Health Technology Assessment (HTA)

HTA Supplement

Title	Denosumab (Prolia®) for the treatment of osteoporosis
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1 Exemplar Code

This supplement includes an example of the code used in R studio to run the network meta-analysis using a Bayesian inference using the BUGSnet package. Different code was used to run the network meta-analysis using a Frequentist inference using the netmeta package.

1.1 An example of code used in R studio to run a network meta-analysis using a Bayesian Inference

```
##################

# Load r packages

#################

library(BUGSnet)

library(metagear)

library(ggplot2)

library(tidyverse)

library(forestplot)

library(igraph)

#################

#upload extracted data

#################

pop.v.fracture<-read.csv("pop.v.fracture.csv")



##########

# add in imputed SD
```

```
##########
pop.v.fracture<-impute_SD(aDataFrame = pop.v.fracture,
                          columnSDnames = "sd.age",
                          columnXnames = "mean.age",
                          method = "Bracken1992"
                          )

write.csv(pop.v.fracture,
          "pop.v.fracture_SD.csv"
          )

#################
#data prep
#################
pop.v.fracture<-data.prep(arm.data = pop.v.fracture,
                          varname.t = "treatment",
                          varname.s = "trial"
)

#################
#NMA characteristics
#################
```

```
nma.pop.v.fracture_n.charac<-net.tab(pop.v.fracture,
                                     outcome= "e",
                                     N="n",
                                     type.outcome="binomial"
)



write.csv(nma.pop.v.fracture_n.charac$intervention,
          "nma.pop.v.fracture_n.charac_intervention.csv"
)


write.csv(nma.pop.v.fracture_n.charac$comparison,
          "nma.pop.v.fracture_n.charac_comparison.csv"
)


write.csv(nma.pop.v.fracture_n.charac$network,
          "nma.pop.v.fracture_n.charac_network.csv"
)


nma.pop.v.fracture_n.charac


##################
```

```
# exploring effect modifiers

#################

#mean age by treatment

nma.pop.v.fracture_p.charac_age.treatment<-data.plot(data = pop.v.fracture,

                                covariate = "mean.age",

                                half.length = "sd.age",

                                by = "treatment",

                                avg.hline=TRUE,

                                text.size = 12

)


nma.pop.v.fracture_p.charac_age.treatment<-nma.pop.v.fracture_p.charac_age.treatment + labs(y =
"Mean age") + labs(x = "Trial")


nma.pop.v.fracture_p.charac_age.treatment


##############################################

##############STOP############################

##############################################




##################
```

```
#network diagram

##################

# by uploading extracted data

pop.v.fracture.nodes <- read.csv("pop.sen.v.fracture_node.csv",

                          header=T,

                          as.is=T

)



pop.v.fracture.arm_<- read.csv("pop.sen.v.fracture_arms.csv",

                        header=T,

                        as.is=T

)



#data prep

pop.v.fracture _net <- graph_from_data_frame(d=pop.v.fracture.arm,

                                  vertices=pop.v.fracture.nodes,

                                  directed=T

)

# Create a diagram shape

C <- layout_in_circle(pop.v.fracture _net)



# Create a vector of color
```

```
coul  <- brewer.pal(4, "Dark2")


#plot
pop.v.fracture _net.graph<-plot(pop.v.fracture _net,
                        edge.arrow.size=0,
                        vertex.color=c("skyblue"),
                        vertex.size=V(pop.v.fracture_meta.reg.age_net)$n/100,
                        vertex.frame.color=NA,
                        vertex.label.color="black",
                        vertex.label.cex=0.7,
                        vertex.label.dist=2,
                        vertex.label.family="Arial",
                        edge.curved=0.0,
                        edge.width=E(pop.v.fracture_meta.reg.age_net)$trials,
                        edge.label.family="Arial",
                        edge.label=E(pop.v.fracture_meta.reg.age_net)$trials,
                        edge.color="gray",
                        layout=C
)


##############################################
##############STOP############################
```

```
##########################################

#########CHOOSE MODEL#########

#################

model

#################

#consistency model

nma.pop.v.fracture_random_cont<-nma.model(pop.v.fracture,

                                outcome="e", #for dichotomous or # "mean" for continuous

                                N="n",

                                sd= NA, #for dichotomous or # "sd" for continuous

  reference="PLB",

                                type = "consistency",

                                family="binomial", #for dichotomous or # "normal" for continuous

                                link="log", # for dichotomous or # "identity" for continuous

                                effect="random",

                                prior.mu = "DEFAULT",

                                prior.d = "DEFAULT",

                                prior.sigma = "DEFAULT",

)
```

```
##runs and burns

nma.pop.v.fracture_random_cont_results<- nma.run(nma.pop.v.fracture_random_cont,

                                    n.adapt=XXXX,

                                    n.burnin=XXXX,

                                    n.iter=XXXX

)



##assessment of convergence

nma.pop.v.fracture_random_cont_convergence<- nma.diag(nma.pop.v.fracture_random_cont_results,

                                        trace=TRUE,

                                        gelman.rubin=TRUE,

                                        geweke=FALSE,

                                        params="all",

                                        plot_prompt = FALSE

)



nma.pop.v.fracture_random_cont_convergence$gelman.rubin



nma.pop.v.fracture_random_cont_convergence$trt.key




#inconsistency model
```

```
nma.pop.v.fracture_random_inc<- nma.model(pop.v.fracture,
                                outcome="e", #for dichotomous or # "mean" for continuous
                                N="n",
                                sd= NA, #for dichotomous or # "sd" for continuous
  reference="PLB",
                                type = "inconsistency",
                                family="binomial", #for dichotomous or # "normal" for continuous
                                link="log", # for dichotomous or # "identity" for continuous
                                effect="random",
                                prior.mu = "DEFAULT",
                                prior.d = "DEFAULT",
                                prior.sigma = "DEFAULT",
)

##runs and burns
nma.pop.v.fracture_random_inc_results<- nma.run(nma.pop.v.fracture_random_inc,
                                     n.adapt=XXXX,
                                     n.burnin=XXXX,
                                     n.iter=XXXX
)

##assessment of convergence
```

```
nma.pop.v.fracture_random_inc_convergence<- nma.diag(nma.pop.v.fracture_random_inc_results,
                                        trace=TRUE,
                                        gelman.rubin=TRUE,
                                        geweke=FALSE,
                                        params="all",
                                        plot_prompt = FALSE
)
nma.pop.v.fracture_random_inc_convergence$gelman.rubin


nma.pop.v.fracture_random_inc_convergence$trt.key




##################
# NMA model selection - consistency vs inconsistency :: AKA nodespilt
##################
par(mfrow = c(1,2)) #plotting format


nma.pop.v.fracture_random_con.model_leverage.plot<-
nma.fit(nma.pop.v.fracture_random_cont_results,
                                    main = "Consistency Model"
)
```

```
nma.pop.v.fracture_random_inc.model_leverage.plot<-
nma.fit(nma.pop.v.fracture_random_inc_results,
                                        main= "Inconsistency Model"
)



#comparing consistency vs inconsistency
#################
par(mfrow = c(1,1)) #plotting format


nma.pop.v.fracture_random_leverage.plot_compare<-
nma.compare(nma.pop.v.fracture_random_con.model_leverage.plot,
nma.pop.v.fracture_random_inc.model_leverage.plot)




##############################################
###############STOP############################
##############################################


#########SELECT CONSISTENCY MODEL #########


#################
#ranking
```

```
#################

nma.pop.v.fracture_rank<- nma.rank(nma.pop.v.fracture_random_cont_results,

                          largerbetter=FALSE,

                          sucra.palette= "Set1"

)




#SUCRA

################

#plot

nma.pop.v.fracture_rank$sucraplot



#table

nma.pop.v.fracture_sucratable<-nma.pop.v.fracture_rank$sucratable

write.csv(nma.pop.v.fracture_sucratable,

        "nma.pop.v.fracture_sucratable.csv"

)



#rank graph

################

nma.pop.v.fracture_rank_graph<-nma.forest(nma.pop.v.fracture_random_cont_results,

                               central.tdcy="mean",
```

```
                                comparator = "PLB",

                                log.scale =FALSE

)

nma.pop.v.fracture_rank_graph



#league table

##################

nma.pop.v.fracture_league.plot <- nma.league(nma.pop.v.fracture_random_cont_results,

                                central.tdcy="mean",

                                order = nma.pop.v.fracture_rank$order,

                                log.scale = FALSE,

                                low.colour = "springgreen4",

                                mid.colour = "white",

                                high.colour = "red",

                                digits = 2

)



#table

nma.pop.v.fracture_league.plot_table<-nma.pop.v.fracture_league.plot$table



write.csv(nma.pop.v.fracture_league.plot_table,

        "nma.pop.v.fracture_league.plot_table.csv"
```

```
)

#################
#heterogeneity
#################
pma(data= pop.v.fracture,
    type.outcome="binomial", #for dichotomous or # "continuous" for continuous
    sm="RR", #for dichotomous or # "MD" for continuous
    outcome = "e", #for dichotomous or # "mean" for continuous
    sd= NA, #for dichotomous or # "sd" for continuous
    N= "n",
    name.trt1 = "DEN",
    name.trt2= "PLB",
    method= "MH",
    method.tau="REML"
    )

#################
#drawing NMA forrest plot
#################

tabletext <- cbind(
```

```
  c("Treatment", ”x”, “x”, “x”, “x”, “x”,”x”,”x”),

  c("Vertebral \n fracture", ”x”, “x”, “x”, “x”, “x”,”x”,”x”), # name and number of events for dichotomous outcomes #coloumn not present for continuous outcomes

  c("Sample \n size", ”x”, “x”, “x”, “x”, “x”,”x”,”x”),

  c("RR", ”x”, “x”, “x”, “x”, “x”,”x”,”x”), #for dichotomous or # "MD" for continuous

  c("95% CrI","[,]","[,]","[,]","[,]","[, ]"),

  c("SUCRA\n Score",”x”, “x”, “x”, “x”, “x”,”x”,”x”),

  c("Rank", "1","2", “3”, “4”, “5”, “6”, “7”,”8”)

)


pop.v.fracture_rank<-structure(list(

  risk  = c(NA, x, x, x, x, x, x, x ,NA), # for dichotomous, # “mean” for continuous outcomes

  lower = c( NA, x, x, x, x, x, x, x, NA),

  upper = c(NA, x, x, x, x, x, x, x,NA),

  colomn.Names = c("mean", "lower", "upper"),

  row.names = c(NA, NA),

  class = "data.frame")

)


pop.v.fracture_rank_final<-forestplot(tabletext,

                                      pop.v.fracture_rank$risk, # for dichotomous, # pop.v.fracture_rank$rmean for continuous outcomes
```

```
pop.v.fracture_rank$lower,

pop.v.fracture_rank$upper,

is.summary= c(TRUE,rep(FALSE,8)),

zero = 1,

cex  = 10,

clip=c(0,x),

lineheight = unit(13,"mm"),

boxsize = .1,

txt_gp = fpTxtGp(label = list(gpar(cex=0.9 )),

                 ticks = gpar(cex=0.9),

                 xlab = gpar(cex=0.9)),

xlab = "Risk Ratio relative to PLB",

col = fpColors(box = "blue",

               line = "black"),

xlog= FALSE,

xticks = c(0, 0.25, 0.5, 0.75, 1, 1.5, 2.0,2.5, 3.0),

graph.pos=4,

ci.vertices= TRUE,

mar = unit(rep(1, times = 8), "mm"),

graphwidth= unit(70, "mm"),

hrzl_lines = list("2" = gpar(lty = 1, columns = c(1:8),

                             "9" = gpar(lwd = 1, columns = c(1:3), col = "#000044")))
```

```
)

##############################################

##############STOP#############################

##############################################


######### META REGRESSION #########


#################

#NMA -- AGE

#################

#################

#data prep

#################

#removing  NA

#################

pop.v.fracture_mean.age<-drop_na(pop.v.fracture$arm.data, mean.age)


pop.v.fracture_mean.age<-data.prep(arm.data = pop.v.fracture_mean.age,

                                   varname.t = "treatment",
```

```
                        varname.s = "trial"
)

##################
#NMA characteristics
##################
nma.pop.v.fracture_n.charac_meta.reg.age<-net.tab(pop.v.fracture_mean.age,
                        outcome= "e",
                        N="n",
                        type.outcome="binomial"
)


write.csv(nma.pop.v.fracture_n.charac_meta.reg.age$intervention,
        "nma.pop.v.fracture_n.charac_intervention_meta.reg.age.csv"
)

write.csv(nma.pop.v.fracture_n.charac_meta.reg.age$comparison,
        "nma.pop.v.fracture_n.charac_comparison_meta.reg.age.csv"
)

write.csv(nma.pop.v.fracture_n.charac_meta.reg.age$network,
```

```
        "nma.pop.v.fracture_n.charac_network_meta.reg.age.csv"
)

nma.pop.v.fracture_n.charac_meta.reg.age

#################
#consistency model
#################
nma.pop.v.fracture_random_cont_meta.reg.age<-nma.model(pop.v.fracture_mean.age,
                                    outcome="e", #for dichotomous or # "mean" for continuous
                                N="n",
                                sd= NA, #for dichotomous or # "sd" for continuous
  reference="PLB",
                                type = "consistency",
                                family="binomial", #for dichotomous or # "normal" for continuous
                                link="log", # for dichotomous or # "identity" for continuous
                                effect="random",
                                prior.mu = "DEFAULT",
                                prior.d = "DEFAULT",
                                prior.sigma = "DEFAULT",
                                    prior.beta="EXCHANGEABLE",
                                    covariate="mean.age"
```

```
)



#runs and burns

nma.pop.v.fracture_random_cont_results_meta.reg.age<-
nma.run(nma.pop.v.fracture_random_cont_meta.reg.age,

                                        n.adapt=XXXX,

                                        n.burnin=XXXX,

                                        n.iter=XXXX

)



##################

#ranking

##################

nma.pop.v.fracture_rank_meta.reg.age<-
nma.rank(nma.pop.v.fracture_random_cont_results_meta.reg.age,

                                    largerbetter=FALSE,

                                    sucra.palette= "Set1",

                                    cov.value= TRUE

)
```

```
#SUCRA

################

#plot

nma.pop.v.fracture_rank_meta.reg.age$sucraplot

nma.pop.v.fracture_rank_SUCRA_meta.reg.age<-nma.pop.v.fracture_rank_meta.reg.age$sucraplot +
labs(y = "Probability of ranking or better (%)")



nma.pop.v.fracture_rank_SUCRA_meta.reg.age



#table

nma.pop.v.fracture_meta.reg.age_sucratable<-nma.pop.v.fracture_rank_meta.reg.age$sucratable

write.csv(nma.pop.v.fracture_meta.reg.age_sucratable,

        "nma.pop.v.fracture_meta.reg.age_sucratable.csv"

)




##ank graph

nma.pop.v.fracture_rank_graph_meta.reg.age<-
nma.forest(nma.pop.v.fracture_random_cont_results_meta.reg.age,

                                        central.tdcy="mean",

                                        comparator = "PLB",
```

```
                                    log.scale =FALSE,

                                    cov.value= TRUE

)

nma.pop.v.fracture_rank_graph_meta.reg.age<-nma.pop.v.fracture_rank_graph_meta.reg.age  +
labs(y = "Risk Ratio to PLB \n (showing posterior mean with 95% CrI)")



nma.pop.v.fracture_rank_graph_meta.reg.age









#################

#league table

#################

nma.pop.v.fracture_league.plot_meta.reg.age                                              <-
nma.league(nma.pop.v.fracture_random_cont_results_meta.reg.age,

                                    central.tdcy="mean",

                                    order = nma.pop.v.fracture_rank_meta.reg.age$order,

                                    log.scale = FALSE,

                                    low.colour = "springgreen4",

                                    mid.colour = "white",

                                    high.colour = "red",
```

```
                                        digits = 2,

                                        cov.value= TRUE

)


##table

nma.pop.v.fracture_league.plot_meta.reg.age_table<-
nma.pop.v.fracture_league.plot_meta.reg.age$table


write.csv(nma.pop.v.fracture_league.plot_meta.reg.age_table,

        "nma.pop.v.fracture_league.plot_meta.reg_table.age.csv"

)




##################

#meta-regression plot

##################

nma.pop.v.fracture_nma.regplot.age                                                    <-
nma.regplot(nma.pop.v.fracture_random_cont_results_meta.reg.age,

                                        x.range = NULL,

                                        lwd = 1,

                                        palette = "Set1"
```

