ERG exploratory analyses following ACD consultation

Responses from Servier

Servier argue that a relative risk of 0.64 (rather than 0.89), obtained over 3 years, should be used for the effect of strontium on hip fracture. Applying this relative risk estimate over the modelled 5 year treatment period in Amgen's model, denosumab goes from being dominant to costing £10,203 per additional QALY in 70 year old women with no prior fracture. For 70 year old women with a prior fracture, the ICER for denosumab versus strontium becomes £5,052 per QALY.

If we use the figure of 0.57 for the 5-year risk, the ICER for denosumab increases to £16,339 per QALY in 70 year old women with no prior fracture, and increases to £8,639 in women with a prior fracture. See Table A1 for additional two-way sensitivity analysis showing how the ICER for denosumab versus strontium varies with changes to the effectiveness of strontium and the administration costs for denosumab.

Applying a RR 0.64 for the effect of strontium on hip fracture within a probabilistic analysis has little impact on conclusions (assuming Amgen's base case costing assumptions). However, increasing the cost of denosumab administration, to include the cost of administering one dose in a secondary care setting each year, resulted in the choice between denosumab and strontium becoming closer (Figures 1 and 2). However, these estimates assume denosumab confers no additional benefit over strontium in terms of improved compliance and persistence, and they also assume no administration costs associated with strontium.

Figure 1: Acceptability curve from Amgen's model assuming a relative risk of 0.64 for the effect strontium on hip fracture and costs for denosumab that include the cost of administering one dose in secondary care each year – for a cohort 70 year old women with a T-score <= -2.5 with no prior fracture

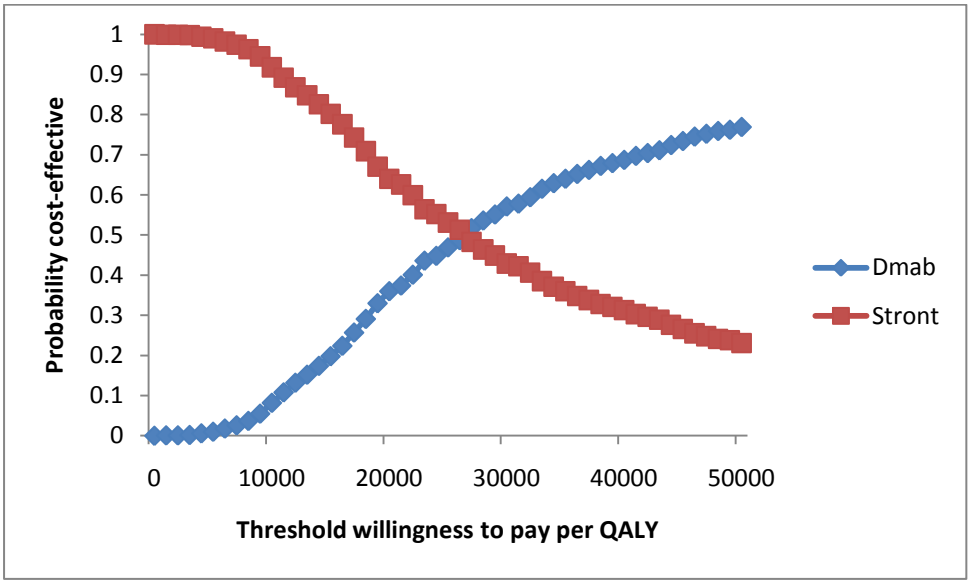
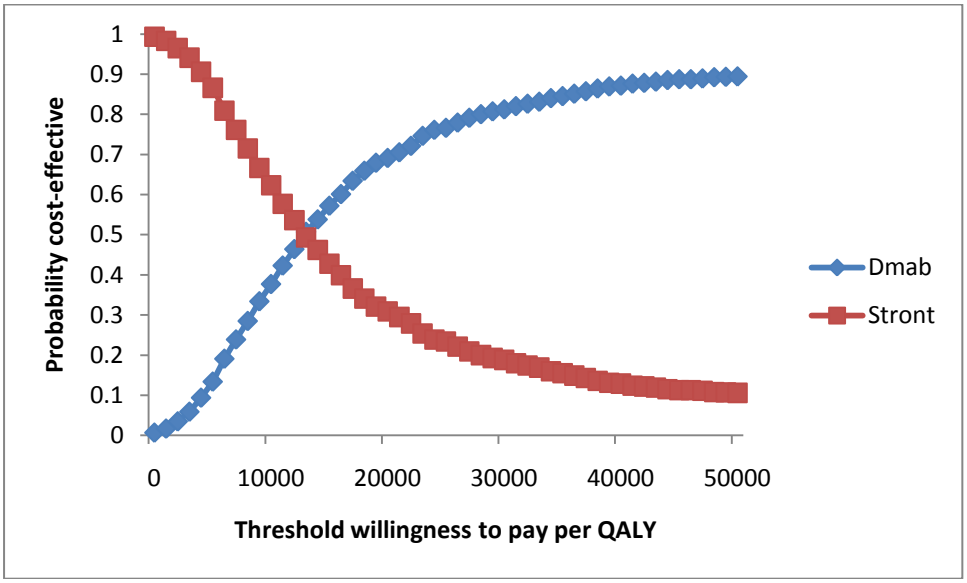


