the Institute's clinical guideline: 'Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk. Furthermore, we extended our review to included studies published up to November 2009. Based on the NCCNSC search criteria, a broad review of the literature was conducted and updated covering women, men, and glucocorticoid induced osteoporosis across a number of therapies with various study designs. A detailed systematic review and meta-analyses were conducted on a subset of the identified studies. To ensure consistency with the NCCNSC identified literature and studies included in the NCCNSC meta-analysis, additional exclusion criteria were applied to identify the specific studies evaluating PMO patients that matched the NCCNSC identified articles across the therapies of interest for this analysis. As part of this effort, it was found that open-label studies were excluded from the meta-analysis within the NCCNSC review. Open-label studies were discussed extensively in the NCCNSC review report as these studies were captured within the systematic review of the literature, but excluded from the meta-analysis.

Throughout the NCCNSC evaluation of the identified studies it was found that blinding was unclear for many studies. In such cases the studies were included in the NCCNSC meta-analysis, we took a consistent approach. An example of this is Durson et al, 2001 (page 29, NCCNSC review) which

evaluated alendronate versus placebo and Hooper et al, 2005 (page 56 of the NCCNSC review) which evaluated risedronate versus placebo. Although the blinding status of these studies was unclear both studies were included within both our and the NCCNSC primary analysis.

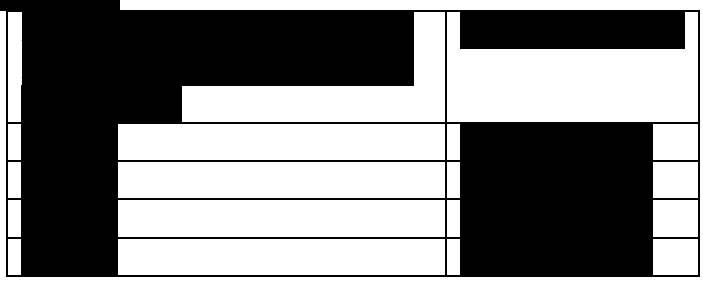
However, studies which were 100% open-label (no blinding was conducted) did not reach the primary meta-analysis phase of either the NCCNSC or our review. An example of such exclusion is provided in the etidronate versus placebo studies where Montessori et al 1997 was excluded (Page 47 of the NCCNSC review) from the primary meta-analysis as this study was not blinded. These studies were only included in sensitivity analysis in the NCCNSC review. Furthermore, studies which were partially open-label were also included in sensitivity analysis in the NCCNSC review. An example of this is Michalska et al 2006 which was a randomised trial with blinding, but included a 1-year open-label extension phase and data was reported including this phase of the study. Based on this potential bias as well as other factors, the study was included only in the form of a sensitivity analysis (Page 200 of the NCCNSC review). We took the same approach within our analysis. The studies identified for meta-analysis included in our analysis match the NCCNSC review. Any discrepancies between studies included in the NCCNSC and our review are described in Section 5.2.2 of our restructured original submission.

A.2 Please clarify why the percentages of drugs used (Table A6) appear to be different to the data from GPRD (page 127). For example, table A6 says that 1.5% of patients receive etidronate but page 127 reports 29%. Please provide a table showing the GPRD data with percentages receiving each drug.

It is correct that the percentages of patients receiving specific treatments is not consistent between the 2009 IMS / CSD data presented in Table A6 and the 1995 to 2008 General Practice Research Database (GPRD) data presented in section 5.8.1 of our restructured original submission. This is to be expected, given that the GPRD study is a longitudinal review of

postmenopausal osteoporosis (PMO) treatments used in a primary care setting between 1995 and 2009 (Amgen data on file; Boston Collaborative Group report, 2009), while the 2009 IMS / CSD data is a current cross-sectional analysis of sales data for all PMO treatments regardless of care setting. As described in our restructured original submission, the GPRD study was performed to evaluate the adherence and persistence of anti-osteoporotic therapies used in the UK. The GPRD study was not designed to estimate the current proportion of patients receiving specific treatments in the UK because these proportions will have evolved dynamically during the 1999 to 2008 timeframe of the database as new treatments became available, new data for existing treatments were published, NICE guidance were published and the prices of the treatments changed. Table A.2.a illustrates that the longitudinal GPRD study included very few recent observations and demonstrates its unsuitability for estimating the current proportion of patients receiving specific treatments in the UK. Furthermore, the GPRD by definition is restricted to General Practice and so not all treatments are included. For example, IV BPs are limited to a secondary care setting by their mode of administration and hence there are very few patients in the GPRD database treated with IV BPs. Specifically, [redacted] patients, out of a total of [redacted], were treated with IV ibandronate and zoledronate respectively (see Table 2 below). Table A.2.b below presents the stable cohort of the GPRD data with percentages receiving each treatment. We are in the process of requesting that the GPRD study data be analysed for proportion of patients receiving specific treatments by year. Unfortunately, owing to the limited time afforded to us by the Institute to respond to these questions, these data are not yet available. However, we remain confident that the IMS / CSD data are the most robust data source for estimating the current proportion of patients receiving specific treatments.

Table A.2.a [redacted]



[redacted]

Table A.2.b [redacted]

[redacted]

A.3 Please provide persistence data for IV ibandronate and zoledronate (as is provided in Table B28 for oral therapies).

As described on page 125 of our restructured original submission [redacted] in the GPRD database. Further as clarified above, the GPRD by definition is restricted to General Practice and so includes too few observations of IV ibandronate and zoledronate ([redacted]) to perform any analysis of persistence with these therapies.

Furthermore, we state on page 171 of our restructured original submission that *"Zoledronate, ibandronate iv and teriparatide have been excluded from persistence sensitivity analyses in view of the absence of evidence on the persistence profile of these therapies".*

Section B Clarification on cost-effectiveness data

B.1 Please provide results of the modelling with tables showing ICERs by bands of both age and T-score (see table below). Previous analyses conducted for NICE appraisals have used predicted risk at the central point in T-score bands to represent the average risk within the band (e.g. risk at – 2.75 is used to model the average risk for individuals in T-score band -2.5 to -2.99). Please provide a repetition of the type of analysis presented in B76 of the amended submission, for all the age groups of interest.

We explained our rationale for using the below threshold approach to fracture risk assessment both in our restructured original submission (page 185) and in our response to clarification questions (page 5 of our response to initial clarification question B.5). To further clarify, a patient with a given mean T-score will not have the mean risk of fracture as risk is non-linear (exponential) with respect to T-score. So, for example, a patient with a mean T-score of -2.75 will not have the mean risk of fracture for patients within the T-score band -2.5 to -3.0. The average fracture risk will be found in an individual with a lower than average T-score (Jenssen's inequality). In our example of the T-score band -2.5 to -3.0, the average fracture risk will be found in patients with a T-score of less than -2.75. Setting the T-score at the central point in the T-score band would underestimate the mean fracture risk in the T-score band. The below threshold approach takes Jenssen's inequality into account and provides a more accurate approximation of mean fracture risk. Therefore, we used the below threshold approach to fracture risk assessment in our restructured original submission. Our position remains that the below threshold approach to fracture risk assessment remains the most robust and that analyses using at threshold T-score for the central point in a T-score

band will underestimate fracture risk in that patient group. However, we have provided the requested subgroup analysis using the central point in both T-score and age bands (see Tables B.1.a and B.1.b below for primary and secondary comparators respectively), but urge that caution be exercised when interpreting these analyses for the aforementioned reasons.