)

nma.pop.v.fracture_nma.regplot.age<-nma.pop.v.fracture_nma.regplot.age+ labs(x = "Values of the covariate of mean age")

nma.pop.v.fracture_nma.regplot.age

##

##############END#############################

##

1.2 An example of code used in R studio to run a network meta-analysis using a Frequentist Inference

```
##################

# Load r packages

##################

library(netmeta)

library(meta)

library(metagear)

library(ggplot2)

library(forestplot)

library(igraph)

##################

##################

# by uploading extracted data

##################

pop.v.fracture<-read.csv("pop.v.fracture.csv")



##########

# add in imputed SD # continuous only

##########

pop.XXX.XX<-impute_SD(aDataFrame = pop.XXX.XX,

                      columnSDnames = "sd_1",
```

```
                columnXnames = "mean_1",

                method = "Bracken1992"

)


pop.XXX.XX <-impute_SD(aDataFrame = pop.XXX.XX,

                columnSDnames = "sd_2",

                columnXnames = "mean_2",

                method = "Bracken1992"

)


pop.XXX.XX


##################

# calcute TE and seTE/ meta-analysis

##################

meta.pop.v.fracture<-metabin(event.e = e_1, #for dichotomous only

                        n.e = n_1,

 mean.e.= NA # for continuous only

 sd.e= NA # for continuous only

                        event.c = e_2, #for dichotomous only

                        n.c = n_2,

 mean.c=NA # for continuous only
```

```
 sd.c=NA # for continuous only

                        studlab = paste(pop.v.fracture$trial),

                        data=pop.v.fracture,

                        method = "MH", #for dichotomous only

                        sm="RR", # dichotomous or # “MD” for continuous

                        comb.fixed= FALSE,

                        comb.random=TRUE,

                        method.tau="REML"

)

pop.v.fracture$TE<-meta.pop.v.fracture$TE

pop.v.fracture$seTE<-meta.pop.v.fracture$seTE



write.csv(meta.pop.v.fracture,

"meta.pop.v.fracture.csv"

)

write.csv(pop.v.fracture,

"pop.v.fracture_TE.csv"

)



pop.v.fracture



##################
```

```
#NMA

#################

nma.pop.v.fracture<-netmeta(TE = TE,

                        seTE = seTE,

                        treat1 = intervention,

                        treat2 = comparator,

                        studlab = paste(pop.v.fracture$trial),

                        data =pop.v.fracture,

                        sm = "RR", # dichotomous or # “MD” for continuous

                        comb.fixed = FALSE,

                        comb.random = TRUE,

                        reference.group = "PLB",

                        sep.trts = " vs "

)

nma.pop.v.fracture



##################

#network diagram

##################

# by uploading extracted data

pop.v.fracture.nodes <- read.csv("pop.sen.v.fracture_node.csv",

                             header=T,
```

```
                        as.is=T
)

pop.v.fracture.arm_<- read.csv("pop.sen.v.fracture_arms.csv",
                        header=T,
                        as.is=T
)

#data prep
pop.v.fracture _net <- graph_from_data_frame(d=pop.v.fracture.arm,
                                vertices=pop.v.fracture.nodes,
                                directed=T
)
# Create a diagram shape
C <- layout_in_circle(pop.v.fracture _net)

# Create a vector of color
coul  <- brewer.pal(4, "Dark2")

#plot
pop.v.fracture _net.graph<-plot(pop.v.fracture _net,
                        edge.arrow.size=0,
```

```
                    vertex.color=c("skyblue"),

                    vertex.size=V(pop.v.fracture_meta.reg.age_net)$n/100,

                    vertex.frame.color=NA,

                    vertex.label.color="black",

                    vertex.label.cex=0.7,

                    vertex.label.dist=2,

                    vertex.label.family="Arial",

                    edge.curved=0.0,

                    edge.width=E(pop.v.fracture_meta.reg.age_net)$trials,

                    edge.label.family="Arial",

                    edge.label=E(pop.v.fracture_meta.reg.age_net)$trials,

                    edge.color="gray",

                    layout=C

)



##############################################

##############STOP############################

##############################################



#################

#league table

#################
```

```
nma.pop.v.fracture_league_table<-netleague(nma.pop.v.fracture,
                                comb.random=TRUE,
                                bracket="(",
                                digits=2
)
write.csv(nma.pop.v.fracture_league_table$random,
        "nma.pop.v.fracture_league_table.csv"
)

#################
#rank
#################
nma.pop.v.fracture_rank<-netrank(nma.pop.v.fracture,
                         small.values="good"
)
write.csv(nma.pop.v.fracture_rank$Pscore.random,
        "nma.pop.v.fracture_rank.csv"
)

#################
#netspilt/ nodesplit
#################
```

```
nma.pop.v.fracture_netspilt<-netsplit(nma.pop.v.fracture,
                                      comb.random = TRUE
)
nma.pop.v.fracture_netspilt

#netspilt/ nodesplit graph
nma.pop.v.fracture_netspilt_graph<-forest(nma.pop.v.fracture_netspilt,
                                          show = "all"
)

#################
#hetrogeneity Q
#################
nma.pop.v.fracture_QStat<-decomp.design(nma.pop.v.fracture)

nma.pop.v.fracture_QStat

#################
#publication bias
################
nma.pop.v.fracture_funnel<-funnel(nma.pop.v.fracture,
                                  order = c("x", "x", "x"),
```

```
                    pch = 19,

                    pooled = "random",

                    col = c("purple", "blue", "…."),

                    linreg= TRUE,

                    xlim= c(0.1,10),

                    ylim= c(0.8,0.0),

                    studlab=TRUE,

                    cex.studlab=0.7

)

##############################################

##############STOP#############################

##############################################


#################

#drawing NMA forest plot

#################


tabletext <- cbind(

  c("Treatment", ”x”, “x”, “x”, “x”, “x”,”x”,”x”),

  c("Vertebral \n fracture", ”x”, “x”, “x”, “x”, “x”,”x”,”x”), # name and number of events for dichotomous outcomes #coloumn not present for continuous outcomes
```

```
  c("Sample \n size", ”x”, “x”, “x”, “x”, “x”,”x”,”x”),
  c("RR", ”x”, “x”, “x”, “x”, “x”,”x”,”x”), #for dichotomous or # "MD" for continuous
  c("95% CrI","[,]","[,]","[,]","[,]","[,]","[, ]"),
  c("P-score",”x”, “x”, “x”, “x”, “x”,”x”,”x”),
  c("Rank", "1","2", “3”, “4”, “5”, “6”, “7”,”8”)
)

pop.v.fracture_rank<-structure(list(
  risk  = c(NA, x, x, x, x, x, x, x ,NA), # for dichotomous, # “mean” for continuous outcomes
  lower = c( NA, x, x, x, x, x, x, x, NA),
  upper = c(NA, x, x, x, x, x, x, x,NA),
  colomn.Names = c("mean", "lower", "upper"),
  row.names = c(NA, NA),
  class = "data.frame")
)

pop.v.fracture_rank_final<-forestplot(tabletext,
                          pop.v.fracture_rank$risk, # for dichotomous, # pop.v.fracture_rank$rmean for
continuous outcomes
                          pop.v.fracture_rank$lower,
                          pop.v.fracture_rank$upper,
                          is.summary= c(TRUE,rep(FALSE,8)),
```

```
                zero = 1,

                cex  = 10,

                clip=c(0,x),

                lineheight = unit(13,"mm"),

                boxsize = .1,

                txt_gp = fpTxtGp(label = list(gpar(cex=0.9 )),

                                 ticks = gpar(cex=0.9),

                                 xlab = gpar(cex=0.9)),

                xlab = "Risk Ratio relative to PLB",

                col = fpColors(box = "blue",

                               line = "black"),

                xlog= FALSE,

                xticks = c(0, 0.25, 0.5, 0.75, 1, 1.5, 2.0,2.5, 3.0),

                graph.pos=4,

                ci.vertices= TRUE,

                mar = unit(rep(1, times = 8), "mm"),

                graphwidth= unit(70, "mm"),

                hrzl_lines = list("2" = gpar(lty = 1, columns = c(1:8),

                                             "9" = gpar(lwd = 1, columns = c(1:3), col = "#000044")))

)



##############################################
```

##############END#########################

##

2 Assessment of convergence for network meta-analyses on postmenopausal women with osteoporosis using a Bayesian inference

This Supplement outlines the findings of the assessment of convergence for network meta-analyses using a Bayesian inference.

2.1 Findings efficacy and effectiveness

2.1.1 Vertebral fractures

Table 1 Assessment of convergence in the network meta-analysis for vertebral fractures in postmenopausal women with osteoporosis

Type of scale reduction factor [a]	Treatment	Point estimate	Upper CI
PSRF	d[2]	1.000032	1.000042
	d[3]	1.000003	1.000003
	d[4]	1.000183	1.000489
	d[5]	1.000019	1.000035
	d[6]	1.000040	1.000121
	sigma	1.000067	1.000231
MPSRF	[1]	1.00015	NA

Abbreviations:
CI: confidence interval; **MPRSF**: multivariate potential scale reduction factor; **NA**: not applicable; **PSRF**: potential scale reduction factor.
Notes:
This table presents the assessment of convergence for a network meta-analysis performed using a Bayesian inference. Convergence was considered met if the PSRF was under 1.05.[1]
[a] Measured using Gelman-Rubin statistic as defined in Brooks and Gelman.[2 3]

2.1.2 Nonvertebral fractures

Table 2 Assessment of convergence in the network meta-analysis for nonvertebral fractures in postmenopausal women with osteoporosis

Type of scale reduction factor [a]	Treatment	Point estimate	Upper CI
PSRF	d[2]	1.000013	1.000033
	d[3]	1.000045	1.000061
	d[4]	1.000011	1.000019
	d[5]	1.000028	1.000092
	d[6]	1.000017	1.000023
	sigma	1.000081	1.000275
MPSRF	[1]	1.00007	NA

Abbreviations:
CI: confidence interval; **MPRSF**: multivariate potential scale reduction factor; **NA**: not applicable; **PSRF**: potential scale reduction factor.
Notes:
This table presents the assessment of convergence for a network meta-analysis performed using a Bayesian inference. Convergence was considered met if the PSRF was under 1.05.[1]
[a] Measured using Gelman-Rubin statistic as defined in Brooks and Gelman.[2 3]

2.1.3 Bone mineral density (BMD)

Femoral neck (FN)

Table 3 Assessment of convergence in the network meta-analysis for FN BMD in postmenopausal women with osteoporosis

Type of scale reduction factor [a]	Treatment	Point estimate	Upper CI
PSRF	d[2]	1.007416	1.007722
	d[3]	1.005455	1.005497
	d[4]	1.007465	1.007470
	d[5]	1.007289	1.007631
	d[6]	1.006387	1.006906
	d[7]	1.006405	1.006423
	d[8]	1.007925	1.008019
	sigma	1.012178	1.021910
MPSRF	[1]	1.002967	NA

Abbreviations:
BMD: bone mineral density; **CI**: confidence interval; **FN**: femoral neck; **MPRSF**: multivariate potential scale reduction factor; **NA**: not applicable; **PSRF**: potential scale reduction factor.
Notes:
This table presents the assessment of convergence for a network meta-analysis performed using a Bayesian inference. Convergence was considered met if the PSRF was under 1.05.[1]
a Measured using Gelman-Rubin statistic as defined in Brooks and Gelman.[2 3]

Lumbar spine (LS)

Table 4 Assessment of convergence in the network meta-analysis for LS BMD in postmenopausal women with osteoporosis

Type of scale reduction factor [a]	Treatment	Point estimate	Upper CI
PSRF	d[2]	1.000475	1.001646
	d[3]	1.000049	1.000058
	d[4]	1.000021	1.000037
	d[5]	1.000458	1.001702
	d[6]	1.000456	1.001651
	d[7]	1.000135	1.000139
	d[8]	1.000047	1.000071
	sigma	1.000319	1.000601
MPSRF	[1]	1.000522	NA

Abbreviations:
BMD: bone mineral density; **CI**: confidence interval; **LS**: lumbar spine; **MPRSF**: multivariate potential scale reduction factor; **NA**: not applicable; **PSRF**: potential scale reduction factor.
Notes:
This table presents the assessment of convergence for a network meta-analysis performed using a Bayesian inference. Convergence was considered met if the PSRF was under 1.05.[1]
[a] Measured using Gelman-Rubin statistic as defined in Brooks and Gelman.[2 3]

Total hip (TH)

Table 5 Assessment of convergence in the network meta-analysis for TH BMD in postmenopausal women with osteoporosis

Type of scale reduction factor [a]	Treatment	Point estimate	Upper CI
PSRF	d[2]	1.012473	1.039289
	d[3]	1.000024	1.000071
	d[4]	1.000050	1.000065
	d[5]	1.012469	1.039304
	d[6]	1.012478	1.039325
	d[7]	1.000051	1.000051
	d[8]	1.000103	1.000220
	sigma	1.000149	1.000405
MPSRF	[1]	1.008564	NA

Abbreviations:
BMD: bone mineral density; **CI**: confidence interval; **MPRSF**: multivariate potential scale reduction factor; **NA**: not applicable; **PSRF**: potential scale reduction factor; **TH**: total hip.
Notes:
This table presents the assessment of convergence for a network meta-analysis performed using a Bayesian inference. Convergence was considered met if the PSRF was under 1.05.[1]
[a] Measured using Gelman-Rubin statistic as defined in Brooks and Gelman.[2 3]

2.2 Findings safety

2.2.1 Mortality

Table 6 Assessment of convergence in the network meta-analysis for mortality in postmenopausal women with osteoporosis

Type of scale reduction factor [a]	Treatment	Point estimate	Upper CI
PSRF	d[2]	1.011006	1.029542
	d[3]	1.000029	1.000109
	d[4]	1.000021	1.000057
	d[5]	1.010764	1.029097
	d[6]	1.000024	1.000093
	d[7]	1.000015	1.000026
	sigma	1.000057	1.000189
MPSRF	[1]	1.005895	NA

Abbreviations:
CI: confidence interval; **MPRSF**: multivariate potential scale reduction factor; **NA**: not applicable; **PSRF**: potential scale reduction factor.
Notes:
This table presents the assessment of convergence for a network meta-analysis performed using a Bayesian inference. Convergence was considered met if the PSRF was under 1.05.[1]
[a] Measured using Gelman-Rubin statistic as defined in Brooks and Gelman.[2 3]

2.2.2 Treatment-related adverse events (AEs)

Table 7 Assessment of convergence in the network meta-analysis for treatment-related AEs in postmenopausal women with osteoporosis

Type of scale reduction factor [a]	Treatment	Point estimate	Upper CI
PSRF	d[2]	1 1.004528	1.016277
	d[3]	1.000782	1.001335
	d[4]	1.000650	1.001938
	d[5]	1.004160	1.015170
	d[6]	1.004923	1.016025
	d[7]	1.000653	1.001060
	d[8]	1.000490	1.000683
	sigma	1.001536	1.002677
MPSRF	[1]	1.004699	NA

Abbreviations:
AEs: adverse events; **CI**: confidence interval; **MPRSF**: multivariate potential scale reduction factor; **NA**: not applicable; **PSRF**: potential scale reduction factor.
Notes:
This table presents the assessment of convergence for a network meta-analysis performed using a Bayesian inference. Convergence was considered met if the PSRF was under 1.05.[1]
[a] Measured using Gelman-Rubin statistic as defined in Brooks and Gelman.[2 3]

2.2.3 Serious adverse events (SAEs)

Table 8 Assessment of convergence in the network meta-analysis for SAEs in postmenopausal women with osteoporosis

Type of scale reduction factor [a]	Treatment	Point estimate	Upper CI
PSRF	d[2]	1.000086	1.000108
	d[3]	1.000057	1.000070
	d[4]	1.000090	1.000101
	d[5]	1.000102	1.000235
	d[6]	1.000045	1.000077
	d[7]	1.000067	1.000121
	d[8]	1.000098	1.000108
	sigma	1.000300	1.001046
MPSRF	[1]	1.000274	NA

Abbreviations:
CI: confidence interval; **MPRSF**: multivariate potential scale reduction factor; **NA**: not applicable; **PSRF**: potential scale reduction factor; **SAEs**: serious adverse events.
Notes:
This table presents the assessment of convergence for a network meta-analysis performed using a Bayesian inference. Convergence was considered met if the PSRF was under 1.05.[1]
a Measured using Gelman-Rubin statistic as defined in Brooks and Gelman.[2 3]

2.2.4 Withdrawal due to treatment-related adverse events (AEs)

Table 9 Assessment of convergence in the network meta-analysis for withdrawal due to treatment-related AEs in postmenopausal women with osteoporosis

Type of scale reduction factor [a]	Treatment	Point estimate	Upper CI
PSRF	d[2]	1.000046	1.000161
	d[3]	1.000007	1.000014
	d[4]	1.000011	1.000011
	d[5]	1.013462	1.033807
	d[6]	1.000016	1.000038
	d[7]	1.000040	1.000086
	sigma	1.000017	1.000043
MPSRF	[1]	1.006424	NA

Abbreviations:
AEs: adverse events; **CI**: confidence interval; **MPRSF**: multivariate potential scale reduction factor; **NA**: not applicable; **PSRF**: potential scale reduction factor.
Notes:
This table presents the assessment of convergence for a network meta-analysis performed using a Bayesian inference. Convergence was considered met if the PSRF was under 1.05.[1]
[a] Measured using Gelman-Rubin statistic as defined in Brooks and Gelman.[2 3]

3 List of excluded trials at full text

This Supplement includes a list of all articles that were excluded from the systematic literature review after full-text review. Each article is organised under one key subheading related to the reason for exclusion, noting that articles may have met more than one criteria for exclusion.