Figure 2: Acceptability curve from Amgen's model assuming a relative risk of 0.64 for the effect strontium on hip fracture and costs for denosumab that include the cost of administering one dose in secondary care each year – for a cohort 70 year old women with a T-score <= -2.5 with a prior fracture



Servier also questioned the approach of excluding the utility data from the FREEDOM trial from the economic model and questioned the costing assumptions for denosumab.

Amgen justified the omission of EQ-5D data from the FREEDOM trial on the grounds that the number of fracture events with associated EQ-5D scores was low. We are prepared to accept that the lack of statistical difference in EQ-5D scores between the denosumab and placebo arms of the FREEDOM trial is explained by this, rather than some possible unidentified adverse effect of denosumab on HRQOL masking the health benefit of fracture prevention. It is also consistent with the previous modelling carried out for T160 and T161 to use utility multipliers associated with fracture events derived from the literature, rather than an extrapolation of EQ-5D differences from a trial based comparison.

Servier suggest that the EQ-5D data should be requested from Amgen for checking. If we did that for denosumab we would have to do it for all comparators too.

Warner Chilcot
Warner Chilcott claim to have data to dispute Amgen's reported ICER for the comparison with oral risedronate, but they do not provide such data.

For the record, Amgen's reported ICER of £21,189 for denosumab versus oral risedronate (daily) is based on daily administration of risedronate at £0.66 per dose (£18.36 for 28 tabs), no administration costs and the same monitoring costs as for denosumab (1 GP visit per year and BMD once every 2 years). The relative risks applied at the different fracture sites for oral daily risedronate were: Hip (0.743); vertebral (0.619 (morphometric)); wrist (0.675); and other (1.00). All were from Amgen's random effects meta-analysis for direct comparison of each comparator with placebo. It should be noted that Amgen stated that they did not anticipate that denosumab would be competing with oral bisphosphonates in the UK, and these analyses were only provided in the appendices.

Novartis
Novartis note that the cost of zoledronate was reduced from £283.74 to £266.72 in January this year.

Holding all else constant, reducing the cost of zoledronate from £283.74 to £266.72 reduces the ICER for zoledronate versus denosumab from £70,900 to £55,885 in the 70 year old cohort with no prior fracture; And from £29,029 to £22,966 in the 70 year old cohort with a prior fragility fracture.

The BNF is our standard source of cost data.

They also draw attention to a published abstract which shows a relative risk of 0.81 for the effect of zoledronate on the prevention of wrist fracture (better than that of denosumab (0.84)). This fits with our assumption (in the absence until now of published data) that the effect of zoledronate on wrist fracture would be expected to be similar to that of denosumab, given similar effects on other fractures

Assigning zoledronate a RR of 0.81 for prevention of wrist fractures (holding all else constant) the ICER (using the Amgen assumptions) for zoledronate versus denosumab falls to £58,764 in those with no prior fracture, and fall to £24,454 in those with prior fracture. Note the RR of 0.81 reported by Novartis is non-significant (as is the RR of 0.84 for the effect of denosumab on wrist fractures).

