Supplemental Material

In this appendix, the different statistical models for the evidence synthesis of bazedoxifene and bisphosphonate trials are presented. The random effect models assume a constant heterogeneity parameter for each treatment comparison as there is not enough evidence to relax this assumption.

Analysis 1

Description: Network meta-analysis based on AD where only those bisphosphonate studies were selected that showed a non-vertebral fracture incidence of the placebo arm similar (i.e. not statistically significantly different at 0.05 level) to the placebo response of FRAX>=20% subgroup in the bazedoxifene trial.

Model 1: Random effects network-meta-analysis model without treatment*covariate interactions for binary outcomes

$$r_{jk} \sim Binomial\,(p_{jk}, n_{jk})$$

$$\text{logit}\ (p_{jk}) = \begin{cases} \mu_{jA} & k = \text{A} \\ \mu_{jA} + \delta_{jAk} & k = \text{B, C, D, E} \end{cases}$$

$$\delta_{jAk} \sim Normal(d_{Ak}, \sigma^2)$$

Where

j = study

k = treatment group

r_{jk} = number of events observed for the treatment *k* in study *j*

p_{jk} = probability of an event for treatment *k* in study *j*

n_{jk} = number of subjects for treatment *k* in study *j*

μ_{jA} = log odds of an event for 'baseline' treatment *A* in study *j*

δ_{jAk} = log odds ratio for treatment *k* relative to treatment *A* in study *j*

d_{Ak} = pooled log odds ratio of an event for treatment *k* versus *A*

σ^2 = Between-study variance or 'heterogeneity parameter'

Analysis 2

Description: Network meta-analysis based on AD for all FRAX subgroups of the bazedoxifene trial and all AD for the published bisphosphonate trials. The model includes covariates that capture the impact of placebo response on the treatment effects (i.e. log odds ratio of vertebral fractures) with oral bisphosphonates and bazedoxifene relative to placebo. The covariates are treatment specific but are assumed to be exchangeable (i.e. described with a normal distribution with a mean covariate effect and a between-treatment variation). With the treatment exchangeable covariate, the treatment-by-covariate effects are assumed to be similar but non-identical. If there is reason to believe the particular effect of the covariate is markedly different for some (or all) treatments, then the exchangeability assumption may not be appropriate. The treatment effects for all interventions indirectly compared were centered at a placebo response for vertebral fractures corresponding to a FRAX≥20% score.

Model 2: Random effects model for combining subgroup data from bazedoxifene trial and overall results from bisphosphonate trials with exchangeable treatment*covariate interactions

AD with study specific subgroup data

$$r_{sjk} \sim binomial(q_{sjk}, n_{sjk})$$

$$\text{logit}(q_{sjk}) = \begin{cases} \mu_{sjA} & k = A \\ \mu_{sjA} + \delta_{sjAk} & k = E \end{cases}$$

$$\delta_{sjAk} \sim Normal(d_{Ak} + \beta_{1Ak} x_{sj}, \sigma^2)$$

AD with only overall group data

$$r_{jk} \sim binomial(p_{jk}, n_{jk})$$

$$\text{logit}(p_{jk}) = \begin{cases} \lambda_{jA} & k = A \\ \lambda_{jA} + \delta_{jbk} & k = B,C,D \end{cases}$$

$$\delta_{jbk} \sim Normal(d_{Ak} + \beta_{1Ak} x_{j}, \sigma^2)$$

$$\beta_{1Ak} \sim N(\beta_1, \sigma_{\beta}^{\ 2})$$

Where

s	=	subgroup
j	=	study
k	=	treatment group
q_{sjk}	=	probability of an event for treatment *k* in study *j* for subgroup *s*
p_{jk}	=	probability of an event for treatment *k* in study *j*
μ_{jA}	=	log odds of an event for 'baseline' treatment *A* in subgroup *s* in study *j*
λ_{jA}	=	average log odds of an event for 'baseline' treatment *b* in study *j*
β_{0j}	=	study and subgroup specific covariate regression term
x_{sj}	=	value of covariate for subgroup *s* in study *j*
d_{Ak}	=	pooled log odds ratio of an event for treatment *k* versus *A*
σ^2	=	between study variance or 'heterogeneity parameter'

β_{1Ak} = Treatment by covariate interaction term for treatment *k* relative to *A*

β_1 = Average treatment by covariate interaction term

σ_β^2 = between intervention variation for impact of covariate on treatment effects

Analysis 3

Description: Network meta-analysis based on IPD for bazedoxifene trial and AD for the published bisphosphonate studies. The model includes a covariate that captures the impact of a 10-year baseline fracture risk on the treatment effects (i.e. log odds ratio of non-vertebral fractures) with oral bisphosphonates and bazedoxifene relative to placebo. The bisphosphonate covariates are treatment specific but are assumed to be exchangeable (i.e. described with a normal distribution with a mean covariate effect and a between treatment variation) whereas the bazedoxifene covariate is independent from the effect with the bisphosphonates. The FRAX score reflects the 10 year fracture risk available for individuals in the bazedoxifene trial. For the bisphosphonate trials the placebo response over the follow-up of the trial (e.g. 1-4 years) was transformed into 10-year (non-vertebral fracture) risk as well. The treatment effects for all interventions indirectly compared were centered at a 10-year fracture risk >=20%.

Model 3: Random effects fractional polynomial model for combining IPD from bazedoxifene trial and AD from bisphosphonate trials with independent treatment*covariate interaction for bazedoxifene and exchangeable treatment*covariate interactions for bisphosphonates

IPD

$$r_{ijk} \sim binomial\left(q_{ijk}, n_{ijk}\right)$$

$$\operatorname{logit}\left(q_{ijk}\right) = \begin{cases} \mu_{jA} + \beta_{0j} x_{ij} & k = A \\ \mu_{jA} + \beta_{0j} x_{ij} + \delta_{jAk} & k = E \end{cases}$$

$$\delta_{jAk} \sim Normal\left(d_{Ak} + \beta_{1Ak} x_{ij} + \beta_{2Ak} x_{ij}^{2}, \sigma^{2}\right)$$

AD

$$r_{jk} \sim binomial\left(p_{jk}, n_{jk}\right)$$

$$\operatorname{logit}\left(p_{jk}\right) = \begin{cases} \lambda_{jA} & k = A \\ \lambda_{jA} + \delta_{jAk} & k = B, C, D \end{cases}$$

$$\delta_{jAk} \sim Normal\left(d_{Ak} + \beta_{1Ak} x_{j}, \sigma^{2}\right)$$

$$\beta_{1Ak} \sim N\left(\beta_{1}, \sigma^{2}\right) \qquad k = B, C, D$$

Where

i	=	Individual
j	=	study
k	=	treatment group
q_{sjk}	=	probability of an event for treatment *k* in study *j* for individual *i*
p_{jk}	=	probability of an event for treatment *k* in study *j*
μ_{jA}	=	log odds of an event for ‘baseline’ treatment *A* in study *j*
λ_{jA}	=	average log odds of an event for ‘baseline’ treatment *A* in study *j*
β_{0j}	=	study and subgroup specific covariate regression term

x_{ij} = value of covariate for subgroup *s* in study *j*

d_{Ak} = pooled log odds ratio of an event for treatment *k* versus *A*

β_{1Ak} = Treatment by covariate interaction term for treatment *k* relative to *A*

β_{2Ak} = Treatment by covariate shape interaction term for treatment *k* relative to *A*

β_{1} = Average treatment by covariate interaction term for treatment *B*,*C*,*D*

σ_{β}^{2} = between intervention variation for impact of covariate on treatment effects