Table B.1.a Subgroup analysis: primary comparison: denosumab, strontium, raloxifene and no treatment (no prior fracture) – using at threshold risk and central point in both T-score and age bands

		QALYs				Costs				ICERs for comparison with Denosumab				
T-score	age	Denosumab	Strontium	Raloxifene	No Treatment	Denosumab	Strontium	Raloxifene	No Treatment	Strontium	Raloxifene	No Treatment	Highest NMHB	Position for Denosumab
-2.75	58	12.074	12.052	12.053	12.049	10,638	10,424	9,954	8,613	9,672	32,905	**81,254**	No Treat	3
-2.75	63	10.451	10.427	10.428	10.422	10,649	10,467	10,012	8,680	7,475	27,385	**67,886**	No Treat	2
-2.75	68	8.778	8.742	8.744	8.728	10,589	10,513	10,105	8,786	2,091	14,090	**36,211**	No Treat	2
-2.75	73	7.160	7.125	7.125	7.114	10,247	10,278	9,913	8,636	Domt	9,540	**34,800**	No Treat	2
-2.75	78	5.650	5.619	5.616	5.611	9,537	9,872	9,633	8,420	Domt	Domt	**28,686**	Dmab	1
-3.25	58	11.936	11.907	11.907	11.900	13,955	13,798	13,353	12,005	5,416	21,122	**54,449**	No Treat	2
-3.25	63	10.324	10.292	10.292	10.283	13,937	13,822	13,398	12,058	3,575	16,928	**45,838**	No Treat	2
-3.25	68	8.669	8.620	8.621	8.599	13,818	13,863	13,511	12,176	Domt	6,392	**23,746**	Dmab	1
-3.25	73	7.076	7.029	7.027	7.011	13,309	13,506	13,211	11,923	Domt	2,008	**21,436**	Dmab	1
-3.25	78	5.588	5.547	5.542	5.535	12,328	12,938	12,808	11,590	**Domt**	Domt	13,722	Dmab	1
-3.75	58	11.750	11.710	11.709	11.698	18,596	18,531	18,127	16,770	1,650	11,582	**35,577**	No Treat	2
-3.75	63	10.153	10.111	10.109	10.096	18,506	18,498	18,122	16,769	179	8,632	**30,261**	No Treat	2
-3.75	68	8.522	8.456	8.454	8.427	18,273	18,504	18,239	16,879	Domt	506	**14,732**	Dmab	1
-3.75	73	6.964	6.901	6.896	6.875	17,490	17,936	17,749	16,442	**Domt**	Domt	11,783	Dmab	1
-3.75	78	5.507	5.453	5.445	5.434	16,114	17,109	17,130	15,903	**Domt**	Domt	2,893	Dmab	1
-4.25	58	11.508	11.454	11.449	11.435	25,070	25,157	24,820	23,447	Domt	4,294	**22,266**	Dmab	1
-4.25	63	9.933	9.875	9.871	9.854	24,826	24,987	24,686	23,314	Domt	2,240	**19,137**	Dmab	1
-4.25	68	8.331	8.244	8.237	8.205	24,375	24,894	24,760	23,366	**Domt**	Domt	7,989	Dmab	1
-4.25	73	6.818	6.734	6.725	6.699	23,140	23,960	23,935	22,599	**Domt**	Domt	4,517	Dmab	1
-4.25	78	5.402	5.332	5.319	5.306	21,181	22,705	22,934	21,692	**Domt**	Domt	Domt	Dmab	1

NMHB, Net Monetary Health Benefit

ICERs for treatments that are recommended by NICE according to age, T-score and prior fracture are provided in bold text to enable readers to compare with recommendations in TA160/161

N.B. Caution be exercised when interpreting these analyses as using at threshold T-score at the central point in the band underestimates the mean fracture risk in the band

Table B.1.a Subgroup analysis: primary comparison: denosumab, strontium, raloxifene and no treatment (prior fracture – using at threshold risk and central point in both T-score and age bands

		QALYs				Costs				ICERs for comparison with Denosumab				
T-score	age	Denosumab	Strontium	Raloxifene	No Treatment	Denosumab	Strontium	Raloxifene	No Treatment	Strontium	Raloxifene	No Treatment	Highest NMHB	Position for Denosumab
-2.75	58	11.808	11.757	11.762	11.733	13,693	13,634	13,232	11,876	1,164	10,111	**24,374**	Dmab	1
-2.75	63	10.239	10.189	10.196	10.165	13,330	13,269	12,873	11,521	1,241	10,594	**24,600**	Dmab	1
-2.75	68	8.629	8.559	8.571	8.519	12,979	13,035	12,702	11,346	Domt	4,775	**14,853**	Dmab	1
-2.75	73	7.075	7.016	7.022	6.985	12,263	12,427	12,128	10,832	**Domt**	**2,582**	15,993	Dmab	1
-2.75	78	5.606	5.563	5.562	5.545	11,121	11,619	11,445	10,230	**Domt**	**Domt**	14,619	Dmab	1
-3.25	58	11.588	11.520	11.523	11.486	18,271	18,370	18,040	16,665	Domt	3,546	**15,820**	Dmab	1
-3.25	63	10.050	9.985	9.991	9.953	17,619	17,696	17,367	15,992	Domt	4,214	**16,662**	Dmab	1
-3.25	68	8.475	8.385	8.396	8.332	17,023	17,268	17,036	15,637	**Domt**	**Domt**	9,706	Dmab	1
-3.25	73	6.965	6.887	6.893	6.846	15,957	16,346	16,156	14,825	**Domt**	**Domt**	9,541	Dmab	1
-3.25	78	5.532	5.475	5.472	5.450	14,380	15,213	15,178	13,945	**Domt**	**Domt**	5,349	Dmab	1
-3.75	58	11.308	11.217	11.216	11.172	24,769	25,129	24,915	23,515	**Domt**	**Domt**	9,241	Dmab	1
-3.75	63	9.812	9.728	9.730	9.685	23,612	23,911	23,687	22,281	**Domt**	**Domt**	10,500	Dmab	1
-3.75	68	8.278	8.162	8.171	8.098	22,593	23,137	23,056	21,604	**Domt**	**Domt**	5,495	Dmab	1
-3.75	73	6.822	6.722	6.724	6.669	20,963	21,694	21,667	20,289	**Domt**	**Domt**	4,395	Dmab	1
-3.75	78	5.435	5.361	5.356	5.329	18,756	20,051	20,208	18,950	**Domt**	**Domt**	Domt	Dmab	1
-4.25	58	10.968	10.848	10.840	10.791	34,031	34,816	34,785	33,352	**Domt**	**Domt**	3,836	Dmab	1
-4.25	63	9.524	9.417	9.414	9.364	31,991	32,645	32,580	31,138	**Domt**	**Domt**	5,345	Dmab	1
-4.25	68	8.034	7.891	7.895	7.816	30,240	31,256	31,397	29,891	**Domt**	**Domt**	1,603	Dmab	1
-4.25	73	6.643	6.515	6.513	6.451	27,691	28,941	29,157	27,720	**Domt**	**Domt**	Domt	Dmab	1
-4.25	78	5.313	5.220	5.211	5.179	24,557	26,481	26,897	25,606	**Domt**	**Domt**	Domt	Dmab	1

NMHB, Net Monetary Health Benefit

ICERs for treatments that are recommended by NICE according to age, T-score and prior fracture are provided in bold text to enable readers to compare with recommendations in TA160/161.