Applying the above two changes simultaneously brings the ICER down to £44,804 for the cohort with no prior fragility fracture and £18,606 in those with a prior fragility fracture (age 70; T-score <= -2.5). ICERs will vary significantly within risk bands contained within these cohorts. For example, considering at threshold risk in a subgroup of 70 year old women with a T-score of -4, no prior fragility fracture, and no other clinical risk factors, the ICER for zoledronate versus denosumab comes to £22,169. This is assuming Amgen's admin costs are correct.

However, the above deterministic results are based on small absolute differences between the strategies, and there is a lot of overlap in the confidence intervals of the relative risk parameters for the two drugs. As a result it remains difficult to choose between denosumab and zoledronate based on the results of probabilistic analysis; even in relatively high risk cohorts (see Figures 3 and 4).

Figure 3: Acceptability curves from Amgen's model assuming the lower price for zoledronate (£266.72) and a relative risk for wrist fracture prevention of 0.81 – for a cohort 70 year old women with a T-score <= -4 with no prior fracture

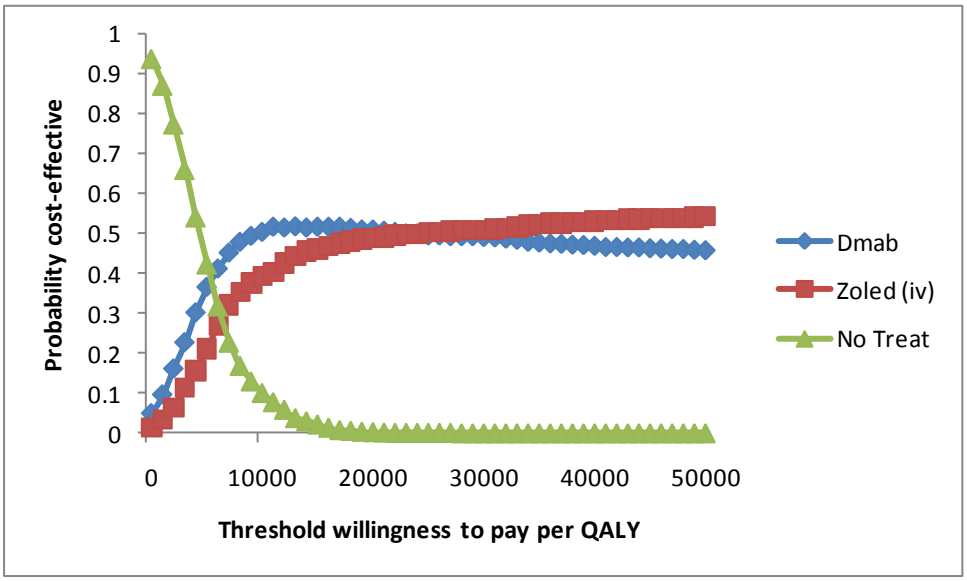


Figure 4: Acceptability curves from Amgen's model assuming the lower price for zoledronate (£266.72) and a relative risk for wrist fracture prevention of 0.81 – for a cohort 70 year old women with a T-score <= -4 with a prior fracture