3.1 Incorrect study design (k=123)

1. Adachi JD, Saag KG, Delmas PD, et al. Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. *Arthritis Rheum* 2001;44(1):202-11. doi: 10.1002/1529-0131(200101)44:1<202::AID-ANR27>3.0.CO;2-W [published Online First: 2001/02/24]
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women. *Journal of musculoskeletal & neuronal interactions* 2017;17(1):444-49. [published Online First: 2017/03/03]

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11. Barrett-Connor E, Cauley JA, Kulkarni PM, et al. Risk-benefit profile for raloxifene: 4-year data From the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized trial. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 2004;19(8):1270-5. doi: 10.1359/JBMR.040406 [published Online First: 2004/07/03]
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European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2019;30(7):1455-64. doi: 10.1007/s00198-019-04963-2 [published Online First: 2019/04/24]

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3.2 Incorrect population (i.e. incorrect country, patient demographics) (k= 176)

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3.7 Incorrect publication date (i.e. published before 1997) (k=0)

NA

3.8 Incorrect perspective (i.e. investment instead of disinvestment)[1] (k=0)

NA

3.9 Inadmissible language (i.e. not English, German, French, or Italian) (k=16)

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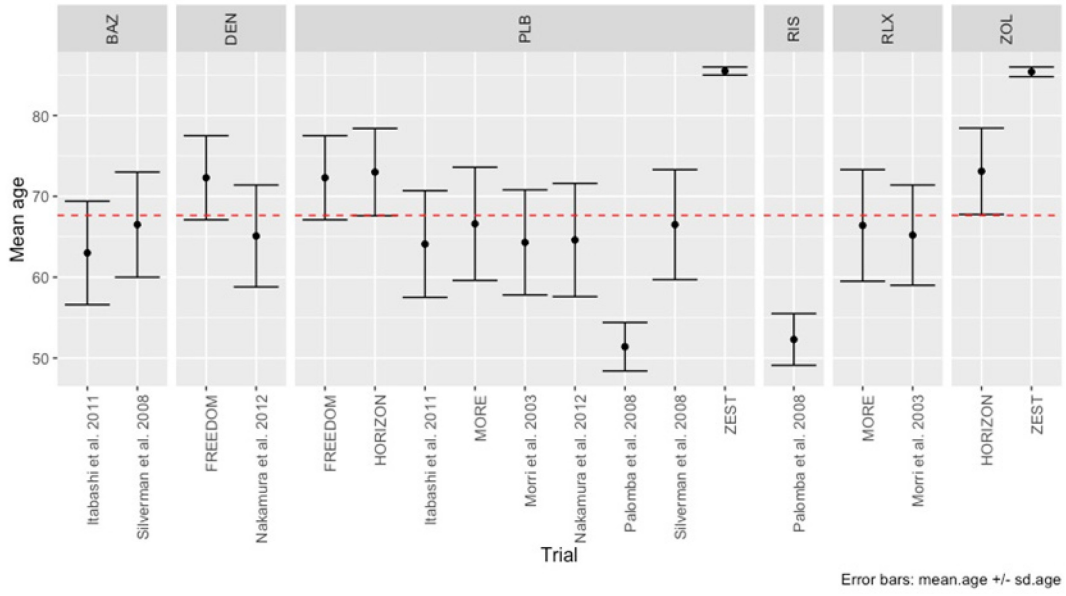
4 Meta-regression of on postmenopausal women with osteoporosis using a Bayesian inference

This Supplement outlines the results of the meta-regressions performed to analyse the impact of any interactions between trial-level covariates and age on the effectiveness and safety of the included interventions/comparators in postmenopausal women with osteoporosis. A figure that details the average age of the population in each trial arm is provided alongside each of the meta-regression plots. The meta-regressions were performed using a Bayesian inference. The complete methods for the meta-regression are detailed in ***Section 7*** of the main HTA report.

4.1 Findings efficacy and effectiveness

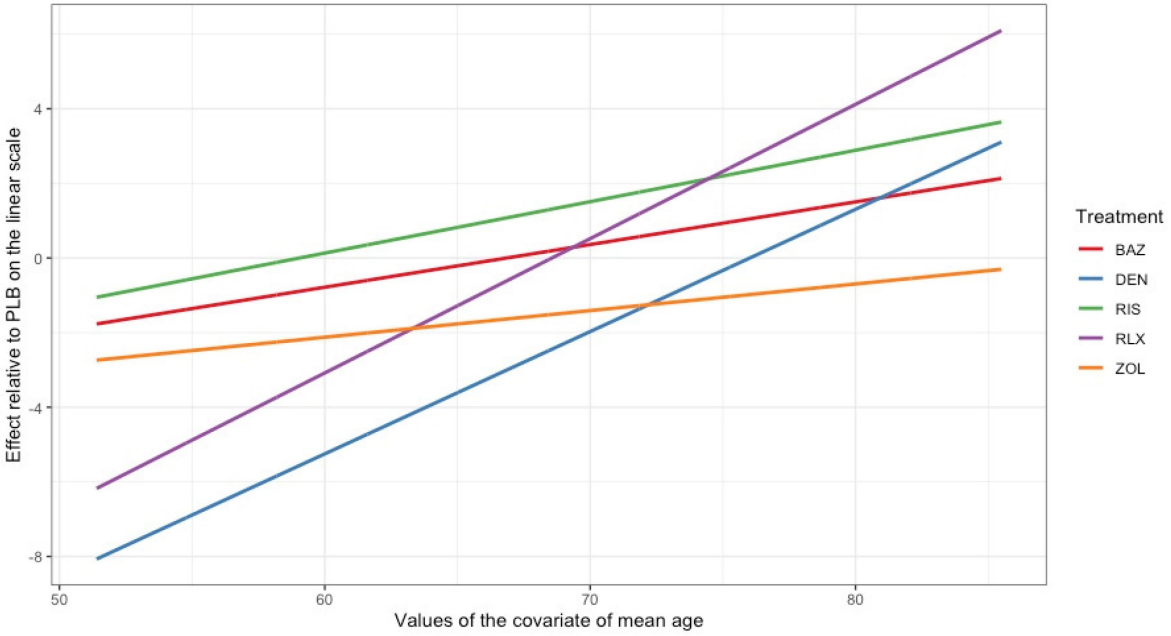
4.1.1 Vertebral fractures

Figure 1 Average patient age of postmenopausal women with osteoporosis in the RCTs that measured vertebral fractures



Abbreviations:
BAZ: bazedoxifene; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **RCT**: randomised control trials; **RLX**: raloxifene; **SD**: standard deviation; **ZOL**: zoledronate.

Figure 2 **Meta-regression of the effect of osteoporosis treatments (relative to placebo) for vertebral fractures in postmenopausal women with osteoporosis when adjusted for age**



Abbreviations:
BAZ: bazedoxifene; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
The y-axis uses a natural logarithmic scale.
This plot is the result of a network meta-analysis performed using a Bayesian inference.

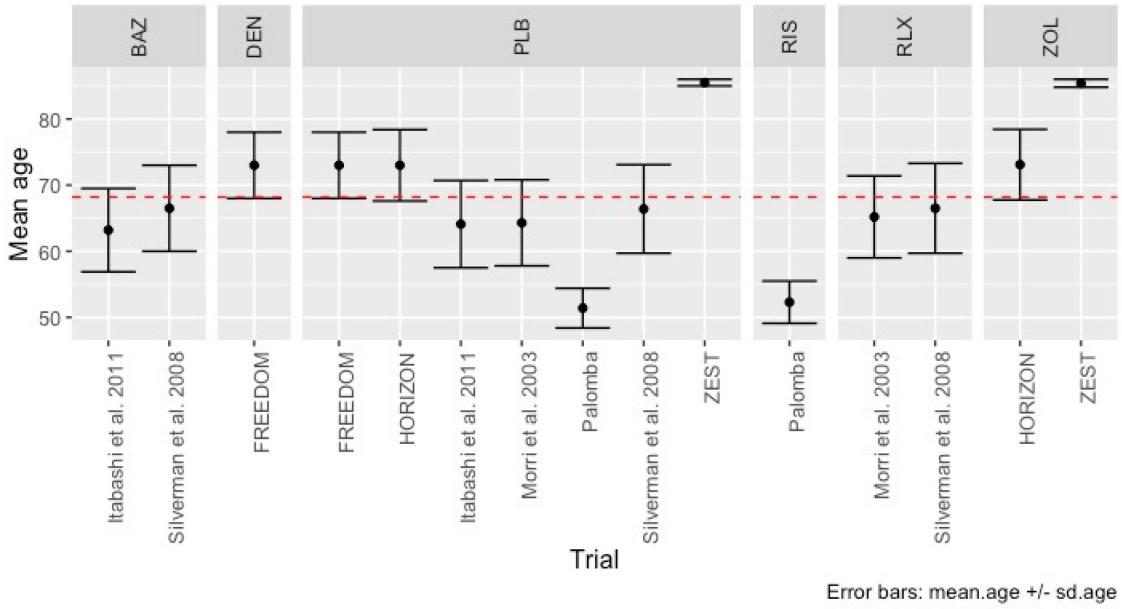
Table 10 **Summary of treatment rankings for vertebral fractures in postmenopausal women with osteoporosis, when adjusted for age**

Treatment	DEN	RLX	ZOL	RIS	BAZ	PLB
SUCRA score	68.55	63.66	50.31	47.62	47.07	22.77
Rank	1	2	3	4	5	6

Abbreviations:
BAZ: bazedoxifene; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **SUCRA**: surface under the cumulative ranking curve; **ZOL**: zoledronate.
Notes:
Surface under the cumulative ranking curve (SUCRA): probability that a specific treatment is among the most effective options (i.e. "best") in the network. A SUCRA value of 100% suggests that the treatment is the most effective treatment included in the network; a SUCRA value of 0% suggests that the included treatment is the least effective treatment in the network.[4]
Rank: position of treatment hierarchy within the network based on the SUCRA score, with 1 representing the most effective treatment.
This plot is the result of a network meta-analysis performed using a Bayesian inference.

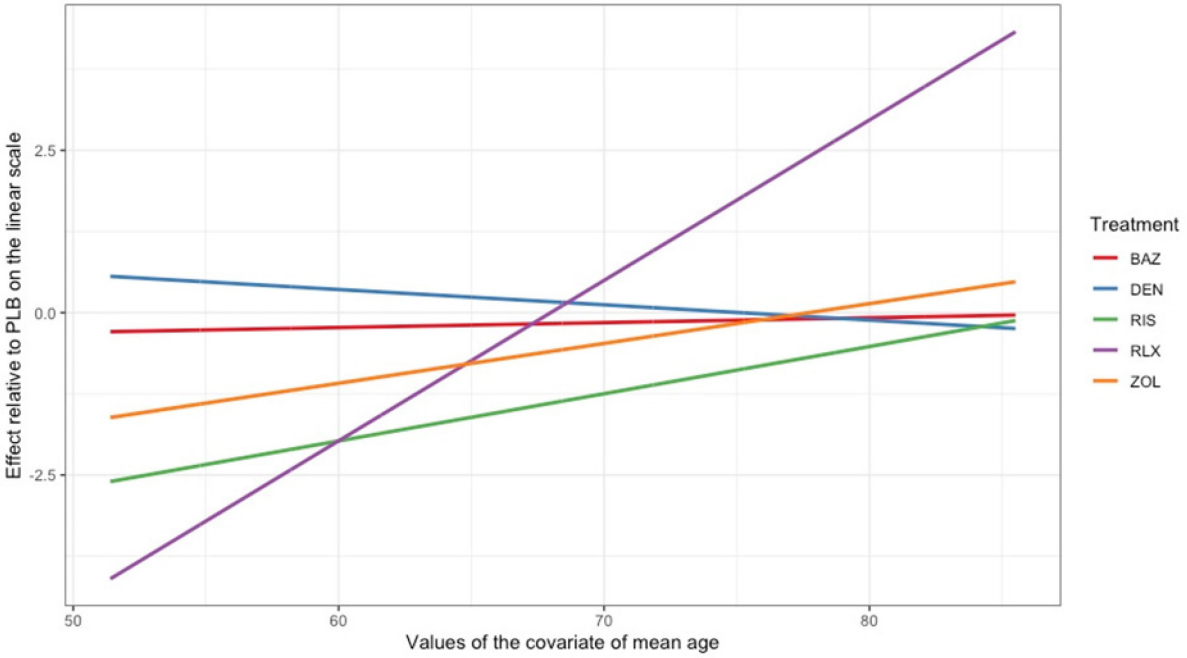
4.1.2 Nonvertebral fractures

Figure 3 Average patient age of postmenopausal women with osteoporosis in the RCTs that measured nonvertebral fractures



Abbreviations:
BAZ: bazedoxifene; **DEN**: denosumab; **PLB**: placebo; **RCT**: randomised control trials; **RIS**: risedronate; **RLX**: raloxifene; **SD**: standard deviation; **ZOL**: zoledronate.

Figure 4 **Meta-regression of the effect of osteoporosis treatments (relative to placebo) for nonvertebral fractures in postmenopausal women with osteoporosis when adjusted for age**



Abbreviations:
BAZ: bazedoxifene; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
The y-axis uses a natural logarithmic scale.
This plot is the result of a network meta-analysis performed using a Bayesian inference.

Table 11 **Summary of treatment rankings for nonvertebral fractures in postmenopausal women with osteoporosis, when adjusted for age**

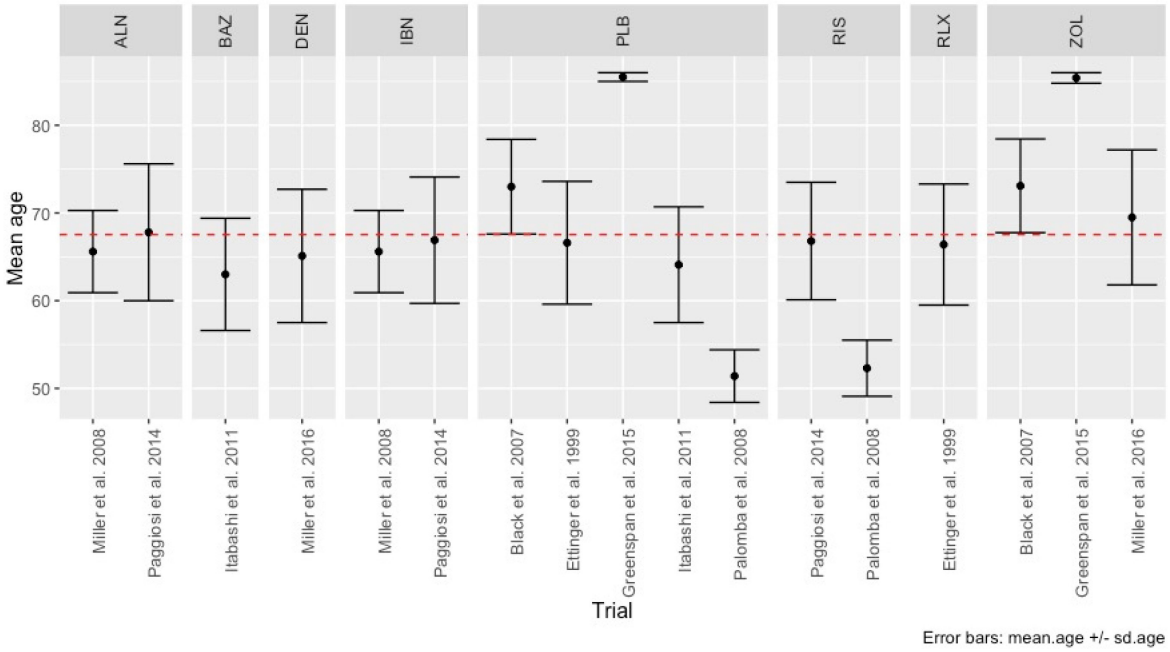
Treatment	RLX	RIS	ZOL	DEN	BAZ	PLB
SUCRA score	63.54	56.38	55.5	46.83	43.23	34.52
Rank	1	2	3	4	5	6

Abbreviations:
BAZ: bazedoxifene; **DEN**: denosumab; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **SUCRA**: surface under the cumulative ranking curve; **ZOL**: zoledronate.
Notes:
Surface under the cumulative ranking curve (SUCRA): probability that a specific treatment is among the most effective options (i.e. "best") in the network. A SUCRA value of 100% suggests that the treatment is the most effective treatment included in the network; a SUCRA value of 0% suggests that the included treatment is the least effective treatment in the network.[4]
Rank: position of treatment hierarchy within the network based on the SUCRA score, with 1 representing the most effective treatment.
This plot is the result of a network meta-analysis performed using a Bayesian inference.