N.B. Caution be exercised when interpreting these analyses as using at threshold T-score at the central point in the band underestimates the mean fracture risk in the band

Table B.1.b Subgroup analysis: secondary comparison: denosumab, ibandronate, zoledronate and teriparatide (no prior fracture) – using at threshold risk and central point in both T-score and age bands

		QALYs				Costs				ICERs for comparison with Denosumab				
T-score	age	Denosumab	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Denosumab	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Highest NMHB	Position for Dmab
-2.75	58	12.07	12.06	12.08	12.08	10,638	13,167	11,005	24,885	Domt	167,417	7,430,561	Dmab	1
-2.75	63	10.45	10.43	10.45	10.46	10,649	13,200	11,015	24,742	Domt	147,541	3,269,486	Dmab	1
-2.75	68	8.78	8.75	8.78	8.79	10,589	13,254	10,948	24,371	Domt	80,582	1,110,914	Dmab	1
-2.75	73	7.16	7.13	7.16	7.18	10,247	12,990	10,594	23,576	Domt	91,581	880,223	Dmab	1
-2.75	78	5.65	5.62	5.65	5.67	9,537	12,584	9,851	21,938	Domt	115,546	716,224	Dmab	1
-3.25	58	11.94	11.91	11.94	11.94	13,955	16,564	14,324	28,116	Domt	124,335	1,733,113	Dmab	1
-3.25	63	10.32	10.30	10.33	10.34	13,937	16,584	14,305	27,926	Domt	110,422	1,239,521	Dmab	1
-3.25	68	8.67	8.62	8.67	8.69	13,818	16,657	14,178	27,421	Domt	60,644	577,059	Dmab	1
-3.25	73	7.08	7.03	7.08	7.10	13,309	16,285	13,654	26,404	Domt	67,570	489,197	Dmab	1
-3.25	78	5.59	5.55	5.59	5.62	12,328	15,757	12,632	24,356	Domt	82,832	428,561	Dmab	1
-3.75	58	11.75	11.71	11.75	11.77	18,596	21,337	18,966	32,619	Domt	92,677	769,761	Dmab	1
-3.75	63	10.15	10.11	10.16	10.18	18,506	21,306	18,876	32,335	Domt	83,436	629,820	Dmab	1
-3.75	68	8.52	8.46	8.53	8.56	18,273	21,380	18,632	31,602	Domt	46,117	331,504	Dmab	1
-3.75	73	6.96	6.90	6.97	7.01	17,490	20,818	17,830	30,233	Domt	50,070	291,205	Dmab	1
-3.75	78	5.51	5.45	5.51	5.55	16,114	20,076	16,402	27,615	Domt	59,123	267,822	Dmab	1
-4.25	58	11.51	11.45	11.51	11.54	25,070	28,027	25,439	38,875	Domt	69,453	408,204	Dmab	1
-4.25	63	9.93	9.87	9.94	9.97	24,826	27,867	25,195	38,408	Domt	63,856	360,855	Dmab	1
-4.25	68	8.33	8.24	8.34	8.39	24,375	27,894	24,729	37,287	Domt	35,528	202,057	Dmab	1
-4.25	73	6.82	6.73	6.83	6.89	23,140	26,997	23,470	35,355	Domt	37,230	180,352	Dmab	1
-4.25	78	5.40	5.32	5.41	5.47	21,181	25,873	21,447	31,950	Domt	41,779	171,199	Dmab	1

NMHB, Net Monetary Health Benefit

No ICER estimates are provided in bold as teriparatide is not recommended by NICE in TA161 and the other interventions have not been appraised by NICE.

N.B. Caution be exercised when interpreting these analyses as using at threshold T-score at the central point in the band underestimates the mean fracture risk in the band

Table B.1.b Subgroup analysis: secondary comparison: denosumab, ibandronate, zoledronate, and teriparatide (prior fracture) – using at threshold risk and central point in both T-score and age bands

		QALYs				Costs				ICERs for comparison with Denosumab				
T-score	age	Denosumab	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Denosumab	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Highest NMHB	Position for Dmab
-2.75	58	11.81	11.76	11.82	11.83	13,693	16,442	14,059	27,717	Domt	51,145	802,789	Dmab	1
-2.75	63	10.24	10.20	10.25	10.25	13,330	16,057	13,699	27,237	Domt	50,970	895,438	Dmab	1
-2.75	68	8.63	8.57	8.64	8.65	12,979	15,843	13,343	26,541	Domt	31,567	578,134	Dmab	1
-2.75	73	7.07	7.02	7.08	7.10	12,263	15,199	12,613	25,384	Domt	39,764	551,420	Dmab	1
-2.75	78	5.61	5.56	5.61	5.63	11,121	14,394	11,432	23,294	Domt	60,673	526,438	Dmab	1
-3.25	58	11.59	11.52	11.60	11.62	18,271	21,246	18,635	32,066	Domt	39,545	413,171	Dmab	1
-3.25	63	10.05	9.99	10.06	10.08	17,619	20,547	17,988	31,315	Domt	40,210	477,770	Dmab	1
-3.25	68	8.48	8.39	8.49	8.52	17,023	20,168	17,389	30,288	Domt	25,124	329,566	Zoled (iv)	2
-3.25	73	6.96	6.89	6.98	7.00	15,957	19,219	16,306	28,739	Domt	30,708	322,800	Dmab	1
-3.25	78	5.53	5.47	5.54	5.57	14,380	18,121	14,680	26,085	Domt	44,793	323,486	Dmab	1
-3.75	58	11.31	11.22	11.32	11.37	24,769	28,116	25,129	38,195	Domt	30,818	233,942	Dmab	1
-3.75	63	9.81	9.73	9.82	9.86	23,612	26,860	23,980	36,980	Domt	32,246	280,680	Dmab	1
-3.75	68	8.28	8.16	8.30	8.34	22,593	26,176	22,959	35,404	Domt	20,405	200,420	Zoled (iv)	2
-3.75	73	6.82	6.72	6.84	6.88	20,963	24,719	21,308	33,239	Domt	23,999	198,203	Zoled (iv)	2
-3.75	78	5.43	5.36	5.44	5.49	18,756	23,143	19,040	29,806	Domt	33,024	205,128	Dmab	1
-4.25	58	10.97	10.84	10.98	11.06	34,031	37,979	34,377	46,863	Domt	24,082	139,863	Zoled (iv)	2
-4.25	63	9.52	9.41	9.54	9.60	31,991	35,745	32,352	44,852	Domt	26,212	174,687	Zoled (iv)	2
-4.25	68	8.03	7.89	8.05	8.13	30,240	34,504	30,599	42,357	Domt	16,870	127,251	Zoled (iv)	2
-4.25	73	6.64	6.51	6.66	6.73	27,691	32,193	28,026	39,210	Domt	18,920	125,095	Zoled (iv)	2
-4.25	78	5.31	5.21	5.32	5.39	24,557	29,822	24,817	34,704	Domt	24,136	131,826	Zoled (iv)	2

NMHB, Net Monetary Health Benefit

N.B. Teriparatide is recommended in patients who are 65 years or older and have a T-score of –4.0 SD or below, or a T-score of –3.5 SD or below plus more than two fractures, or who are aged 55–64 years and have a T-score of –4 SD or below plus more than two fractures

N.B. Caution be exercised when interpreting these analyses as using at threshold T-score at the central point in the band underestimates the mean fracture risk in the band

B.2 In addition to B1 above, please provide subgroup analysis for patients with none, one and two or more independent clinical risk factors (within each sub-group defined by age and T-score) and present results for all relevant comparators (i.e. strontium, raloxifene, teriparatide, zoledronate and IV ibandronate, but not the oral BPs).