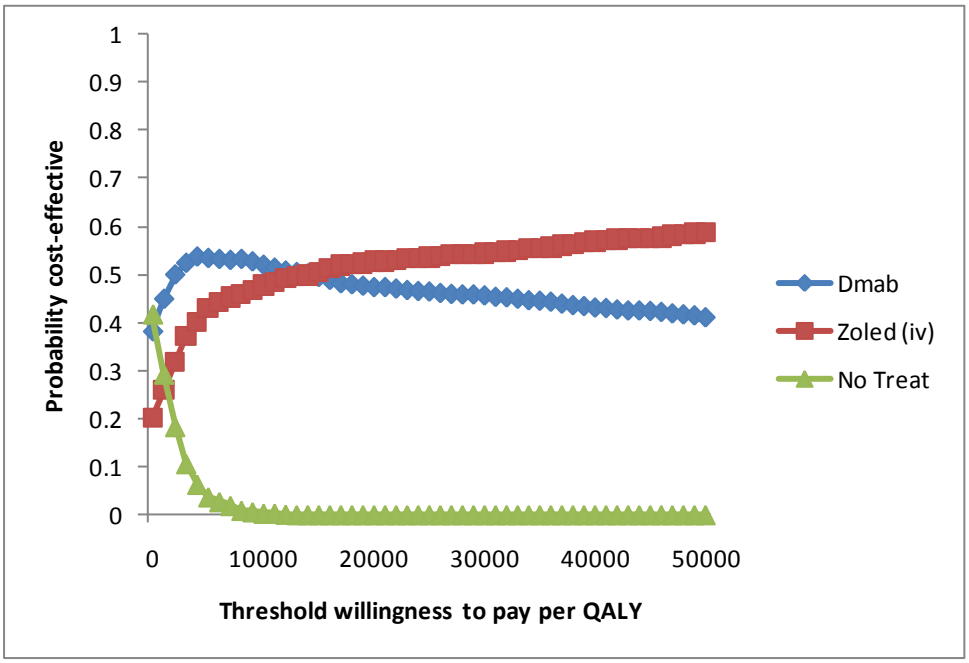


Table A1: Cost-effectiveness of denosumab versus Strontium ranelate for the primary and secondary prevention of fractures in 70 year old women (T_score <= -2.5); applying alternative estimates for the relative risk of hip fracture conferred by strontium, and alternative costing assumptions for the administration of denosumab

RR of hip fracture with strontium versus placebo	**Incremental costs**	**Incremental QALYs**	**Exploratory analysis ICERs**
With Amgen's Original costing assumptions			
0.89 (base case)	-£4 (primary prevention) -£155 (secondary prevention)	0.0411 (primary prevention) 0.0757 (secondary prevention)	Dominant (primary prevention) Dominant (secondary prevention)
0.64 (over 3 yrs, proposed by Servier)	£247 (primary prevention) £251 (secondary prevention)	0.0242 (primary prevention) 0.0496 (secondary prevention)	£10,203 (primary prevention) £5,052 (secondary prevention)
0.57 (over 5yrs proposed by Servier)	£317 (primary prevention) £365 (secondary prevention)	0.0194 (primary prevention) 0.0422 (secondary prevention)	£16,339 (primary prevention) £8,639 (secondary prevention)
Assuming denosumab administration requires one secondary care appointment each year			
0.89 (base case)	£392 (primary prevention) £240 (secondary prevention)	0.0411 (primary prevention) 0.0757 (secondary prevention)	£9,548 (primary prevention) £3,176 (secondary prevention)
0.64 (over 3 yrs, proposed by Servier)	£643 (primary prevention) £647 (secondary prevention)	0.0242 (primary prevention) 0.0496 (secondary prevention)	£26,614 (primary prevention) £13,042 (secondary prevention)
0.57 (over 5yrs proposed by Servier)	£714 (primary prevention) £761 (secondary prevention)	0.0194 (primary prevention) 0.0422 (secondary prevention)	£36,783 (primary prevention) £18,023 (secondary prevention)
Assuming denosumab administration requires two secondary care appointments each year			
0.89 (base case)	£652 (primary prevention) £500	0.0411 (primary prevention) 0.0757	£15,866 (primary prevention) £6,606

	(secondary prevention)	(secondary prevention)	(secondary prevention)
0.64 (over 3 yrs, proposed by Servier)	£902 (primary prevention) £906 (secondary prevention)	0.0242 (primary prevention) 0.0496 (secondary prevention)	£37,324 (primary prevention) £18,256 (secondary prevention)
0.57 (over 5yrs proposed by Servier)	£972 (primary prevention) £1,020 (secondary prevention)	0.0194 (primary prevention) 0.0422 (secondary prevention)	£50,125 (primary prevention) £24,148 (secondary prevention)

Novartis raise the issue of duration of treatment effect, and suggest that the effect of zoledronate may last for longer than that of denosumab. There is some evidence to support this from two studies of zoledronate in osteopenia (NB not osteoporosis), one in men with HIV. Bolland and colleagues (2008) reported that the effect of zoledronate on bone turnover markers and BMD lasted for 24 months after the last injection.
McClung and colleagues (2009) in a study of post-menopausal women with low bone mass, randomised one group to a single infusion of zoledronate at baseline and found that this prevented bone loss for two years.
The studies do not tell us about duration of effect on fracture risk.

Aberdeen HTA group 26th July 2010.