4.1.3 Bone mineral density (BMD)

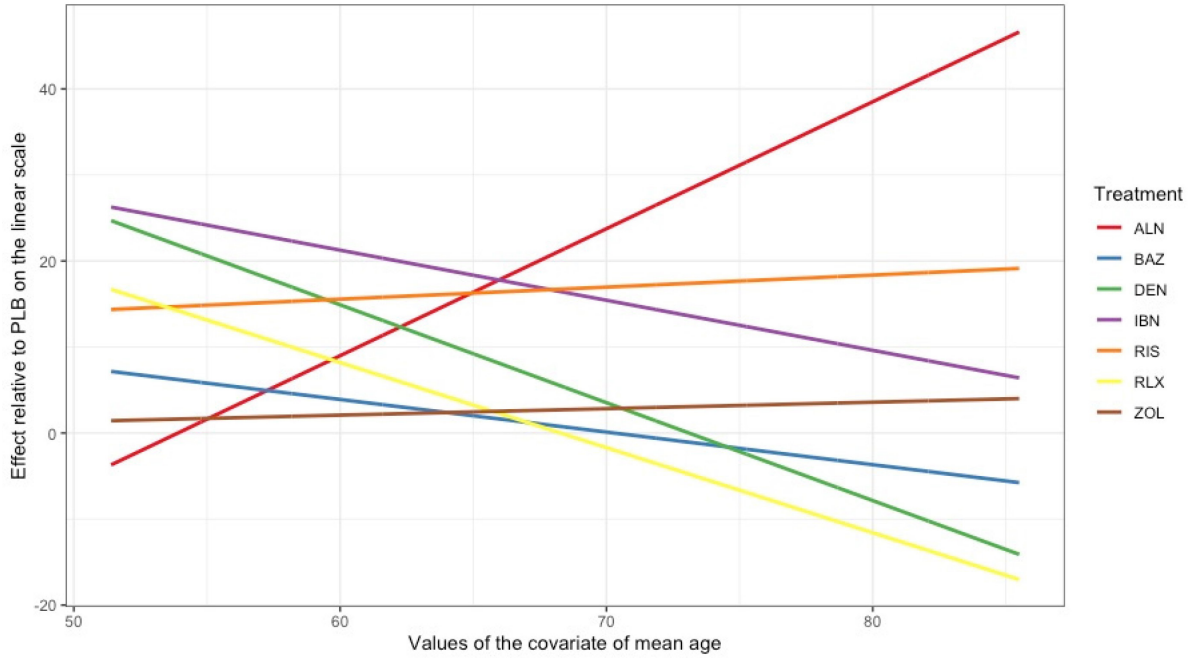
Femoral neck (FN)

Figure 5 Average patient age of postmenopausal women with osteoporosis in the RCTs that measured FN BMD



Abbreviations:
ALN: alendronate; **BAZ**: bazedoxifene; **BMD**: bone mineral density; **DEN**: denosumab; **FN**: femoral neck; **IBN:** ibandronate **PLB**: placebo; **RCT**: randomised control trials; **RIS**: risedronate; **RLX**: raloxifene; **SD**: standard deviation; **ZOL**: zoledronate.

Figure 6 Meta-regression of the effect of osteoporosis treatments (relative to placebo) for FN BMD in postmenopausal women with osteoporosis when adjusted for age



Abbreviations:
ALN: alendronate; **BAZ**: bazedoxifene; **BMD**: bone mineral density; **DEN**: denosumab; **FN**: femoral neck; **IBN:** ibandronate; **PLB**: placebo; **RCT**: randomised control trials; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
The y-axis uses a natural logarithmic scale.
This plot is the result of a network meta-analysis performed using a Bayesian inference.

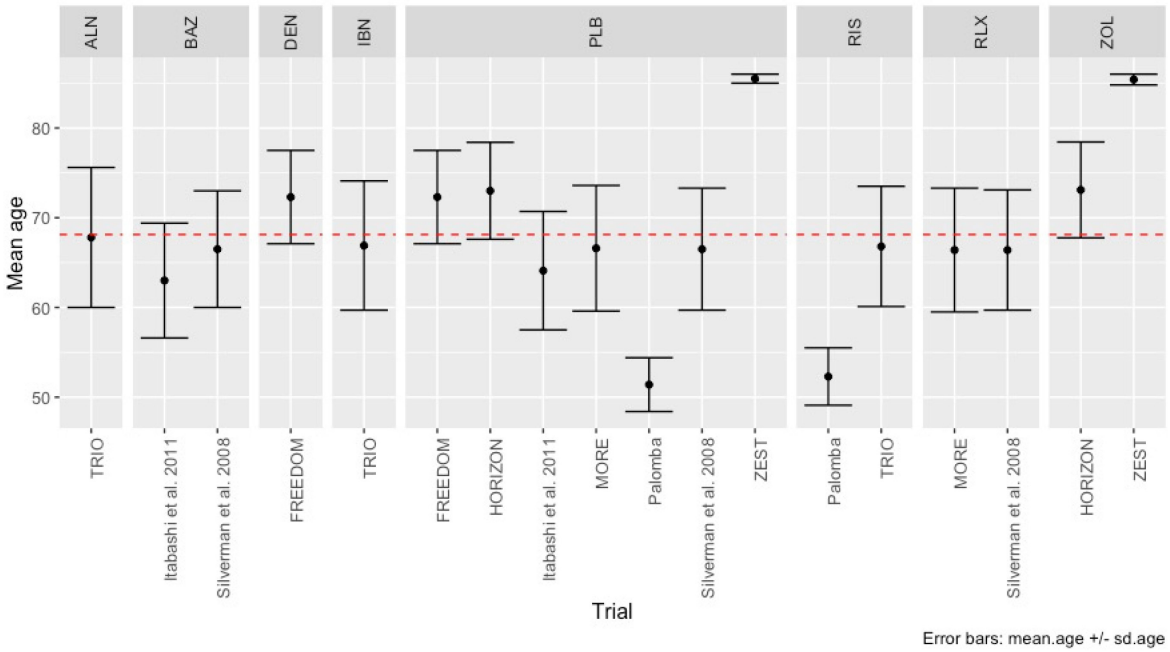
Table 12 Summary of treatment rankings for FN BMD in postmenopausal women with osteoporosis, when adjusted for age

Treatment	ALN	IBN	RIS	DEN	BAZ	RLX	ZOL	PLB
SUCRA score	66.61	61.73	57.25	49.80	47.82	41.22	38.06	37.53
Rank	1	2	3	4	5	6	7	8

Abbreviations:
ALN: alendronate; **BAZ**: bazedoxifene; **BMD:** bone mineral density; **DEN**: denosumab; **FN**: femoral neck; **IBN:** ibandronate; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **SUCRA**: surface under the cumulative ranking curve; **ZOL**: zoledronate.
Notes:
Surface under the cumulative ranking curve (SUCRA): probability that a specific treatment is among the most effective options (i.e. "best") in the network. A SUCRA value of 100% suggests that the treatment is the most effective treatment included in the network; a SUCRA value of 0% suggests that the included treatment is the least effective treatment in the network.[4]
Rank: position of treatment hierarchy within the network based on the SUCRA score, with 1 representing the most effective treatment.

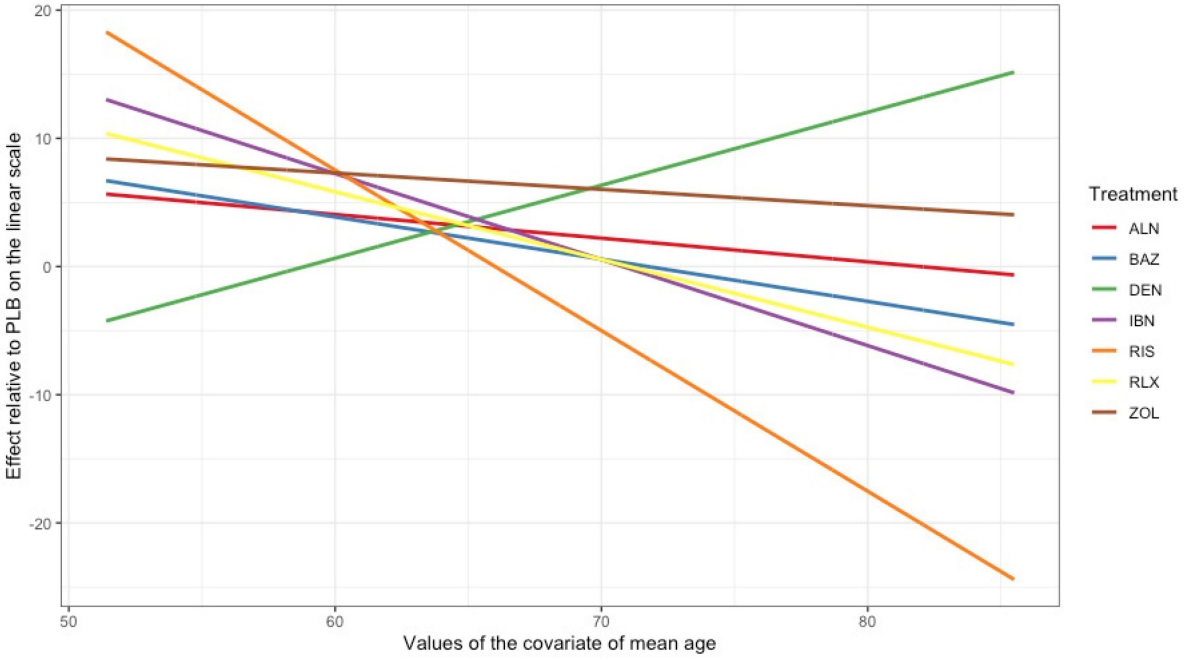
Lumbar spine (LS)

Figure 7 Average patient age of postmenopausal women with osteoporosis in the RCTs that measured LS BMD



Abbreviations:
ALN: alendronate; **BAZ**: bazedoxifene; **BMD**: bone mineral density; **DEN**: denosumab; **IBN**: ibandronate; **LS**: lumbar spine; **PLB**: placebo; **RCT**: randomised control trials; **RIS**: risedronate; **RLX**: raloxifene; **SD**: standard deviation; **ZOL**: zoledronate.

Figure 8 Meta-regression of the effect of osteoporosis treatments (relative to placebo) for LS BMD in postmenopausal women with osteoporosis when adjusted for age



Abbreviations:
ALN: alendronate; **BAZ**: bazedoxifene; **BMD**: bone mineral density; **DEN**: denosumab; **IBN**: ibandronate; **LS**: lumbar spine; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
The y-axis uses a natural logarithmic scale.
This plot is the result of a network meta-analysis performed using a Bayesian inference.

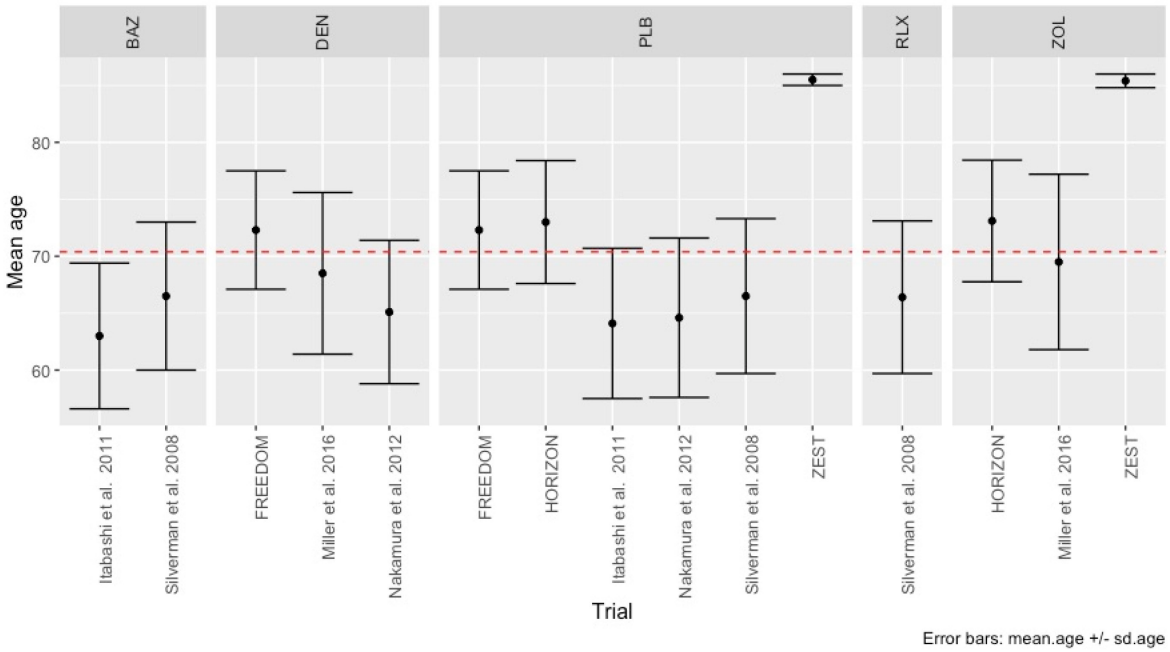
Table 13 Summary of treatment rankings for LS BMD in postmenopausal women with osteoporosis, when adjusted for age

Treatment	IBN	RIS	ALN	BAZ	RLX	ZOL	DEN	PLB
SUCRA score	59.92	58.52	57.01	53.00	48.98	48.47	45.24	28.88
Rank	1	2	3	4	5	6	7	8

Abbreviations:
ALN: alendronate; **BAZ**: bazedoxifene; **BMD:** bone mineral density; **DEN**: denosumab; **IBN:** ibandronate; **LS:** lumbar-spine; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **SUCRA**: surface under the cumulative ranking curve; **ZOL**: zoledronate.
Notes:
Surface under the cumulative ranking curve (SUCRA): probability that a specific treatment is among the most effective options (i.e. "best") in the network. A SUCRA value of 100% suggests that the treatment is the most effective treatment included in the network; a SUCRA value of 0% suggests that the included treatment is the least effective treatment in the network.[4]
Rank: position of treatment hierarchy within the network based on the SUCRA score, with 1 representing the most effective treatment.

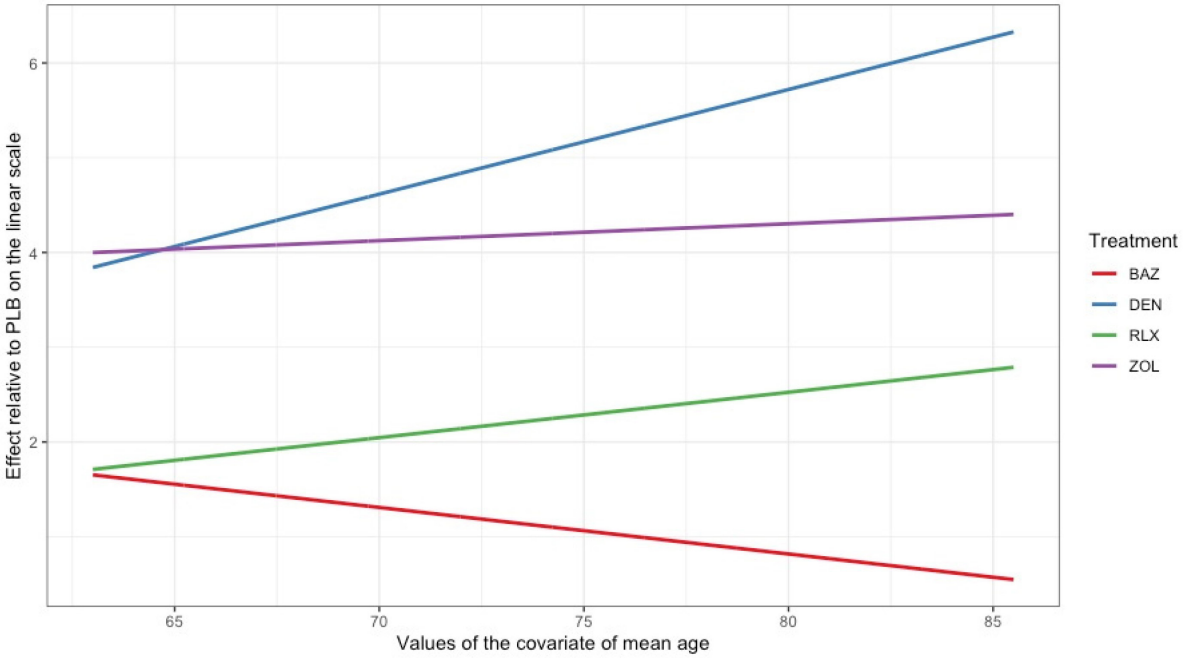
Total hip (TH)

Figure 9 Average patient age of postmenopausal women with osteoporosis in the RCTs that measured TH BMD



Abbreviations:
BAZ: bazedoxifene; **BMD**: bone mineral density; **DEN**: denosumab; **PLB**: placebo; **RCT**: randomised control trials; **RLX**: raloxifene; **SD**: standard deviation; **TH**: total hip; **ZOL**: zoledronate.