As requested, we have provided further sensitivity analyses using FRAX® to include none, one and two independent clinical risk factors for both primary and secondary comparators. As explained in section 6.6.1 on page 234 of our restructured original submission, our implementation of FRAX® was limited to parental history of hip fracture and rheumatoid arthritis because in TA160/161 the FRAX® algorithm for daily alcohol intake was adjusted from 3 or more to 4 or more units per day and we do not have the details of this adjustment. Here we present further sensitivity analyses on our base–case (mean age 70 years) using FRAX for T-score at the central point in the T-score band, prior fracture status and with no independent clinical risk factors; with rheumatoid arthritis and no parental fracture (one independent clinical risk factor); with no rheumatoid arthritis and parental fracture (one independent clinical risk factor); and with both rheumatoid arthritis and parental fracture (one independent clinical risk factors). These additional analyses are presented in Tables B.2.a and B.2.b below and extend to some 336 ICERs (seven T-scores, multiplied by four combinations of independent clinical risk factors, multiplied two options for prior fracture status, multiplied by six primary and secondary comparators). We considered this amount of analyses inordinately large and so have chosen not to perform additional analyses for each age band at this stage as it would have resulted in some 2016 ICERs (336 multiplied by 6 age bands). We would be happy to perform these analyses if required, but request that the Institute give careful consideration to their need for such a large quantity of analyses given the Institute's earlier request for us to restructure and reduce the size of our main evidence submission in order that the evidence review group and appraisal committee have sufficient time to review within the set timelines of the STA process.

Table B2a Sensitivity analyses (base-case run on FRAX®): primary comparisons: cost-effectiveness results for denosumab, strontium, raloxifene and no treatment

	Abs risks		QALYs				Costs				ICERs for comparison with Denosumab		
T score	Hip fracture	Major fracture	Denosumab	Strontium	Raloxifene	No Treatment	Denosumab	Strontium	Raloxifene	No Treatment	Strontium	Raloxifene	No Treatment
No prior fracture, no rheumatoid arthritis, no parental fracture (i.e., no independent clinical risk factors)*													
–2.5	3.80%	14.23%	8.36	8.33	8.33	8.32	8,079	7,950	7,517	6,216	4,631	21,878	51,271
–2.75	4.86%	16.00%	8.26	8.23	8.23	8.22	9,107	9,019	8,603	7,300	2,823	16,921	43,344
–3	6.20%	18.04%	8.16	8.12	8.13	8.11	10,334	10,296	9,903	8,596	1,077	12,420	36,240
–3.25	7.90%	20.43%	8.05	8.01	8.01	8.00	11,795	11,819	11,453	10,143	Domt	8,389	29,900
–3.5	10.03%	23.20%	7.93	7.89	7.89	7.87	13,529	13,630	13,298	11,982	Domt	4,818	24,263
–3.75	12.68%	26.42%	7.81	7.76	7.75	7.73	15,579	15,775	15,484	14,163	Domt	1,670	19,260
–4	15.97%	30.14%	7.67	7.61	7.61	7.59	17,992	18,306	18,066	16,737	Domt	Domt	14,818
No prior fracture, rheumatoid arthritis, no parental fracture (i.e., one independent clinical risk factor)*													
–2.5	7.96%	22.98%	8.22	8.18	8.18	8.16	12,828	12,845	12,482	11,154	Domt	8,255	27,841
–2.75	10.12%	25.88%	8.11	8.06	8.06	8.04	14,679	14,771	14,442	13,107	Domt	4,814	22,846
–3	12.80%	29.21%	7.98	7.92	7.92	7.90	16,861	17,046	16,759	15,415	Domt	1,764	18,361
–3.25	16.12%	33.03%	7.84	7.78	7.77	7.75	19,423	19,724	19,487	18,134	Domt	Domt	14,329
–3.5	20.17%	37.36%	7.70	7.62	7.62	7.59	22,422	22,864	22,690	21,325	Domt	Domt	10,689
–3.75	25.06%	42.24%	7.54	7.46	7.45	7.42	25,917	26,533	26,436	25,057	Domt	Domt	7,373
–4	30.83%	47.64%	7.37	7.28	7.26	7.24	29,973	30,803	30,798	29,405	Domt	Domt	4,308
No prior fracture, no rheumatoid arthritis, parental fracture (i.e., one independent clinical risk factor)*													
–2.5	5.36%	18.37%	8.30	8.27	8.27	8.26	10,056	9,983	9,577	8,264	2,122	14,848	37,974
–2.75	6.83%	20.63%	8.20	8.16	8.16	8.14	11,415	11,395	11,014	9,696	505	10,663	31,826
–3	8.69%	23.25%	8.08	8.04	8.04	8.02	13,028	13,074	12,722	11,399	Domt	6,920	26,306
–3.25	11.02%	26.27%	7.96	7.91	7.91	7.89	14,934	15,063	14,748	13,418	Domt	3,599	21,362
–3.5	13.92%	29.74%	7.83	7.78	7.77	7.75	17,181	17,411	17,141	15,802	Domt	661	16,936
–3.75	17.50%	33.72%	7.69	7.63	7.62	7.60	19,818	20,174	19,958	18,610	Domt	Domt	12,967
–4	21.84%	38.24%	7.54	7.47	7.46	7.44	22,902	23,411	23,263	21,903	Domt	Domt	9,388
No prior fracture, rheumatoid arthritis, parental fracture (i.e., two independent clinical risk factors)*													
–2.5	11.12%	29.30%	8.13	8.08	8.08	8.05	16,209	16,324	16,014	14,658	Domt	3,672	20,246
–2.75	14.05%	32.88%	8.00	7.94	7.94	7.91	18,595	18,808	18,544	17,176	Domt	823	16,280
–3	17.65%	36.93%	7.86	7.79	7.79	7.76	21,390	21,725	21,516	20,135	Domt	Domt	12,676
–3.25	22.04%	41.49%	7.71	7.63	7.62	7.59	24,652	25,136	24,996	23,600	Domt	Domt	9,380
–3.5	27.28%	46.54%	7.55	7.46	7.45	7.42	28,445	29,115	29,056	27,644	Domt	Domt	6,329
–3.75	33.43%	52.06%	7.37	7.27	7.26	7.23	32,836	33,734	33,775	32,345	Domt	Domt	3,454
–4	40.44%	57.93%	7.19	7.08	7.06	7.03	37,892	39,070	39,231	37,784	Domt	Domt	677

Domt, denosumab dominant. * Independent clinical risk factors are defined as per NICE TA160/161, but are limited to rheumatoid arthritis and parental history of hip fracture because in TA160/161 the FRAX® algorithm for daily alcohol intake was adjusted from three or more to four or more units per day, the details of this were not available.

Table B2a Sensitivity analyses (base-case run on FRAX®): primary comparisons: cost-effectiveness results for denosumab, strontium, raloxifene and no treatment

	Abs risks		QALYs				Costs				ICERs for comparison with Denosumab		
T score	Hip fracture	Major fracture	Denosumab	Strontium	Raloxifene	No Treatment	Denosumab	Strontium	Raloxifene	No Treatment	Strontium	Raloxifene	No Treatment
Prior fracture, no rheumatoid arthritis, no parental fracture (i.e., no independent clinical risk factors)*													
–2.5	5.82%	22.09%	8.27	8.23	8.24	8.22	11,110	11,045	10,651	9,320	1,669	13,049	32,239
–2.75	7.42%	24.62%	8.16	8.12	8.12	8.10	12,572	12,562	12,195	10,856	236	9,229	27,248
–3	9.43%	27.49%	8.05	8.00	8.00	7.98	14,299	14,356	14,022	12,674	Domt	5,800	22,715
–3.25	11.95%	30.77%	7.92	7.87	7.87	7.84	16,332	16,473	16,178	14,819	Domt	2,739	18,601
–3.5	15.06%	34.48%	7.79	7.73	7.73	7.70	18,718	18,964	18,717	17,346	Domt	10	14,862
–3.75	18.89%	38.67%	7.65	7.58	7.57	7.54	21,510	21,885	21,698	20,311	Domt	Domt	11,450
–4	23.51%	43.35%	7.50	7.41	7.41	7.38	24,766	25,299	25,185	23,782	Domt	Domt	8,312
Prior fracture, rheumatoid arthritis, no parental fracture (i.e., one independent clinical risk factor)*													
–2.5	12.05%	34.37%	8.09	8.03	8.03	8.00	17,765	17,882	17,598	16,198	Domt	2,911	17,804
–2.75	15.20%	38.17%	7.95	7.89	7.89	7.85	20,295	20,512	20,277	18,861	Domt	267	14,468
–3	19.06%	42.41%	7.81	7.73	7.73	7.70	23,249	23,591	23,415	21,981	Domt	Domt	11,381
–3.25	23.73%	47.09%	7.65	7.57	7.56	7.53	26,689	27,184	27,081	25,627	Domt	Domt	8,497
–3.5	29.28%	52.17%	7.49	7.39	7.38	7.35	30,681	31,366	31,351	29,875	Domt	Domt	5,766
–3.75	35.74%	57.60%	7.31	7.20	7.19	7.16	35,292	36,214	36,305	34,808	Domt	Domt	3,123
–4	43.03%	63.25%	7.12	7.00	6.99	6.95	40,589	41,803	42,022	40,504	Domt	Domt	496
Prior fracture, no rheumatoid arthritis, parental fracture (i.e., one independent clinical risk factor)*													
–2.5	8.17%	28.04%	8.19	8.15	8.15	8.12	13,914	13,916	13,566	12,203	Domt	7,837	24,189
–2.75	10.37%	31.16%	8.07	8.02	8.02	7.99	15,809	15,882	15,568	14,192	Domt	4,657	20,235
–3	13.12%	34.67%	7.95	7.88	7.89	7.86	18,033	18,195	17,924	16,533	Domt	1,807	16,613
–3.25	16.51%	38.61%	7.81	7.74	7.74	7.71	20,637	20,908	20,690	19,283	Domt	Domt	13,286
–3.5	20.65%	43.00%	7.66	7.58	7.58	7.55	23,675	24,082	23,929	22,503	Domt	Domt	10,211
–3.75	25.63%	47.84%	7.50	7.41	7.41	7.37	27,210	27,785	27,710	26,265	Domt	Domt	7,337
–4	31.50%	53.09%	7.33	7.24	7.22	7.19	31,306	32,090	32,108	30,643	Domt	Domt	4,609
Prior fracture, rheumatoid arthritis, parental fracture (i.e., two independent clinical risk factors)*													
–2.5	16.65%	42.66%	7.97	7.89	7.89	7.86	22,363	22,595	22,393	20,928	Domt	Domt	13,139
–2.75	20.83%	47.06%	7.82	7.74	7.73	7.70	25,572	25,934	25,797	24,308	Domt	Domt	10,350
–3	25.86%	51.85%	7.66	7.57	7.56	7.52	29,300	29,824	29,766	28,253	Domt	Domt	7,701
–3.25	31.79%	56.96%	7.49	7.39	7.38	7.34	33,619	34,344	34,380	32,844	Domt	Domt	5,143
–3.5	38.60%	62.31%	7.31	7.19	7.18	7.14	38,597	39,573	39,723	38,163	Domt	Domt	2,612
–3.75	46.20%	67.75%	7.11	6.99	6.97	6.93	44,297	45,586	45,873	44,292	Domt	Domt	31
–4	54.33%	73.08%	6.91	6.77	6.75	6.71	50,762	52,440	52,890	51,292	Domt	Domt	Domt

Domt, denosumab dominant. * Independent clinical risk factors are defined as per NICE TA160/161, but are limited to rheumatoid arthritis and parental history of hip fracture because in TA160/161 the FRAX® algorithm for daily alcohol intake was adjusted from three or more to four or more units per day, the details of this were not available.

Table B2b Sensitivity analyses (base-case run on FRAX®): secondary comparisons: cost-effectiveness results for denosumab, ibandronate (iv), zoledronate (iv) and teriparatide

	Abs risks		QALYs				Costs				ICERs for comparison with Denosumab		
T score	Hip fracture	Major fracture	Denosumab	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Denosumab	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Ibandronate (iv)	Zoledronate (iv)	Teriparatide
No prior fracture, no rheumatoid arthritis, no parental fracture (i.e., no independent clinical risk factors)*													
–2.5	3.80%	14.23%	8.36	8.34	8.36	8.37	8,079	10,656	8,435	21,890	Domt	106,885	2,154,892
–2.75	4.86%	16.00%	8.26	8.24	8.27	8.27	9,107	11,738	9,463	22,847	Domt	96,568	1,394,014
–3	6.20%	18.04%	8.16	8.13	8.16	8.17	10,334	13,033	10,690	23,988	Domt	87,084	965,755
–3.25	7.90%	20.43%	8.05	8.01	8.06	8.07	11,795	14,580	12,150	25,346	Domt	78,386	697,652
–3.5	10.03%	23.20%	7.93	7.89	7.94	7.96	13,529	16,420	13,883	26,956	Domt	70,424	518,383
–3.75	12.68%	26.42%	7.81	7.75	7.81	7.84	15,579	18,601	15,931	28,857	Domt	63,153	393,083
–4	15.97%	30.14%	7.67	7.61	7.68	7.72	17,992	21,177	18,341	31,089	Domt	56,522	302,686
No prior fracture, rheumatoid arthritis, no parental fracture (i.e., one independent clinical risk factor)*													
–2.5	7.96%	22.98%	8.22	8.19	8.23	8.24	12,828	15,615	13,193	26,397	Domt	71,445	697,092
–2.75	10.12%	25.88%	8.11	8.06	8.11	8.13	14,679	17,570	15,044	28,124	Domt	64,765	518,777
–3	12.80%	29.21%	7.98	7.92	7.98	8.01	16,861	19,882	17,225	30,158	Domt	58,645	393,994
–3.25	16.12%	33.03%	7.84	7.78	7.85	7.88	19,423	22,605	19,787	32,541	Domt	53,042	303,863
–3.5	20.17%	37.36%	7.70	7.62	7.70	7.75	22,422	25,802	22,783	35,323	Domt	47,910	237,188
–3.75	25.06%	42.24%	7.54	7.45	7.55	7.61	25,917	29,541	26,274	38,556	Domt	43,203	186,924
–4	30.83%	47.64%	7.37	7.26	7.38	7.45	29,973	33,896	30,324	42,295	Domt	38,868	148,431
No prior fracture, no rheumatoid arthritis, parental fracture (i.e., one independent clinical risk factor)*													
–2.5	5.36%	18.37%	8.30	8.27	8.31	8.31	10,056	12,713	10,417	23,768	Domt	85,685	1,204,768
–2.75	6.83%	20.63%	8.20	8.16	8.20	8.21	11,415	14,145	11,777	25,036	Domt	77,649	850,461
–3	8.69%	23.25%	8.08	8.04	8.09	8.11	13,028	15,850	13,390	26,538	Domt	70,273	622,153
–3.25	11.02%	26.27%	7.96	7.91	7.97	7.99	14,934	17,870	15,296	28,312	Domt	63,515	466,536
–3.5	13.92%	29.74%	7.83	7.77	7.84	7.87	17,181	20,258	17,541	30,399	Domt	57,330	356,272
–3.75	17.50%	33.72%	7.69	7.62	7.70	7.74	19,818	23,070	20,176	32,843	Domt	51,673	275,899
–4	21.84%	38.24%	7.54	7.46	7.55	7.60	22,902	26,368	23,256	35,693	Domt	46,499	216,028
No prior fracture, rheumatoid arthritis, parental fracture (i.e., two independent clinical risk factors)*													
–2.5	11.12%	29.30%	8.13	8.08	8.14	8.16	16,209	19,142	16,585	29,602	Domt	58,800	467,724
–2.75	14.05%	32.88%	8.00	7.94	8.01	8.04	18,595	21,666	18,971	31,829	Domt	53,616	357,742
–3	17.65%	36.93%	7.86	7.79	7.87	7.91	21,390	24,632	21,765	34,431	Domt	48,857	277,479
–3.25	22.04%	41.49%	7.71	7.62	7.72	7.77	24,652	28,105	25,025	37,461	Domt	44,484	217,613
–3.5	27.28%	46.54%	7.55	7.45	7.55	7.62	28,445	32,158	28,815	40,973	Domt	40,450	172,167
–3.75	33.43%	52.06%	7.37	7.26	7.38	7.46	32,836	36,869	33,200	45,026	Domt	36,706	137,149
–4	40.44%	57.93%	7.19	7.06	7.20	7.29	37,892	42,317	38,247	49,671	Domt	33,191	109,794