Figure 10 Meta-regression of the effect of osteoporosis treatments (relative to placebo) for TH BMD in postmenopausal women with osteoporosis when adjusted for age



Abbreviations:
BAZ: bazedoxifene; **BMD**: bone mineral density; **DEN**: denosumab; **PLB**: placebo; **RLX**: raloxifene; **TH**: total hip; **ZOL**: zoledronate.
Notes:
The y-axis uses a natural logarithmic scale.
This plot is the result of a network meta-analysis performed using a Bayesian inference.

Table 14 Summary of treatment rankings for TH BMD in postmenopausal women with osteoporosis, when adjusted for age

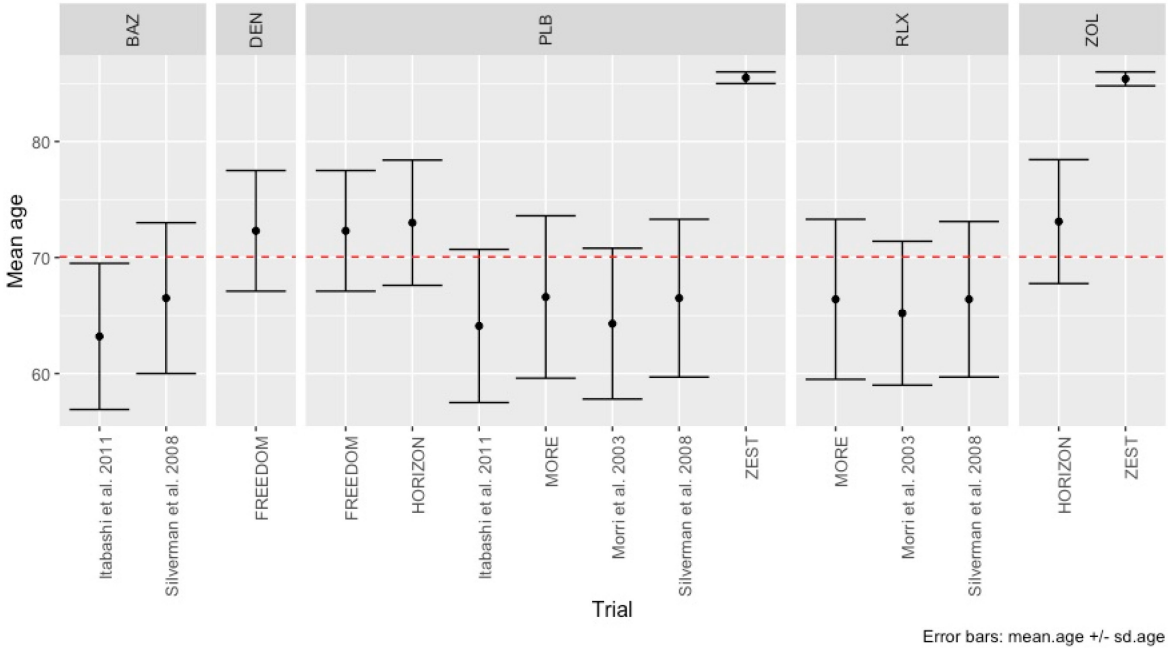
Treatment	ZOL	BAZ	RLX	PLB	DEN
SUCRA score	58.79	57.48	46.45	45.52	41.74
Rank	1	2	3	4	5

Abbreviations:
BAZ: bazedoxifene; **BMD:** bone mineral density; **DEN**: denosumab; **PLB**: placebo; **RLX**: raloxifene; **SUCRA**: surface under the cumulative ranking curve; **TH**: total hip; **ZOL**: zoledronate.
Notes:
Surface under the cumulative ranking curve (SUCRA): probability that a specific treatment is among the most effective options (i.e. "best") in the network. A SUCRA value of 100% suggests that the treatment is the most effective treatment included in the network; a SUCRA value of 0% suggests that the included treatment is the least effective treatment in the network.[4]
Rank: position of treatment hierarchy within the network based on the SUCRA score, with 1 representing the most effective treatment.

4.2 Findings safety

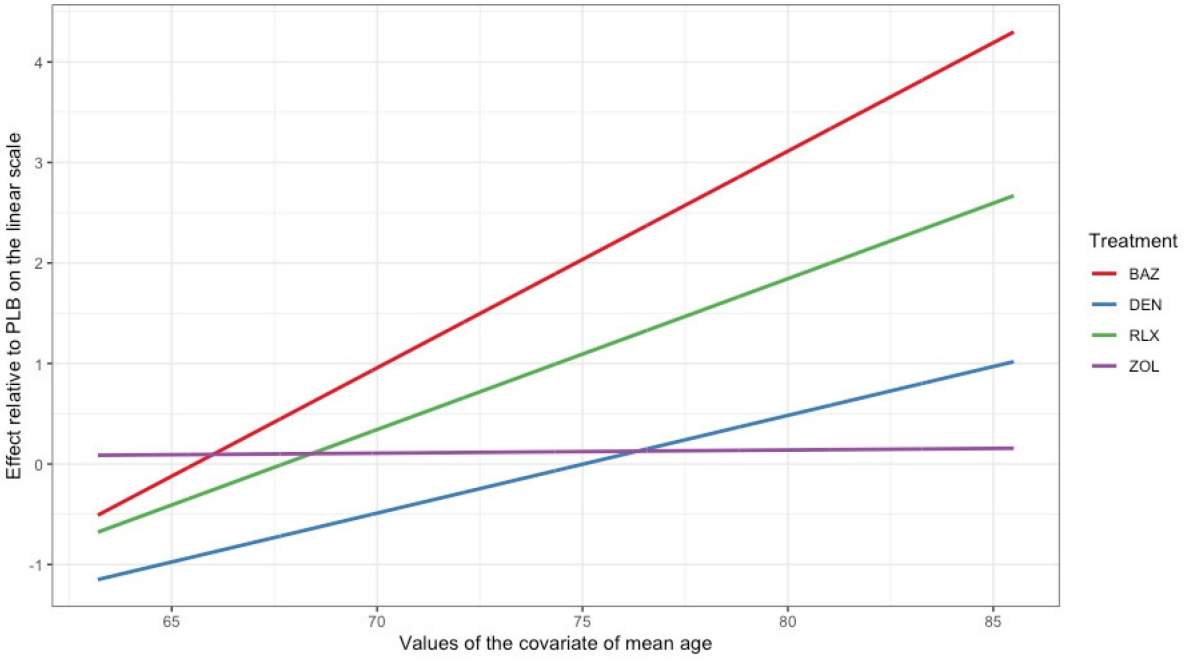
4.2.1 Mortality

Figure 11 Average patient age of postmenopausal women with osteoporosis in RCTs that measured mortality



Abbreviations:
BAZ: bazedoxifene; **DEN**: denosumab; **PLB**: placebo; **RCT**: randomised control trials; **RLX**: raloxifene; **SD**: standard deviation; **ZOL**: zoledronate.

Figure 12 Meta-regression of the effect of osteoporosis treatments (relative to placebo) for mortality in postmenopausal women with osteoporosis when adjusted for age



Abbreviations:
BAZ: bazedoxifene; **DEN**: denosumab; **PLB**: placebo; **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
The y-axis uses a natural logarithmic scale.
This plot is the result of a network meta-analysis performed using a Bayesian inference.

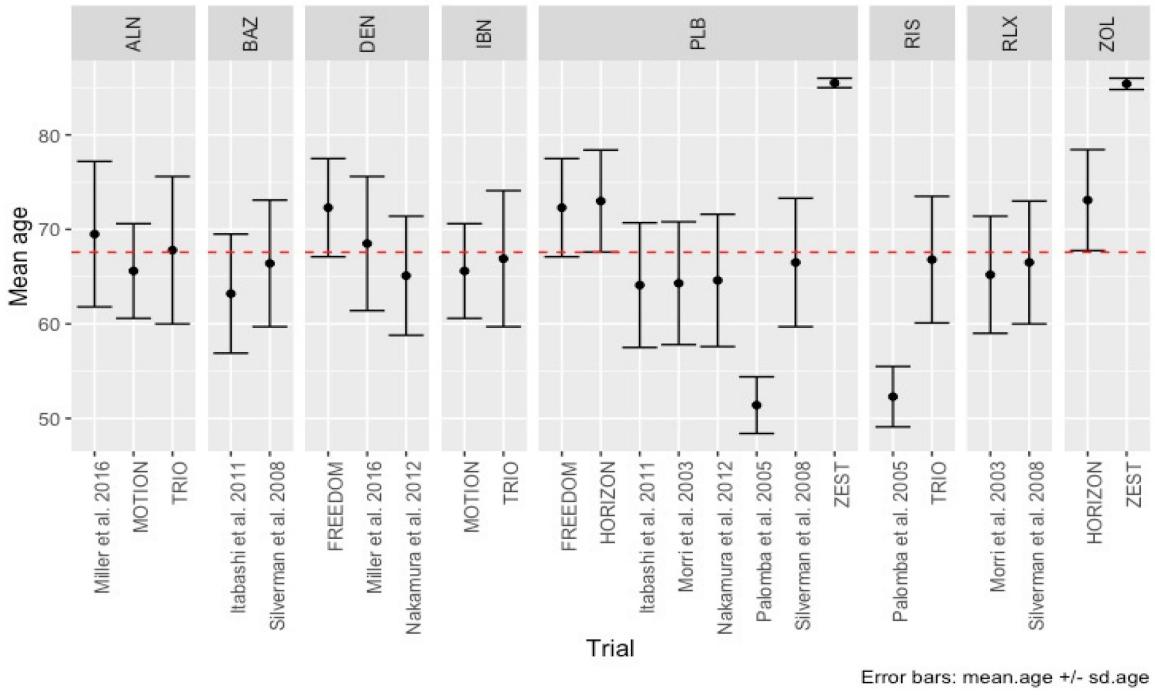
Table 15 Summary of treatment rankings for mortality in postmenopausal women with osteoporosis, when adjusted for age

Treatment	BAZ	RLX	DEN	ZOL	PLB
SUCRA score	63.13	57.08	53.14	38.52	38.13
Rank	1	2	3	4	5

Abbreviations:
BAZ: bazedoxifene; **DEN**: denosumab; **PLB**: placebo; **RLX**: raloxifene; **SUCRA**: surface under the cumulative ranking curve; **ZOL**: zoledronate.
Notes:
Surface under the cumulative ranking curve (SUCRA): probability that a specific treatment is among the most effective options (i.e. "best") in the network. A SUCRA value of 100% suggests that the treatment is the most effective treatment included in the network; a SUCRA value of 0% suggests that the included treatment is the least effective treatment in the network.[4]
Rank: position of treatment hierarchy within the network based on the SUCRA score, with 1 representing the most effective treatment.

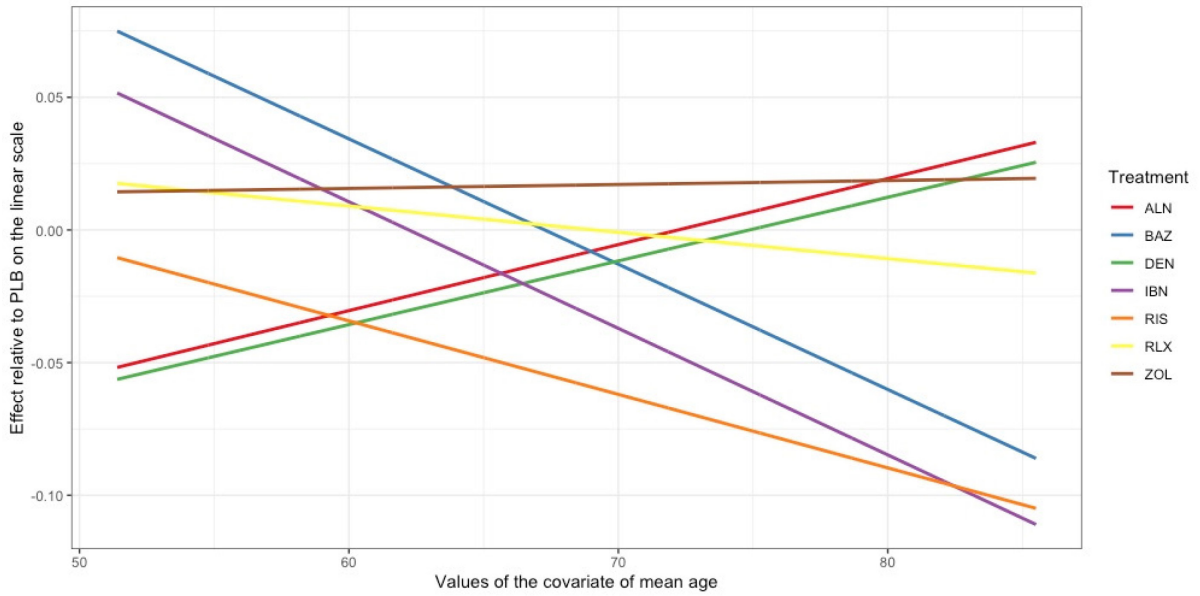
4.2.2 Treatment-related adverse events (AEs)

Figure 13 Average patient age of postmenopausal women with osteoporosis in RCTs that measured treatment-related AEs



Abbreviations:
AEs: adverse events; **ALN**: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **IBN**: ibandronate; **PLB**: placebo; **RCT**: randomised control trials; **RIS**: risedronate; **RLX**: raloxifene; **SD**: standard deviation; **ZOL**: zoledronate.

Figure 14 Meta-regression of the effect of osteoporosis treatments (relative to placebo) for treatment-related AEs in postmenopausal women with osteoporosis when adjusted for age



Abbreviations:
AEs: adverse events; **ALN**: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **IBN**: ibandronate; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
The y-axis uses a natural logarithmic scale.
This plot is the result of a network meta-analysis performed using a Bayesian inference.

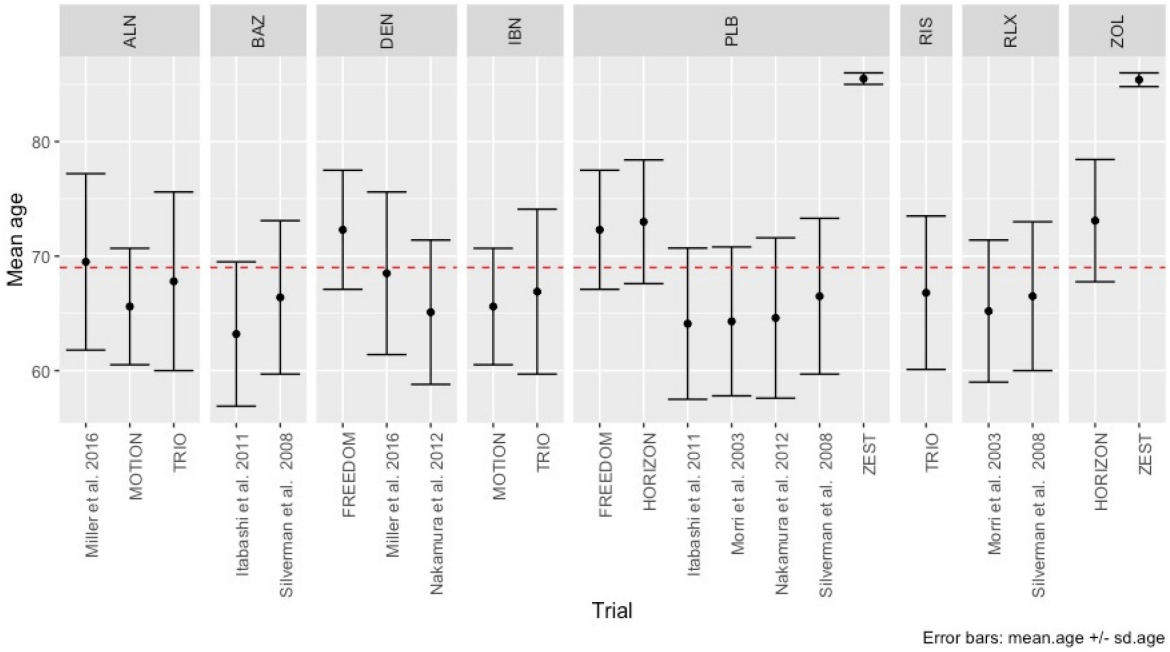
Table 16 Summary of treatment rankings for treatment related AEs in postmenopausal women with osteoporosis, when adjusted for age

Treatment	DEN	ALN	PLB	ZOL	RIS	RLX	IBN	BAZ
SUCRA score	60.2	55.77	52.51	50.95	49.3	49	43.53	38.74
Rank	1	2	3	4	5	6	7	8

Abbreviations:
AE: adverse events; **ALN**: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **IBN:** ibandronate; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **SUCRA**: surface under the cumulative ranking curve; **ZOL**: zoledronate.
Notes:
Surface under the cumulative ranking curve (SUCRA): probability that a specific treatment is among the most effective options (i.e. "best") in the network. A SUCRA value of 100% suggests that the treatment is the most effective treatment included in the network; a SUCRA value of 0% suggests that the included treatment is the least effective treatment in the network.[4]
Rank: position of treatment hierarchy within the network based on the SUCRA score, with 1 representing the most effective treatment.