Domt, denosumab dominant. * Independent clinical risk factors are defined as per NICE TA160/161, but are limited to rheumatoid arthritis and parental history of hip fracture because in TA160/161 the FRAX® algorithm for daily alcohol intake was adjusted from three or more to four or more units per day, the details of this were not available.

Table B2b Sensitivity analyses (base-case run on FRAX®): secondary comparisons: cost-effectiveness results for denosumab, ibandronate (iv), zoledronate (iv) and teriparatide

	Abs risks		QALYs				Costs				ICERs for comparison with Denosumab		
T score	Hip fracture	Major fracture	Denosumab	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Denosumab	Ibandronate (iv)	Zoledronate (iv)	Teriparatide	Ibandronate (iv)	Zoledronate (iv)	Teriparatide
Prior fracture, no rheumatoid arthritis, no parental fracture (i.e., no independent clinical risk factors)*													
–2.5	5.82%	22.09%	8.27	8.24	8.28	8.29	11,110	13,784	11,483	24,773	Domt	72,761	1,079,651
–2.75	7.42%	24.62%	8.16	8.13	8.17	8.18	12,572	15,323	12,947	26,138	Domt	66,532	771,954
–3	9.43%	27.49%	8.05	8.00	8.05	8.07	14,299	17,145	14,675	27,747	Domt	60,810	569,754
–3.25	11.95%	30.77%	7.92	7.87	7.93	7.96	16,332	19,296	16,709	29,639	Domt	55,558	430,075
–3.5	15.06%	34.48%	7.79	7.73	7.80	7.83	18,718	21,829	19,095	31,855	Domt	50,737	330,133
–3.75	18.89%	38.67%	7.65	7.57	7.66	7.70	21,510	24,803	21,887	34,443	Domt	46,309	256,734
–4	23.51%	43.35%	7.50	7.41	7.50	7.56	24,766	28,282	25,140	37,451	Domt	42,236	201,723
Prior fracture, rheumatoid arthritis, no parental fracture (i.e., one independent clinical risk factor)*													
–2.5	12.05%	34.37%	8.09	8.03	8.10	8.12	17,765	20,718	18,161	31,081	Domt	51,941	432,179
–2.75	15.20%	38.17%	7.95	7.89	7.96	7.99	20,295	23,391	20,693	33,442	Domt	47,939	332,288
–3	19.06%	42.41%	7.81	7.73	7.82	7.86	23,249	26,522	23,649	36,193	Domt	44,256	258,836
–3.25	23.73%	47.09%	7.65	7.56	7.66	7.72	26,689	30,181	27,089	39,388	Domt	40,857	203,711
–3.5	29.28%	52.17%	7.49	7.38	7.50	7.57	30,681	34,443	31,078	43,084	Domt	37,701	161,643
–3.75	35.74%	57.60%	7.31	7.19	7.32	7.41	35,292	39,388	35,686	47,338	Domt	34,743	129,069
–4	43.03%	63.25%	7.12	6.99	7.14	7.24	40,589	45,095	40,976	52,202	Domt	31,923	103,502
Prior fracture, no rheumatoid arthritis, parental fracture (i.e., one independent clinical risk factor)*													
–2.5	8.17%	28.04%	8.19	8.15	8.20	8.21	13,914	16,693	14,300	27,434	Domt	60,240	687,811
–2.75	10.37%	31.16%	8.07	8.02	8.08	8.10	15,809	18,690	16,198	29,204	Domt	55,425	512,789
–3	13.12%	34.67%	7.95	7.89	7.95	7.98	18,033	21,039	18,424	31,277	Domt	51,002	390,053
–3.25	16.51%	38.61%	7.81	7.74	7.82	7.85	20,637	23,799	21,029	33,699	Domt	46,937	301,245
–3.5	20.65%	43.00%	7.66	7.58	7.67	7.72	23,675	27,030	24,067	36,518	Domt	43,196	235,446
–3.75	25.63%	47.84%	7.50	7.41	7.51	7.57	27,210	30,803	27,601	39,789	Domt	39,739	185,771
–4	31.50%	53.09%	7.33	7.22	7.35	7.42	31,306	35,194	31,694	43,567	Domt	36,525	147,675
Prior fracture, rheumatoid arthritis, parental fracture (i.e., two independent clinical risk factors)*													
–2.5	16.65%	42.66%	7.97	7.89	7.98	8.01	22,363	25,502	22,781	35,430	Domt	44,838	303,814
–2.75	20.83%	47.06%	7.82	7.73	7.83	7.87	25,572	28,898	25,992	38,422	Domt	41,748	237,860
–3	25.86%	51.85%	7.66	7.56	7.67	7.73	29,300	32,858	29,722	41,889	Domt	38,887	187,995
–3.25	31.79%	56.96%	7.49	7.38	7.50	7.57	33,619	37,464	34,040	45,891	Domt	36,218	149,693
–3.5	38.60%	62.31%	7.31	7.18	7.32	7.41	38,597	42,798	39,014	50,487	Domt	33,692	119,856
–3.75	46.20%	67.75%	7.11	6.97	7.13	7.23	44,297	48,938	44,708	55,726	Domt	31,246	96,295
–4	54.33%	73.08%	6.91	6.75	6.92	7.05	50,762	55,946	51,160	61,631	Domt	28,796	77,421

Domt, denosumab dominant. * Independent clinical risk factors are defined as per NICE TA160/161, but are limited to rheumatoid arthritis and parental history of hip fracture because in TA160/161 the FRAX® algorithm for daily alcohol intake was adjusted from three or more to four or more units per day, the details of this were not available.

B.3 Please provide comment and clarification on the following with regard to cost assumptions, providing sensitivity analyses where appropriate:

- The assumed cost of administration of denosumab (i.e given during the course of a normal consultation) appears to be unrealistic, given that denosumab is a new and specialist drug. The decision to start it would be taken in secondary care, so at least one hospital appointment would be necessary.

Denosumab is a newly licensed innovative drug and is the only osteoporosis therapy with a unique physiological mechanism of action that mimics the body's natural bone-protection mechanism by inhibiting the action of RANKL through the same pathway as osteoprotegerin (OPG), the physiologic inhibitor of RANKL. In this context it could be considered that denosumab is an innovative and "specialist" drug. However, we do not agree with the assertion that the decision to initiate denosumab would be taken in a secondary care setting. The [redacted] Clearly this supports the administration of denosumab in a primary care and community setting as subcutaneous injections are routinely administered in this setting.

[redacted]

[redacted]

[redacted]

Despite our contesting the assertion that the decision to initiate denosumab would be taken in a secondary care, in our restructured original submission we performed two sensitivity analyses around the cost of administration of denosumab (section 6.5.5, page 226). Firstly, the cost of administration for one visit per year was reduced to zero (under the assumption that denosumab was self-administered). Secondly, the cost was increased to £127 (under the assumption that denosumab was administered in a secondary care setting). The £127 cost was equivalent to the NHS reference cost for a first attendance face to face non-admitted specialist orthopaedic consultation (T110N), indexed to year 2009. It is noted that this latter cost may over-estimate consultation costs since costs for a follow-up attendance would be lower than the first attendance costs stated.

In response to this clarification question we have performed further sensitivity analyses on our base case assuming that the decision to start and the initial administration of denosumab would occur in a secondary care setting and that subsequent administration would occur in primary care (see Tables B.3.a and B.3.b below). Consistent with our approach to the cost of administration of denosumab in secondary care setting in our restructured original submission, we have assumed a cost of £127 for the secondary care administration of denosumab. The analyses presented in Tables B.3.a and B.3.b below show that the small additional cost associated with initiating treatment with denosumab in a secondary care setting has only a marginal impact on the

cost-effectiveness of denosumab compared with both primary and secondary comparators. However, given that both denosumab would be less costly and therefore more cost-effective when administered in primary care; and that [redacted], we would anticipate that recommendations be made to encourage the administration of denosumab in a primary care setting in order to ensure the most efficient use of NHS resources.

Table B.3.a Primary comparisons: sensitivity analysis on base-case cost-effectiveness for denosumab, strontium, raloxifene and no treatment assuming initial administration of denosumab would occur in a secondary care setting

	ICER for comparison with Denosumab			
	Base case		Sensitivity analysis	
	LYs	QALYs	LYs	QALYs
No prior fracture				
No Treatment	47,220	29,223	49,744	30,785
Raloxifene[b]	26,383	9,289	32,783	11,543
Strontium	Denosumab dominant	Denosumab dominant	Denosumab dominant	Denosumab dominant
Prior fracture				
No Treatment	17,719	12,381	18,791	13,131
Raloxifene	4,820	2,046	8,088	3,434
Strontium	Denosumab dominant	Denosumab dominant	Denosumab dominant	Denosumab dominant

[b] Raloxifene is not recommended by NICE in patients with no prior fracture.

Table B.3.b Secondary comparisons: sensitivity analysis on base-case cost-effectiveness for denosumab, ibandronate iv, zoledronate iv and teriparatide assuming initial administration of denosumab would occur in a secondary care setting

	ICER vs. low-cost comparator (Denosumab)			
	Base case		Sensitivity analysis	
	LYs	QALYs	LYs	QALYs
No prior fracture				
Zoledronate (iv)[a]	88,386	70,900	66,042	52,976
Ibandronate (iv)[a]	Denosumab dominant	Denosumab dominant	Denosumab dominant	Denosumab dominant
Teriparatide[b]	2,073,082	772,424	2,059,374	767,316
Prior fracture				
Zoledronate (iv)[a]	34,292	29,029	25,738	21,788
Ibandronate (iv)[a]	Denosumab dominant	Denosumab dominant	Denosumab dominant	Denosumab dominant
Teriparatide	1,580,601	451,269	1,569,952	448,229

[a] NICE has not appraised ibandronate iv or zoledronate iv.

[b] Teriparatide is not recommended by NICE in patients with no prior fracture.

- If treatment with denosumab was continued in primary care, it is expected that GPs would not regard it as part of GMS, but would require an enhanced service payment.

Regardless of whether an enhanced service payment would be considered appropriate for the delivery of denosumab in primary care, there is no case for a change to the cost inputs in the model. It is important to distinguish between the costs of resources which are directly utilised in providing denosumab and the funding arrangements for primary care. The model fully accounts for the former – with respect to primary care, this is covered by the acquisition cost of denosumab and the cost of the GP visit to administer the injection. Even if the delivery of denosumab in primary care became an enhanced service, the resource costs incurred by the NHS in providing it to a given patient would

remain unchanged to those in the model. The enhanced service arrangements would be used as an additional income stream into general practice but would not alter the resource costs of delivering the service to a patient. Therefore, to include the fee provided to general practice for any enhanced service as an *additional* cost in the model would be inappropriate.

- The submission states (section 1.12) that no extra follow-up would be necessary, but it is expected that before each dose, bone marker estimation would be required. If low/very low, the next dose might be postponed.

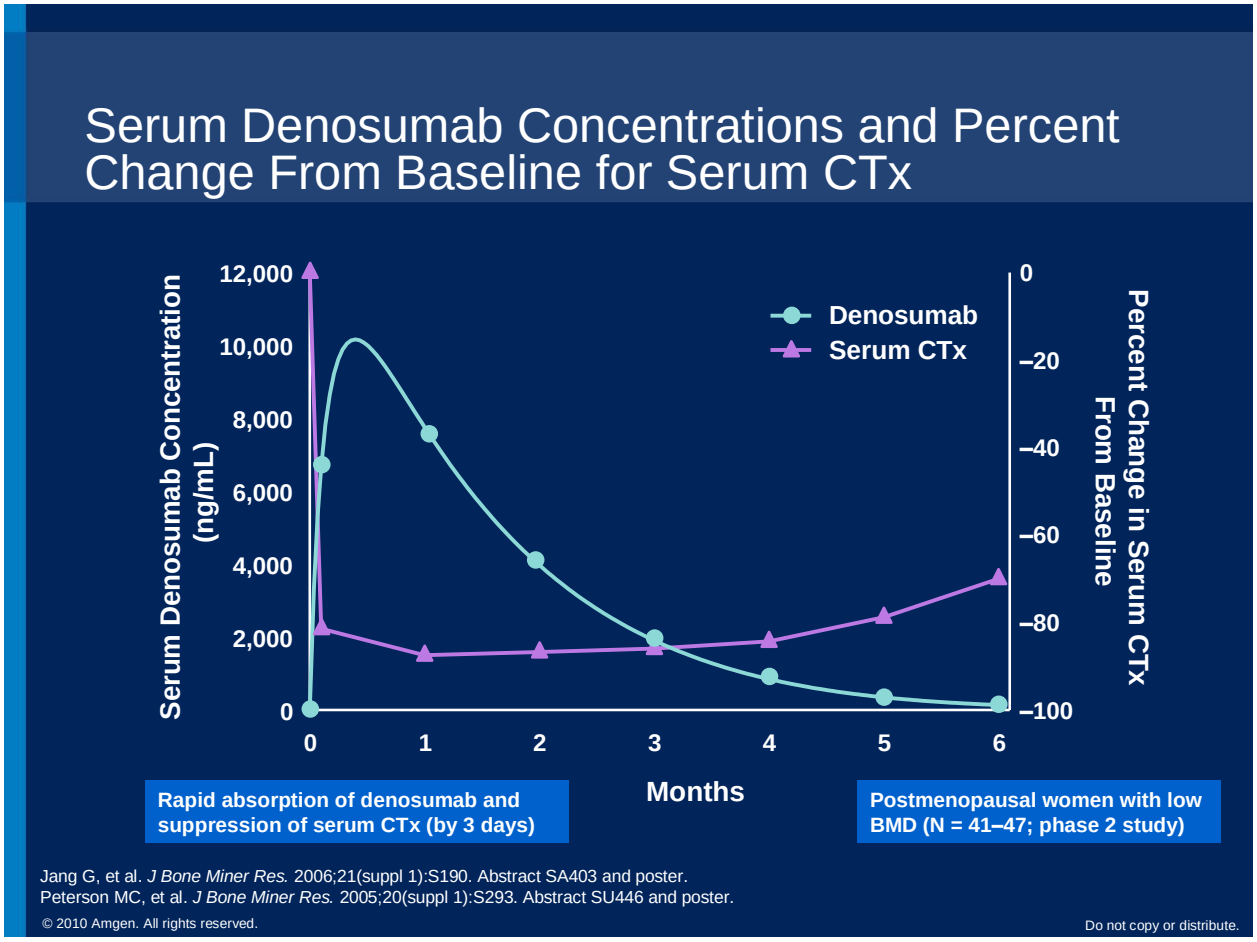
We are not aware of any information to support the Institute's expectation that bone turnover marker (BTM) estimation would be required before each dose and that the next dose might be postponed. The denosumab [redacted]. Indeed, there is a significant body of evidence presented below which supports the argument that BTM estimation is not necessary. Furthermore, BTM estimation is not current clinical practice for any of the licensed treatments for PMO and it would be impractical to use BTM estimation in clinical practice. Given this, we consider it inappropriate to perform sensitivity analysis with regard cost assumptions associated with BTM estimation before each dose.