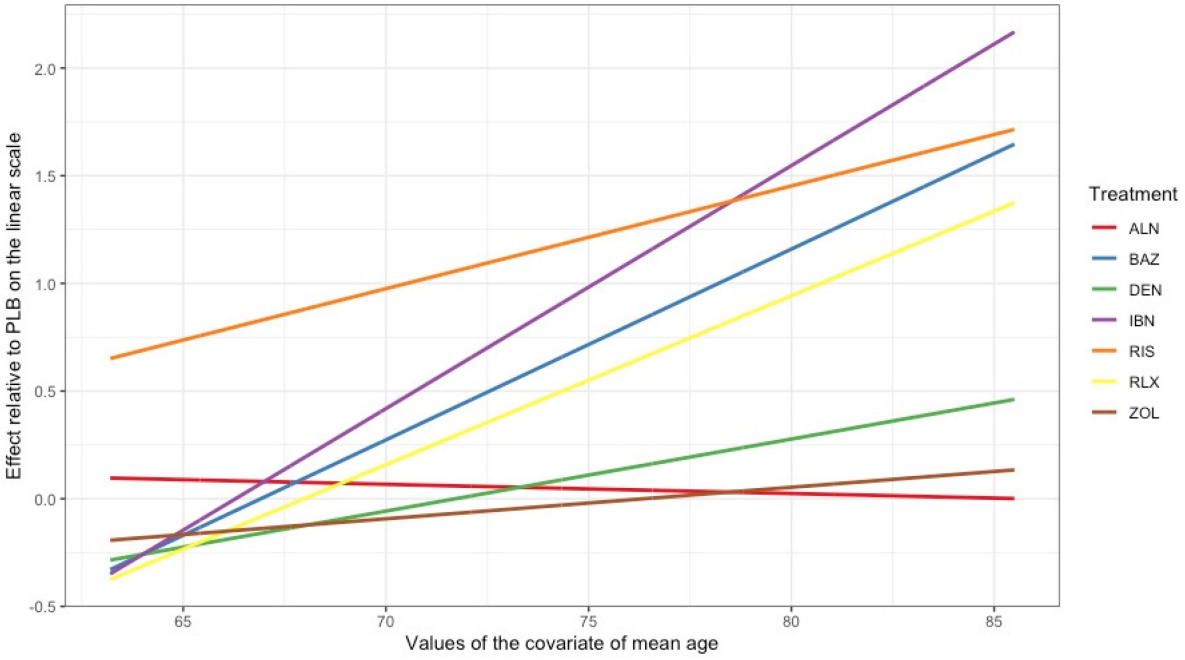
4.2.3 Serious adverse events (SAEs)

Figure 15 Average patient age of postmenopausal women with osteoporosis in RCTs that measured SAEs



Abbreviations:
ALN: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **IBN**: ibandronate; **PLB**: placebo; **RCT**: randomised control trials; **RIS**: risedronate; **RLX**: raloxifene; **SAEs**: serious adverse events; **SD**: standard deviation; **ZOL**: zoledronate.

Figure 16 Meta-regression of the effect of osteoporosis treatments (relative to placebo) for SAEs in postmenopausal women with osteoporosis when adjusted for age



Abbreviations:
ALN: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **IBN**: ibandronate; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
The y-axis uses a natural logarithmic scale.
This plot is the result of a network meta-analysis performed using a Bayesian inference.

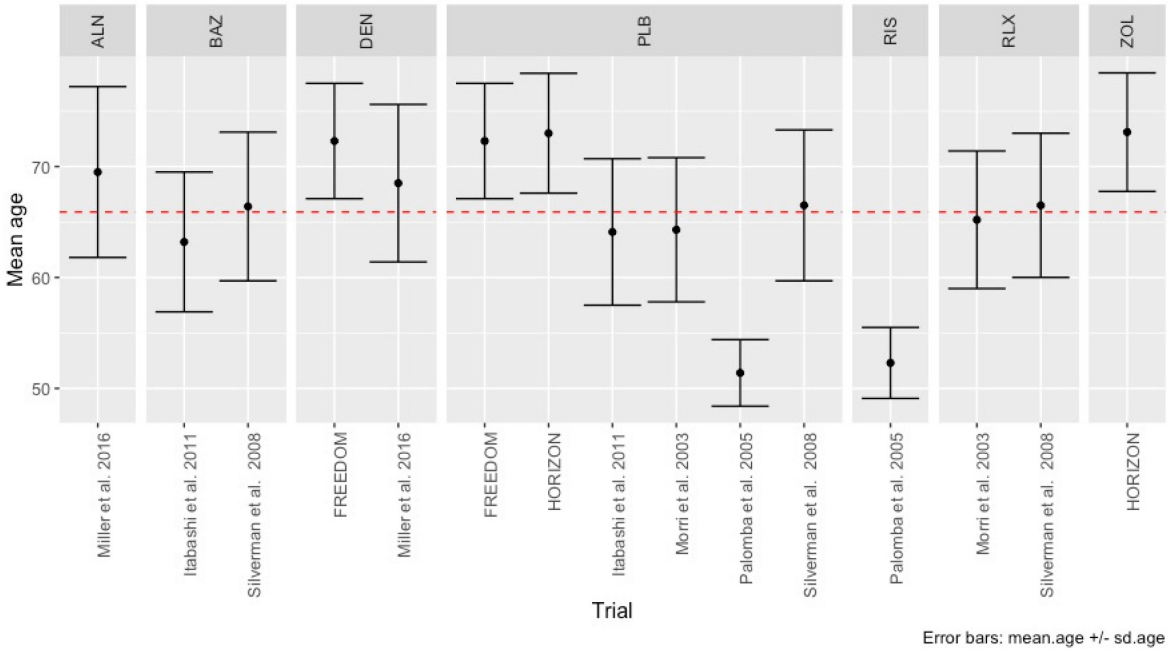
Table 17 Summary of treatment rankings for SAEs in postmenopausal women with osteoporosis, when adjusted for age

Treatment	BAZ	IBN	RLX	DEN	RIS	ZOL	ALN	PLB
SUCRA score	62.07	60.54	56.73	50.96	45.90	45.62	43.76	34.41
Rank	1	2	3	4	5	6	7	8

Abbreviations:
SAE: serious adverse events; **ALN**: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **IBN:** ibandronate; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **SUCRA**: surface under the cumulative ranking curve; **ZOL**: zoledronate.
Notes:
Surface under the cumulative ranking curve (SUCRA): probability that a specific treatment is among the most effective options (i.e. "best") in the network. A SUCRA value of 100% suggests that the treatment is the most effective treatment included in the network; a SUCRA value of 0% suggests that the included treatment is the least effective treatment in the network.[4]
Rank: position of treatment hierarchy within the network based on the SUCRA score, with 1 representing the most effective treatment.

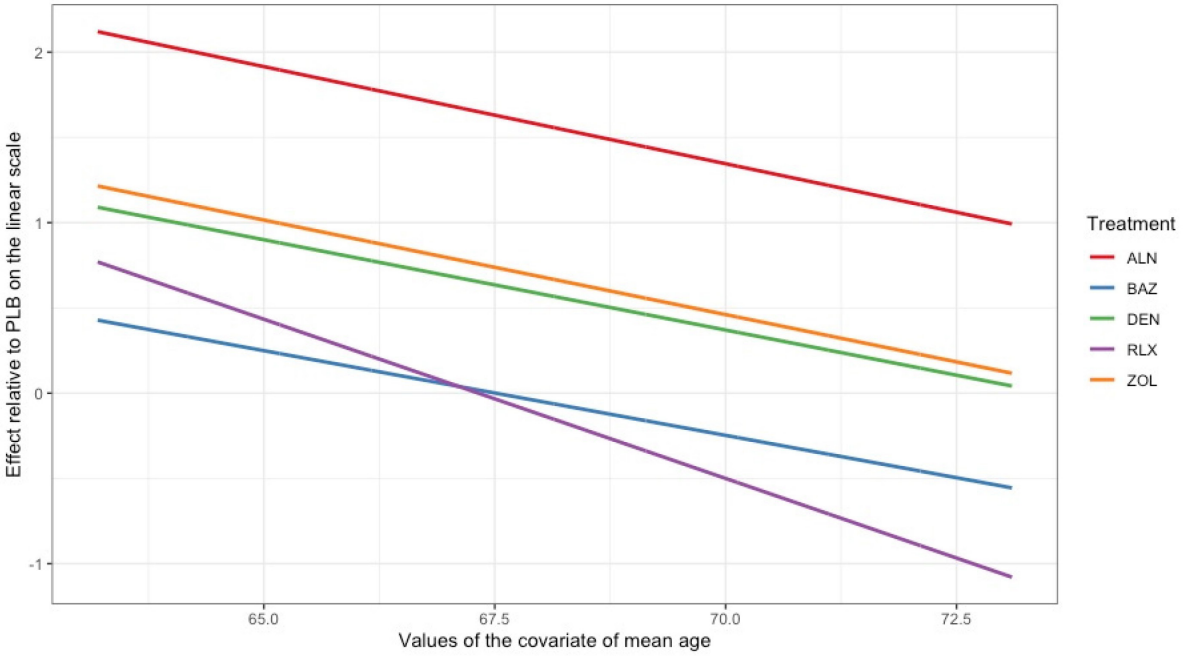
4.2.4 Withdrawal due to treatment-related adverse events (AEs)

Figure 17 Average patient age of postmenopausal women with osteoporosis in RCTs that measured withdrawals due to treatment-related AEs



Abbreviations:
AEs: adverse events; **ALN**: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **PLB**: placebo; **RCT**: randomised control trials; **RIS**: risedronate; **RLX**: raloxifene; **SD**: standard deviation; **ZOL**: zoledronate.

Figure 18 Meta-regression of the effect of osteoporosis treatments (relative to placebo) for withdrawals due to treatment-related AEs in postmenopausal women with osteoporosis when adjusted for age



Abbreviations:
AEs: adverse events; **ALN**: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **PLB**: placebo; **RCT**: randomised control trials; **RIS**: risedronate; **RLX**: raloxifene; **ZOL**: zoledronate.
Notes:
The y-axis uses a natural logarithmic scale.
This plot is the result of a network meta-analysis performed using a Bayesian inference.

Table 18 Summary of treatment rankings for withdrawals due to treatment-related AEs in postmenopausal women with osteoporosis, when adjusted for age

Treatment	PLB	BAZ	DEN	ZOL	ALN	RLX
SUCRA score	66.61	49.89	48.49	48.06	44.49	42.47
Rank	1	2	3	4	5	6

Abbreviations:
SAE: serious adverse events; **ALN**: alendronate; **BAZ**: bazedoxifene; **DEN**: denosumab; **IBN:** ibandronate; **PLB**: placebo; **RIS**: risedronate; **RLX**: raloxifene; **SUCRA**: surface under the cumulative ranking curve; **ZOL**: zoledronate.
Notes:
Surface under the cumulative ranking curve (SUCRA): probability that a specific treatment is among the most effective options (i.e. "best") in the network. A SUCRA value of 100% suggests that the treatment is the most effective treatment included in the network; a SUCRA value of 0% suggests that the included treatment is the least effective treatment in the network.[4]
Rank: position of treatment hierarchy within the network based on the SUCRA score, with 1 representing the most effective treatment.

5 Sensitivity analyses

This Supplement details the sensitivity analyses conducted to explore the possible effect modifiers of imprecision (aggerating all four populations) as well as high and moderate risk of bias of reporting bias (i.e. selective reporting), attrition bias (i.e. missing outcomes) and selection bias (i.e. randomisation) on the pre-determined outcomes in the included populations. Since the risk of performance bias (i.e. blinding of participant/ personnel) and detection bias (i.e. measurement of outcomes) were mainly low across the included RCTs, the impact of these effect modifiers were not explored. The results of the sensitivity analysis are presented across two tables.

5.1 Sensitivity analyses conducted using a Bayesian inference

Table 19 Results of sensitivity analyses conducted using a Bayesian inference

Outcome	Treatment	Comparator	Events	Sample size	Effect size		95 CrI	SUCRA score	Heterogeneity (I^2)		Inconsistency			
					MD	RR			Total	Comparison-specific [a]	Local [b]	Global (DIC) score [c]		
												Model type		Importance of difference [d]
												Consistency	Inconsistency	
Combined populations														
Vertebral fractures	***DEN †§	***PLB*	***115*	***5,496*	***NA*	***0.31*	***0.10, 0.57*	***84.98*		37.50				
	RIS	PLB	12	40	NA	0.52	0.09, 1.67	68.02		--				
	ZOL	PLB	114	3,817	NA	0.50	0.21, 1.15	64.06		58.90				
	RLX	PLB	148	2,349	NA	0.58	0.10, 1.36	54.51	36.96	0.0	No	--	--	--
	ALN	PLB	6	148	NA	1.61	0.13, 7.11	32.64		--				
	BAZ	PLB	19	638	NA	0.96	0.26, 2.47	29.87		0.0				
	NA	PLB	933	12,270	NA	--	--	15.91		NA				
	**RIS	PLB	1	40	NA	0.14	0.00, 0.61	94.03	29.12	--	No	--	--	---

Nonvertebral fractures	***ALN#***	***PLB***	***14***	***999***	***NA***	***0.49***	***0.04, 1.67***	***69.86***		0.0				
	IBN	PLB	14	874	NA	0.58	0.04, 2.36	64.87		--				
	*****DEN †#‡§***	***PLB***	***376***	***5,697***	***NA***	***0.67***	***0.44, 0.95***	***56.04***		54.90				
	RLX	PLB	90	1,939	NA	0.83	0.37, 1.41	37.09		16.70				
	ZOL	PLB	315	4,749	NA	0.88	0.56, 1.41	32.79		22.10				
	BAZ	PLB	94	2,018	NA	0.90	0.45, 1.57	31.14		0.0				
	NA	PLB	1,052	12,760	NA	--	--	14.18		NA				
BMD measured at FN	*****RIS #***	***PLB***	***NA***	***283***	***5.47***	***NA***	***1.83, 9.33***	***82.62***	90.84	98.2	No	84.35	84.47	Minimal
	IBN §	***PLB***	***NA***	***750***	***4.36***	***NA***	***-0.76, 9.55***	***65.96***		--				
	*****ALN §***	***PLB***	***NA***	***984***	***4.04***	***NA***	***0.64, 7.50***	***63.45***		0.0				
	*****DEN †***	***PLB***	***NA***	***1,745***	***3.03***	***NA***	***0.15, 5.88***	***48.95***		37.6				
	*****ZOL†***	***PLB***	***NA***	***3,917***	***3.00***	***NA***	***0.61, 5.34***	***47.86***		66.2				
	BAZ	PLB	NA	132	2.77	NA	-3.97, 9.53	46.86		--				
	RLX	PLB	NA	1,490	1.90	NA	-4.42, 8.13	36.5		--				
	NA	PLB	NA	6,852	--	NA	--	7.81		NA				
BMD measured at LS	**IBN	PLB	NA	103	6.62	NA	2.49, 10.89	76.79	87.4	--	No	107.13	107.33	Minimal
	**ALN	PLB	NA	302	6.07	NA	3.02, 9.21	70.44		0.0				
	**ZOL	PLB	NA	753	6.01	NA	4.05, 7.99	70.4		40.7				
	**DEN	PLB	NA	1,660	5.78	NA	3.19, 8.41	66.31		86.9				
	*****RIS #***	***PLB***	***NA***	***332***	***5.60***	***NA***	***2.73, 8.66***	***62.49***		96.8				
	RLX	PLB	NA	3,339	2.61	NA	-1.44, 6.55	26.95		0.0				
	BAZ	PLB	NA	2,018	2.28	NA	-1.73, 6.22	23.58		87.9				
	NA	PLB	NA	6,256	--	NA	--	3.05		NA				
BMD measured at TH	***DEN §***	***PLB***	***NA***	***2,029***	***3.39***	***NA***	***-0.10, 6.84***	***76.43***	98.9	89.9	No	100.86	103.00	Minimal
	RLX	PLB	NA	1,849	1.88	NA	-6.77,10.46	54.36		--				
	IBN §‡	***PLB***	***NA***	***128***	***1.68***	***NA***	***-6.47, 9.99***	***52.27***		--				
	BAZ	PLB	NA	2,018	1.53	NA	-5.39, 8.37	51.04		0.0				