The anti-fracture efficacy for denosumab has been established for the 60mg dose given every 6 months and there are no fracture efficacy data on longer windows of administration (Cummings 2009). The efficacy of denosumab on vertebral, non-vertebral and hip fractures has been established with the fixed dose of 60 mg SC every 6 months. In the phase 3 FREEDOM study, where denosumab was given at a dose of 60mg every 6 months (N = 7,808), a bone-marker substudy (N =160) showed an 86% relative reduction in sCTx levels at month 1 with denosumab compared with placebo. All denosumab-treated subjects had sCTX levels below the lower limit of the premenopausal reference range (< 0.2 ng/mL) at 1 month. The reduction in sCTX was sustained (72% reduction) through 3 years of treatment with denosumab (Cummings 2009). The reduction in BTMs was associated with a significantly

reduced risk of new vertebral, nonvertebral, and hip fractures by 68% (95% CI: 59%–74%), 20% (95% CI: 5%–33%), and 40% (95% CI: 3%–63%) over 3 years, respectively (Cummings 2009). The vertebral fracture risk reduction in the FREEDOM trial was consistent year after year over the 3-year observation period. The Kaplan-Meier curves for hip and non-vertebral fractures demonstrate a consistent fracture risk reduction over time (see Figures B5 and B6 on page 87 of our restructured original submission).

Continuous treatment with denosumab is required to maintain efficacy. As shown in the Figure B.3.a below, attenuation of serum CTX inhibition can be observed prior to the next dose when denosumab serum concentration decreases. (Peterson 2005; Jang 2006; Eastel 2009).

Figure B.3.a: Serum denosumab concentrations and percent change from baseline for serum CTx



Bone turnover markers, whilst useful for clinical population studies, are not practical for individual monitoring in clinical practice. A review by Szul et. al. has shown that BTM are a useful tool in clinical studies (Szul 2008). They have shown that an increased bone turnover rate is associated with higher fracture risk. Conversely, decrease in BTM induced by anti-resorptives is associated with a decrease in fracture risk. However, in the same review, the authors also state the practical use of BTM in clinical practice is very limited.

[redacted] Moreover, denosumab reduced the risk of new vertebral fracture regardless of the level of baseline bone turnover (Eastell 2009).

- The submission notes the lack of wrist fracture data for zoledronate, and then assumes no reduction, thereby imposing an extra cost of hospital care compared with denosumab. The comparison of efficacy for reducing other fractures shows that denosumab and zoledronate have similar effect, so it is implausible to assume that zoledronate has no effect on wrist fractures. Please provide the modelling with the assumption that denosumab and zoledronate have the same effect on wrist fractures.

In the absence of wrist fracture data for zoledronate we assumed no effect. While it is apparent from the adjusted indirect comparison and mixed treatment comparison that denosumab and zoledronate appear to have similar effect across other fracture sites, we do not consider this sufficiently robust evidence to bestow zoledronate with proven denosumab efficacy in wrist fracture. It is also apparent from our adjusted indirect comparison and mixed treatment comparison that it is equally possible for treatments to have similar effect at one or more fracture sites, while having different effects at other sites. For example, strontium and raloxifene have very similar effect in non-vertebral fracture (RR = 0.88 and 0.87 respectively), but very different effect in clinical vertebral (RR = 0.65 and 0.40 respectively). Similarly,

teriparatide and zoledronate have very similar effect in morphometric vertebral fracture (RR = 0.34 and 0.30 respectively), but very different effect in hip (RR = 0.16 and 0.58 respectively) and non-vertebral fracture (RR = 0.47 and 0.75 respectively). It is our position that the onus should be placed on the manufacturer to develop evidence for their own treatment. We think it most unlikely that the Institute would consider it acceptable for us to claim zoledronate efficacy if data were missing for denosumab. However, we have performed the requested sensitivity analysis for the comparison of denosumab with zoledronate by bestowing the proven denosumab effect on wrist fracture to zoledronate, setting the zoledronate wrist fracture RR to 0.84. The analyses presented in Table B.3.d below show that bestowing the denosumab wrist fracture efficacy to zoledronate has a marginal impact on the cost-effectiveness of zoledronate compared with denosumab.

Table B.3.d Secondary comparison: sensitivity analysis on base-case cost-effectiveness for denosumab and zoledronate iv assuming equal wrist fracture efficacy for denosumab and zoledronate

	ICER vs. low-cost comparator (Denosumab)			
	Base case		Sensitivity analysis	
	LYs	QALYs	LYs	QALYs
No prior fracture				
Zoledronate (iv)[a]	88,386	70,900	80,415	60,687
Prior fracture				
Zoledronate (iv)[a]	34,292	29,029	30,670	25,202

[a] NICE has not appraised zoledronate iv.

B.4 The modelling does not appear to include any reduction in breast cancer with raloxifene – please confirm that this is the case.

This is correct. In order to be consistent with the approach used to model the cost-effectiveness of raloxifene in NICE Technology Appraisal 161 (TA161)

we have not included any reduction in breast cancer with raloxifene. Specifically, paragraph 4.2.11 of TA161 states that:

"For raloxifene, 4-year follow-up data from the MORE study were used, and it was assumed that women with low BMD have a lower breast cancer risk than women with normal BMD. The cost effectiveness was modelled excluding the breast cancer benefit, the risk of VTE and the effect on cardiovascular events.

Further paragraph 4.3.31 of TA161 states:

The Committee noted that a higher proportion of the overall benefit associated with raloxifene was attributable to its effect on the prevention of breast cancer than to its effect on the prevention of osteoporotic fragility fractures. The Committee agreed that, in principle, the side effects of using a drug should be considered; however, there were a number of reasons why the Committee considered that the breast cancer benefit should not be the sole factor in deciding whether raloxifene is a cost-effective option for treatment for the secondary prevention of osteoporotic fragility fractures, as follows:

• *From the evidence presented, raloxifene was not as effective as the bisphosphonates for treating osteoporosis.*

• *Raloxifene's effect on the prevention of breast cancer has not been assessed by the regulatory authorities.*

• *Full assessment of raloxifene's effect on the prevention of breast cancer and its cost effectiveness in this indication would require consideration of how it compares with other drugs that could be used for breast cancer prevention."*

Section C Executable model

C.1 Response C2 to the previous request for clarification says that an executable version of the model with FRAX enabled would be supplied, but the revised version does not seem to have FRAX fully

enabled. Please contact us to ensure we have a fully executable model.

As we explained in our response to C2 in the previous clarification request we are not the owners of the information contained within FRAX®. The owner of FRAX® has now agreed that we can provide the NICE project team and the Evidence Review Group with a copy of the encrypted FRAX® executable file necessary to make our model executable with FRAX® enabled. The encrypted FRAX® executable file is provided to the Institute strictly commercial in confidence.

References

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