	ZOL § †	***PLB***	***NA***	***4,085***	***1.22***	***NA***	***-1.69, 4.10***	***47.73***		21.0				
	ALN §	***PLB***	***NA***	***324***	***1.21***	***NA***	***-3.64, 6.05***	***47.26***		99.3				
	RIS ‡	***PLB***	***NA***	***284***	***0.96***	***NA***	***-4.46, 6.44***	***44.25***		91.6				
	NA	PLB	NA	7,733	--	NA	--	26.64		NA				
BMD measured at TRO	***RIS ‡ §***	***PLB***	***NA***	***266***	***4.38***	***NA***	***-1.69, 10.57***	***68.68***	93.99	96.5	No	32.24	32.02	Minimal
	ZOL	PLB	NA	57	4.01	NA	-3.57, 11.68	63.62		30.4				
	DEN ‡ §	***PLB***	***NA***	***234***	***3.51***	***NA***	***-4.01, 10.91***	***58.80***		88.7				
	BAZ	PLB	NA	132	1.98	NA	-8.69, 12.66	43.18		--				
	NA	PLB	NA	591	--	NA	-	15.71		NA				
Mortality	RIS	PLB	2	191	NA	0.31	0.03, 1.19	90.33	0.0	--	No	--	--	--
	IBN	PLB	2	874	NA	0.74	0.03, 3.81	74.13		--				
	DEN	PLB	214	6,577	NA	0.85	0.60, 1.14	56.59		0.0				
	RLX	PLB	42	4,498	NA	0.85	0.48, 1.36	56.01		71.8				
	ALN	PLB	6	1,063	NA	1.46	0.21, 5.36	36.45		--				
	NA	PLB	443	16,194	NA	--	--	33.9		--				
	ZOL	PLB	162	4,945	NA	1.02	0.65, 1.39	33.07		0.0				
	BAZ	PLB	24	2,029	NA	1.31	0.61, 2.39	19.53		NA				
AEs	RIS	PLB	149	289	NA	0.91	0.75, 1.09	89.65	76.0	0.0	No	103.48	96.83	Substantial
	NA	PLB	12,141	13,599	NA	--	--	65.77		NA				
	DEN	PLB	6,060	6,876	NA	1.01	0.95, 1.07	58.31		0.0				
	RLX	PLB	1,809	1,941	NA	1.01	0.89, 1.14	57.54		0.0				
	BAZ	PLB	1,941	2,029	NA	1.02	0.92, 1.13	54.02		34.7				
	ALN §	***PLB***	***1,023***	***1,440***	***NA***	***1.05***	***0.94, 1.18***	***37.22***		0.0				
	IBN	PLB	673	931	NA	1.11	0.93, 1.36	20.13		--				
	ZOL	PLB	4,538	4,890	NA	1.08	1.01, 1.18	17.35		90.5				
Serious AEs	IBN	PLB	51	1,003	NA	0.83	0.51, 1.30	84.26	0.0	--	No	--	--	--

	ZOL	PLB	1,423	5,028	NA	0.96	0.85, 1.06	67.15		0.0				
	RLX	PLB	349	1,941	NA	0.97	0.78, 1.14	64.14		0.0				
	NA	PLB	3,588	13,916	NA	--	--	51.52		NA				
	ALN	PLB	136	1,524	NA	1.04	0.78, 1.40	42.12		0.0				
	BAZ	PLB	391	2,029	NA	1.04	0.84, 1.23	36.76		40.4				
	DEN	PLB	1,839	6,876	NA	1.05	0.95, 1.16	32.28		0.0				
	RIS	PLB	42	299	NA	1.25	0.74, 2.03	21.75		12.2				
Withdrawal due to AEs	***RIS †**	***PLB**	***0**	***40**	***NA**	***0.15**	***0.00, 0.58**	***98.38**		--				
	ZOL	PLB	116	4,917	NA	0.97	0.56, 1.42	59.34		0.0				
	NA	PLB	480	11,888	NA	--	--	56.65		NA				
	DEN	PLB	132	5,202	NA	1.05	0.55, 1.59	48.96	0.0	22.5	No	--	--	--
	RLX	PLB	280	1,941	NA	1.30	0.69, 2.64	30.42		28.7				
	BAZ	PLB	299	2,029	NA	1.28	0.70, 2.43	30.23		12.1				
	ALN	PLB	21	545	NA	1.41	0.49, 2.85	26.03		--				
AEs upon denosumab discontinuation	Unable to conduct analysis as only single arm studies were included													
Postmenopausal women with osteoporosis														
Low sample size														
Nonvertebral fractures	RLX	PLB	90	1,939	NA	0.80	0.23, 1.70	63.08		16.7				
	DEN	PLB	264	3,902	NA	0.92	0.24, 2.54	60.43		--				
	BAZ	PLB	94	2,018	NA	0.92	0.32, 2.04	51.72	38.4	0	No	24.48	24.42	Minimal
	ZOL	PLB	304	3,950	NA	1.04	0.42, 2.52	45.97		71.2				
	NA	PLB	838	9,983	NA	--	--	28.80		--				
Risk of bias														
Randomisation														
Vertebral fractures	Unable to conduct analysis as none of the low-risk trials included denosumab													
Nonvertebral fractures	Unable to conduct analysis as none of the low-risk trials included denosumab													

BMD measured at FN	Unable to conduct analysis as none of the low-risk trials included denosumab													
BMD measured at LS	Unable to conduct analysis as none of the low-risk trials included denosumab													
BMD measured at TH	Unable to conduct analysis as none of the low-risk trials included denosumab													
BMD measured at TRO	The trials included in the original analysis did not report denosumab data													
Mortality	Unable to conduct analysis as none of the low-risk trials included denosumab													
AEs	Unable to conduct analysis as none of the low-risk trials included denosumab													
Serious AEs	Unable to conduct analysis as none of the low-risk trials included denosumab													
Withdrawal due to AEs	Unable to conduct analysis as none of the low-risk trials included denosumab													
AEs upon denosumab discontinuation	Unable to conduct sensitivity analysis as included trial was single-arm													
Selective reporting														
Vertebral fractures	DEN	PLB	86	3,756	NA	0.36	0.07, 1.03	89.54	--	--	No	--	--	NA
	ZOL	PLB	6	89	NA	0.96	0.13, 3.51	44.03		--	No			
	NA	PLB	272	3,838	NA	--	--	16.43		NA	No			
Nonvertebral fractures	DEN	PLB	264	3,902	NA	0.83	0.40, 1.57	85.15	--	--	No	8.1	7.93	No
	NA	PLB	343	3,998	NA	--	--	48.74		NA	No			
	ZOL	PLB	12	89	NA	1.84	0.55, 4.60	16.10		--	No			
BMD measured at FN	Unable to conduct analysis as none of the low-risk trials included denosumab													
BMD measured at LS	Unable to conduct analysis as none of the low-risk trials included denosumab													

BMD measured at TH	ZOL	PLB	NA	54	4.09	NA	-1.37, 9.54	75.51	--	--	No	7.99	7.95	No
	DEN	PLB	NA	54	3.71	NA	-1.56, 8.94	68.64		--	No			
	NA	PLB	NA	118	--	NA	--	5.85		NA	No			
BMD measured at TRO	The trials included in the original analysis did not report denosumab data													
Mortality	DEN	PLB	70	3,886	NA	0.76	0.29, 1.65	85.31	--	--	No	7.88	7.73	No
	NA	PLB	102	3,968	NA	--	--	35.62		NA	No			
	ZOL	PLB	14	89	NA	0.97	0.42, 1.92	29.07		--	No			
AEs	DEN	PLB	3,652	3,940	NA	0.99	0.94, 1.04	69.07	0.0	0.0	No	10.16	10.04	No
	NA	PLB	3,744	4,022	NA	--	--	54.24		NA	No			
	ZOL	PLB	87	89	NA	1.02	0.95, 1.10	26.70		--	No			
Serious AEs	NA	PLB	1,031	4,022	NA	--	--	72.68	0.0	NA	No	9.78	10.06	No
	DEN	PLB	1,008	3,940	NA	1.03	0.87, 1.20	54.86		0.0	No			
	ZOL	PLB	60	89	NA	1.13	0.87, 1.46	22.47		--	No			
Withdrawal due to AEs [e]	DEN	PLB	93	3,902	NA	1.15	0.86, 1.54	NA	NA	--	No	NA	NA	NA
	NA	PLB	81	3,906	NA	--	--	--		NA	No			
AEs upon denosumab discontinuation	Unable to conduct analysis as there was only one study in this analysis.													
Missing outcome data														
Vertebral fractures	Unable to conduct analysis as none of the low-risk trials included denosumab													
Nonvertebral fractures	Unable to conduct analysis as none of the low-risk trials included denosumab													
BMD measured at FN	Unable to conduct analysis as none of the low-risk trials included denosumab													
BMD measured at LS	Unable to conduct analysis as none of the low-risk trials included denosumab													

BMD measured at TH	Unable to conduct analysis as none of the low-risk trials included denosumab
BMD measured at TRO	The trials included in the original analysis did not report denosumab data
Mortality	Unable to conduct analysis as none of the low-risk trials included denosumab
AEs	Unable to conduct analysis as none of the low-risk trials included directly or indirectly connected denosumab to placebo (referent comparator)
SAEs	Unable to conduct analysis as none of the low-risk trials included directly or indirectly connected denosumab to placebo (referent comparator)
Withdrawal due to AEs	Unable to conduct analysis as none of the low-risk trials included directly or indirectly connected denosumab to placebo (referent comparator)
AEs upon denosumab discontinuation	Unable to conduct analysis as there was only one study in this analysis

Abbreviations:
AAIT: adjuvant aromatase therapy; **AE**: adverse events; **ALN**: alendronate; **BAZ**: bazedoxifene; **BMD**: bone mineral density; **CrI**: credible interval; **DEN**: denosumab; **DIC**: deviance information criterion; **FN**: femoral neck; **HAT**: hormone ablation therapy; **IBN**: ibandronate; **LS**: lumbar spine; **MD**: mean difference; **NA**: not applicable; **PLB**: placebo; **RCT**: randomised controlled trial; **RIS**: risedronate; **RLX**: raloxifene; **RR**: risk ratio; **SAE**: serious adverse events; **SUCRA**: surface under the cumulative ranking curve; **TH**: total hip; **TRO**: trochanter; **ZOL**: zoledronate; **--**: not generated.
Notes:
Credible interval: An interval within which RR or MD values will fall with a specific probability. A credible interval can be interpreted as a confidence interval.[5]
Surface under the cumulative ranking curve (SUCRA): Probability that a specific treatment is among the most effective options (i.e. "best") in the network. A SUCRA value of 100% suggests that the treatment is the most effective treatment included in the network; a value of 0% suggests that the included treatment is the least effective treatment in the network.[4]
[a] Comparison-specific heterogeneity could not be calculated (generated) if only one RCT provided data for the comparison.
[b] The absence of a correlation between the posterior mean differences of each of the data point produced by the consistency and inconsistency models.[6]
[c] DIC scores can only be calculated (generated) if the relevant network has a 'closed-loop'.
[d] Importance of difference in DIC scores between models: 0 to 5 between models was considered minimal; 5 to 10 was substantial; difference greater than 10 is significant.[7]
[e] Pairwise meta-analysis that only included data from a single RCT.
** statistical significance
† Sensitivity analysis results differ significantly from those of the original analysis on postmenopausal women with osteoporosis.
‡ Sensitivity analysis results differ significantly from those of the original analysis on women with breast cancer receiving AAIT.
§ Sensitivity analysis results differ significantly from those of the original analysis on men with osteoporosis who have an increase fracture risk.
# Sensitivity analysis results differ significantly from those of the original analysis on men with prostate cancer on HAT.
The results presented in the table are the result of a network meta-analyses performed using a Bayesian inference.

5.2 Sensitivity analyses conducted using a Frequentist inference

Table 20 Results of sensitivity analyses conducted using a Frequentist inference

Outcome	Treatment	Comparator	Events	Sample size	Effect size		95% CI	P-score	Heterogeneity (I^2)		Inconsistency	
					MD	RR			Total	Comparison-specific [a]	Local [b] (present)	Global [c, d] (present)
Women with breast cancer receiving AAIT												
Randomisation												
Vertebral fractures	No difference from the analysis reported in ***Section 7.4.5.5***											
Nonvertebral fractures	No difference from the analysis reported in ***Section 7.4.5.5***											
BMD measured at FN	No difference from the analysis reported in ***Section 7.4.5.5***											
BMD measured at LS	No difference from the analysis reported in ***Section 7.4.5.5***											
BMD measured at TH	No difference from the analysis reported in ***Section 7.4.5.5***											
BMD measured at TRO	No difference from the analysis reported in ***Section 7.4.5.5***											
Mortality	No difference from the analysis reported in ***Section 7.4.5.5***											
AEs	No difference from the analysis reported in ***Section 7.4.5.5***											
SAEs	No difference from the analysis reported in ***Section 7.4.5.5***											
Withdrawal due to AEs	No difference from the analysis reported in ***Section 7.4.5.5***											
AEs upon denosumab discontinuation	Unable to conduct analysis as there was only one, single-arm study in this analysis											
Selective reporting												
Vertebral fractures [e]	**DEN	PLB	27	835	NA	0.53	0.34, 0.85	NA	NA	NA	NA	NA
	NA	PLB	49	809	NA	--	--	NA		NA		
Nonvertebral fractures [e]	***DEN** [‡]	***PLB***	***65***	***835***	***NA***	***0.49***	***0.37, 0.65***	***NA***	NA	NA	NA	NA
	NA	PLB	129	809	NA	--	--	NA		NA		

Outcome	Treatment	Comparator	Events	Sample size	Effect size		95% CI	P-score	Heterogeneity (I^2)		Inconsistency	
					MD	RR			Total	Comparison-specific [a]	Local [b] (present)	Global [c, d] (present)
BMD measured at FN [e]	**DEN	PLB	NA	490	3.30	NA	2.76, 3.84	NA	NA	NA	NA	NA
	NA	PLB	NA	505	--	NA	--	NA		NA		
BMD measured at LS [e]	**DEN	PLB	NA	480	5.75	NA	5.24, 6.26	NA	NA	NA	NA	NA
	NA	PLB	NA	506	--	NA	--	NA		NA		
BMD measured at TH [e]	**DEN	PLB	NA	488	3.87	NA	3.36, 4.38	NA	NA	NA	NA	NA
	NA	PLB	NA	504	--	NA	--	NA		NA		
BMD measured at TRO	Unable to conduct analysis as none of the low-risk trials included denosumab											
Mortality [e]	DEN	PLB	98	1,711	NA	0.90	0.69, 1.17	NA	NA	NA	NA	NA
	NA	PLB	109	1,709	--	NA	--	NA		NA		
AEs [e]	DEN	PLB	1,367	1,636	NA	1.03	1.00,1.06	NA	NA	NA	NA	NA
	NA	PLB	1,339	1,646	--	NA	--	NA		NA		
SAEs [e]	DEN	PLB	521	1,636	NA	1.02	0.92, 1.13	NA	NA	NA	NA	NA
	NA	PLB	515	1,646	--	NA	--	NA		NA		
Withdrawal due to AEs	No difference from the analysis reported in ***Section 7.4.5.5***											
AEs upon denosumab discontinuation	Unable to conduct analysis as there was only one, single-arm study in this analysis											
Missing outcome data												
Vertebral fractures [e]	***DEN*** [‡]	***PLB***	***0***	***106***	***NA***	***Not estimable***	***Not estimable***	***NA***	NA	NA	NA	NA
	NA	PLB	0	99	NA	--	--	NA		NA		
Nonvertebral fractures [e]	DEN	PLB	8	106	NA	0.93	0.36, 2.39	NA	NA	NA	NA	NA
	NA	PLB	8	99	NA	--	--	NA		NA		
BMD measured at FN [e]	**DEN	PLB	NA	123	2.49	NA	1.41, 3.57	NA	NA	NA	NA	NA
	NA	PLB	NA	122	--	NA	--	NA		NA		
	**DEN	PLB	NA	123	5.50	NA	4.75, 6.25	1.00	--	--	No	NA

Outcome	Treatment	Comparator	Events	Sample size	Effect size		95% CI	P-score	Heterogeneity (I^2)		Inconsistency	
					MD	RR			Total	Comparison-specific [a]	Local [b] (present)	Global [c, d] (present)
BMD measured at LS	**RIS	PLB	NA	166	2.10	NA	0.71, 3.49	0.49		--		
	NA	PLB	NA	43	--	NA	--	0.00		--		
BMD measured at TH	**DEN	PLB	NA	123	3.75	NA	3.13, 4.37	1.00	--	--	No	NA
	**RIS	PLB	NA	43	2.10	NA	1.67, 2.53	0.50		--		
	NA	PLB	NA	166	--	NA	--	0		--		
BMD measured at TRO	No difference from the analysis reported in ***Section 7.4.5.5***											
Mortality [e]	DEN	PLB	1	129	NA	0.93	0.06, 14.71	NA	NA	NA	NA	NA
	NA	PLB	1	120	--	NA	--	NA		NA		
AEs	DEN	PLB	117	129	NA	1.01	0.93, 1.09	NA	NA	NA	NA	NA
	NA	PLB	108	120	--	NA	--	NA		NA		
SAEs	DEN	PLB	19	129	NA	1.61	0.80, 3.23	NA	NA	NA	NA	NA
	NA	PLB	11	120	NA	NA	NA	NA		NA		
Withdrawal due to AEs	No difference from the analysis reported in ***Section 7.4.5.5***											
AEs upon denosumab discontinuation	Unable to conduct analysis as there was only one study in this analysis											
Men with an increase fracture risk												
Randomisation												
Vertebral fractures [e]	DEN	PLB	0	120	NA	0.33	0.01, 8.10	NA	NA	NA	NA	NA
	NA	PLB	1	120	NA	--	--	NA		NA		
Nonvertebral fractures [e]	DEN	PLB	1	120	NA	0.50	0.05. 5.44	NA	NA	NA	NA	NA
	NA	PLB	2	120	NA	--	--	NA		NA		
BMD measured at FN [e]	**DEN	PLB	NA	111	NA	2.30	1.40, 3.20	NA	NA	NA	NA	NA
	NA	PLB	NA	117	NA	--	--	NA		NA		
BMD measured at LS [e]	**DEN	PLB	NA	111	NA	5.00	4.20, 5.80	NA	NA	NA	NA	NA
	NA	PLB	NA	117	NA	--	--	NA		NA		

Outcome	Treatment	Comparator	Events	Sample size	Effect size		95% CI	P-score	Heterogeneity (I^2)		Inconsistency	
					MD	RR			Total	Comparison-specific [a]	Local [b] (present)	Global [c, d] (present)
BMD measured at TH [e]	**DEN	PLB	NA	111	NA	2.00	1.43, 2.57	NA	NA	NA	NA	NA
	NA	PLB	NA	117	NA	--	--	NA		NA		
BMD measured at TRO [e]	**DEN	PLB	NA	111	NA	2.40	1.47, 3.33	NA	NA	NA	NA	NA
	NA	PLB	NA	117	NA	--	--	NA		NA		
Mortality [e]	DEN	PLB	1	120	NA	1.00	0.06, 15.80	NA	NA	NA	NA	NA
	NA	PLB	1	120	NA	--	--	NA		NA		
AEs [e]	DEN	PLB	87	120	NA	1.00	0.86, 1.17	NA	NA	NA	NA	NA
	NA	PLB	87	120	NA	--	--	NA		NA		
SAEs [e]	DEN	PLB	13	120	NA	1.18	0.55, 2.53	NA	NA	NA	NA	NA
	NA	PLB	11	120	NA	--	--	NA		NA		
Withdrawal due to AEs [e]	DEN	PLB	4	120	NA	9.00	0.49, 165.35	NA	NA	NA	NA	NA
	NA	PLB	0	120	NA	--	--	NA		NA		
AEs upon denosumab discontinuation	Unable to conduct sensitivity analysis as no trials (RCT or single-arm) were included in the original analysis											
Selective reporting												
Vertebral fractures	Unable to conduct analysis as none of the low-risk trials included denosumab											
Nonvertebral fractures	Unable to conduct analysis as none of the low-risk trials included denosumab											
BMD measured at FN	Unable to conduct analysis as none of the low-risk trials included denosumab											
BMD measured at LS	Unable to conduct analysis as none of the low-risk trials included denosumab											
BMD measured at TH	Unable to conduct analysis as none of the low-risk trials included denosumab											
BMD measured at TRO	Unable to conduct analysis as none of the low-risk trials included denosumab											
Mortality	Unable to conduct analysis as none of the low-risk trials included denosumab											
AEs	Unable to conduct analysis as none of the low-risk trials included denosumab											

Outcome	Treatment	Comparator	Events	Sample size	Effect size		95% CI	P-score	Heterogeneity (I^2)		Inconsistency	
					MD	RR			Total	Comparison-specific [a]	Local [b] (present)	Global [c, d] (present)
SAEs	Unable to conduct analysis as none of the low-risk trials included denosumab											
Withdrawal due to AEs	Unable to conduct analysis as none of the low-risk trials included denosumab											
AEs upon denosumab discontinuation	Unable to conduct sensitivity analysis as no trials (RCT or single-arm) were included in the original analysis											
Missing outcome data												
Vertebral fractures	ZOL	PLB	1	588	NA	0.35	0.04, 3.32	0.66	--	--	No	NA
	DEN	PLB	0	120	NA	0.33	0.01, 8.10	0.63	--	--		
	NA	PLB	4	731	NA	--	--	0.21		--		
Nonvertebral fractures	No difference from the analysis reported in ***Section 7.4.5.5***											
BMD measured at FN	Unable to conduct analysis as none of the low-risk trials included denosumab											
BMD measured at LS	Unable to conduct analysis as none of the low-risk trials included denosumab											
BMD measured at TH	Unable to conduct analysis as none of the low-risk trials included denosumab											
BMD measured at TRO	Unable to conduct analysis as none of the low-risk trials included denosumab											
Mortality	RIS	PLB	2	191	NA	0.32	0.06, 1.91	0.83	--	--	No	No
	ZOL	PLB	15	588	NA	0.87	0.44, 1.70	0.45		--		
	DEN	PLB	1	120	NA	1.00	0.06, 15.80	0.40		--		
	NA	PLB	22	824	NA	--	--	0.31		--		
AEs	RIS	PLB	134	191	NA	0.96	0.82, 1.12	0.78	--	--	No	NA
	DEN	PLB	87	120	NA	1.00	0.86, 1.17	0.61		--		
	NA	PLB	621	824	NA	--	--	0.60		--		
	**ZOL	PLB	534	588	NA	1.19	1.13, 1.25	0.01		--		
SAEs	RIS	PLB	29	191	NA	0.94	0.53, 1.67	0.62	--	--	No	NA
	NA	PLB	180	824	NA	--	--	0.54		--		

Outcome	Treatment	Comparator	Events	Sample size	Effect size		95% CI	P-score	Heterogeneity (I^2)		Inconsistency	
					MD	RR			Total	Comparison-specific [a]	Local [b] (present)	Global [c, d] (present)
	ZOL	PLB	149	588	NA	1.01	0.83, 1.22	0.52		--		
	DEN	PLB	13	120	NA	1.18	0.55, 2.53	0.33		--		
Withdrawal due to AEs	NA	PLB	11	731	NA	--	--	0.73	--	--	No	NA
	ZOL	PLB	11	588	NA	1.04	0.45, 2.38	0.69		--		
	DEN	PLB	4	120	NA	9.00	0.49, 165.35	0.08		--		
AEs upon denosumab discontinuation	Unable to conduct sensitivity analysis as no trials (RCT or single-arm) were included in the original analysis											
Men with prostate cancer on HAT												
Randomisation												
Vertebral fractures	Unable to conduct analysis as none of the low-risk trials included denosumab											
Nonvertebral fractures	Unable to conduct analysis as none of the low-risk trials included denosumab											
BMD measured at FN	Unable to conduct analysis as none of the low-risk trials included denosumab											
BMD measured at LS	Unable to conduct analysis as none of the low-risk trials included denosumab											
BMD measured at TH	Unable to conduct analysis as none of the low-risk trials included denosumab											
BMD measured at TRO	The trials included in the original analysis did not report denosumab data											
Mortality	Unable to conduct analysis as none of the low-risk trials included denosumab											
AEs	Unable to conduct analysis as none of the low-risk trials included denosumab											
SAEs	Unable to conduct analysis as none of the low-risk trials included denosumab											
Withdrawal due to AEs	Unable to conduct analysis as none of the low-risk trials included denosumab											
AEs upon denosumab discontinuation	Unable to conduct sensitivity analysis as no trials (RCT or single-arm) were included in the original analysis											
Selective reporting												

Outcome	Treatment	Comparator	Events	Sample size	Effect size		95% CI	P-score	Heterogeneity (I^2)		Inconsistency	
					MD	RR			Total	Comparison-specific [a]	Local [b] (present)	Global [c, d] (present)
Vertebral fractures	Unable to conduct analysis as none of the low-risk trials included denosumab											
Nonvertebral fractures	Unable to conduct analysis as none of the low-risk trials included denosumab											
BMD measured at FN	Unable to conduct analysis as none of the low-risk trials included denosumab											
BMD measured at LS	Unable to conduct analysis as none of the low-risk trials included denosumab											
BMD measured at TH	Unable to conduct analysis as none of the low-risk trials included denosumab											
BMD measured at TRO	The trials included in the original analysis did not report denosumab data											
Mortality	Unable to conduct analysis as none of the low-risk trials included denosumab											
AEs	Unable to conduct analysis as none of the low-risk trials included denosumab											
SAEs	Unable to conduct analysis as none of the low-risk trials included denosumab											
Withdrawal due to AEs	Unable to conduct analysis as none of the low-risk trials included denosumab											
AEs upon denosumab discontinuation	Unable to conduct sensitivity analysis as no trials (RCT or single-arm) were included in the original analysis											
Missing outcome data												
Vertebral fractures	Unable to conduct analysis as none of the included RCTs presented a low-risk of reporting bias											
Nonvertebral fractures	Unable to conduct analysis as none of the low-risk trials included denosumab											
BMD measured at FN	Unable to conduct analysis as none of the low-risk trials included denosumab											
BMD measured at LS	Unable to conduct analysis as none of the low-risk trials included denosumab											
BMD measured at TH	Unable to conduct analysis as none of the low-risk trials included denosumab											
BMD measured at TRO	The trials included in the original analysis did not report denosumab data											

Outcome	Treatment	Comparator	Events	Sample size	Effect size		95% CI	P-score	Heterogeneity (I^2)		Inconsistency	
					MD	RR			Total	Comparison-specific [a]	Local [b] (present)	Global [c, d] (present)
Mortality	Unable to conduct analysis as none of the low-risk trials included denosumab											
AEs	Unable to conduct analysis as none of the low-risk trials included denosumab											
SAEs	Unable to conduct analysis as none of the low-risk trials included denosumab											
Withdrawal due to AEs	Unable to conduct analysis as none of the low-risk trials included denosumab											
AEs upon denosumab discontinuation	Unable to conduct sensitivity analysis as no trials (RCT or single-arm) were included in the original analysis											

Abbreviations:
AAIT: adjuvant aromatase inhibitors therapy; **AE**: adverse events; **BMD**: bone mineral density; **CI**: confidence interval; **DEN**: denosumab; **FN**: femoral neck; **HAT**: hormone ablation therapy; **IBN**: ibandronate; **LS**: lumbar spine; **MD**: mean difference; **NA**: not applicable; **PLB**: placebo; **RCT**: randomised controlled trial; **RIS**: risedronate; **RLX**: raloxifene; **RR**: risk ratio; **SAE**: serious adverse events; **TH**: total hip; **TRO**: trochanter; **ZOL**: zoledronate; **--**: not generated.
Notes:
P-score: Extent of certainty that a treatment is superior to its comparators (closest score to 1 being the "best").[8]
[a] Comparison-specific heterogeneity could not be calculated (generated) if only one RCT provided data for the comparison.
[b] The presence of inconsistency at the local level was assessed by node-splitting.[9 10]
[c] The presence of inconsistency global level was evaluated using the Cochrane's Q-statistic for inconsistency (Q^{inc}).[9-11]
[d] Cochrane's Q^{inc} statistic could not be calculated as none of the networks had closed loops.[9]
[e] Pairwise meta-analysis that only included data from a single RCT.
** statistical significance
† Sensitivity analysis results differ significantly from those of the original analysis on postmenopausal women with osteoporosis.
‡ Sensitivity analysis results differ significantly from those of the original analysis on women with breast cancer receiving AAIT.
§ Sensitivity analysis results differ significantly from those of the original analysis on men with osteoporosis who have an increase fracture risk.
# Sensitivity analysis results differ significantly from those of the original analysis on men with prostate cancer on HAT.
The results presented in the table are the result of a network meta-analyses performed using a Frequentist inference.

6 Data extraction table for included health economic studies

This Supplement presents the data extracted from the included health economic studies.

Table 21 Evidence table for the included health economic evaluation studies

Study	Country	Patient population	Intervention	Comparator(s)	Perspective	Results (Primary analysis)	Funding source
Chau, 2012[12]	Canada	Postmenopausal women <u>*Base case:*</u> Population characteristics as per the FREEDOM trial	Denosumab (Prolia®)	- Alendronate - Risedronate - Raloxifene - No treatment	Government payer	ICER for denosumab vs. next least costly alternative (alendronate) of CAN$60,266 per QALY. ICER alendronate vs. next least costly alternate (no treatment) of CAN$14,708 per QALY. Risedronate dominated by alendronate.	Amgen Inc.
Coyle, 2019[13]	Canada	Postmenopausal women <u>*Base case:*</u> - 70 to 74 years of age - No previous fracture - Able to tolerate bisphosphonates	Denosumab (Prolia®)	- Alendronate - Etidronate - Risedronate - Zoledronate - No treatment	Government payer	ICER for denosumab vs. next least costly, undominated alternative (zoledronate) of CAN$13.0 million. ICER zoledronate vs. next least costly alternative (alendronate) of CAN$666,285 ICER alendronate vs. next least costly alternative (no therapy) of CAN$3,751. Etidronate & risedronate were dominated.	None

Study	Country	Patient population	Intervention	Comparator(s)	Perspective	Results (Primary analysis)	Funding source
Darbà, 2015[14]	Spain	Postmenopausal women *Base case:* - T-score ≤ –2.5 SD - Start age of 65 years - 28% prevalence osteoporotic fracture	Denosumab (Prolia®)	- Alendronate - Risedronate - Ibandronate - Strontium ranelate - No treatment	Government payer	ICER for denosumab vs. - No treatment: €6,823 - Alendronate: €16,294 - Risedronate: €4,895 - Ibandronate: €2,205 - Strontium ranelate: denosumab is dominant	Amgen SA Barcelona, Spain, and GSK.
de Waure, 2014[15]	Italy	Postmenopausal women *Base case:* - Start age of 65 years - T-score <–4 SD	Denosumab (Prolia®)	- Alendronate - Risedronate - Ibandronate - Strontium ranelate	Government payer	ICER for denosumab vs. - Risedronate: €10,302 - Generic alendronate: €18,047 - Branded alendronate: €17,133 - Ibandronate: €2,158 - Strontium ranelate: €69	Amgen Inc.
Hiligsmann & Reginster, 2010[16]	Belgium	Postmenopausal women *Base case:* Population characteristics as per the FREEDOM trial	Denosumab (Prolia®)	No treatment	Government payer	ICER for denosumab vs. no treatment: €28,441	Amgen Inc.

Study	Country	Patient population	Intervention	Comparator(s)	Perspective	Results (Primary analysis)	Funding source
Hiligsmann & Reginster, 2011[17]	Belgium	Postmenopausal women <u>*Base case:*</u> - Age of 70 years, and either: i. T-score of -2.5 or less, *or* ii. Prevalent vertebral fracture	Denosumab (Prolia®)	- Risedronate - Alendronate	Government payer	Women with BMD T-score of ≤ – 2.5 ICER for denosumab vs. - Branded alendronate: €14,120 - Generic alendronate: €22,220 - Risedronate: denosumab is dominant Women with prevalent vertebral fracture: ICER for denosumab vs. - Branded alendronate: €14,166 - Generic alendronate: €19,718 - Risedronate: €4,456	Amgen Inc.
Jönsson, 2011[18]	Sweden	Postmenopausal women <u>*Base case:*</u> - 71 years of age - T-score at femoral neck ≤ –2.5 SD - 34% prevalence morphometric vertebral fracture	Denosumab (Prolia®)	- Alendronate - Risedronate - Strontium ranelate - No treatment	Societal	ICER for denosumab vs, - No treatment: €14,458 - Generic alendronate: €27,090 - Risedronate: €11,545 - Strontium ranelate: €5,015	Amgen Inc.
Karnon, 2016[19]	Australia	Postmenopausal women <u>*Base case:*</u> Population characteristics as per the FREEDOM trial	Denosumab (Prolia®)	Alendronate	Government payer	ICER for denosumab vs. alendronate: AUD$246,749	None

Study	Country	Patient population	Intervention	Comparator(s)	Perspective	Results (Primary analysis)	Funding source
Le, 2019[20]	US	Postmenopausal women *Base case:* - 73.3 years of age - Average total hip T-score of –2.5	Denosumab (Prolia®)	- Alendronate - Risedronate - Zoledronic acid - Teriparatide - Abalopatride - No treatment	Third-party payer or potential inclusion of government payment	For a WTP threshold: - ≤USD $36,745 per QALY, alendronate was the most cost-effective option - USD $36,745 – $409,017, denosumab was the most cost-effective option - >USD $409,017, abaloparatide was the most cost-effective option	Funding through PhRMA Foundation Value Assessment Challenge Award.
Makras, 2015[21]	Greece	Men and women over 50 years of age *Base case:* NA	Treatment	No treatment	Third-party payer or potential inclusion of government payment	Osteoporosis treatment becomes cost-effective when absolute 10-year probabilities for hip fracture and MOF reach 2.5% and 10%, respectively, among both men & women under the age of 75 years. For older patients, the proposed intervention thresholds are raised to 10-year probabilities of 5% and 15%, respectively. A WTP threshold of €30,000 was used in these analyses.	NR
Marques, 2016[22]	Portugal	Men and women over 50 years of age with osteoporosis *Base case:* - 65 years of age - T-score of -–2.5 - Previous fracture	Denosumab (Prolia®)	- Alendronate - Zoledronic acid - Teriparatide - No treatment	Societal	ICER for denosumab vs. no treatment of €128,503 Note: All active interventions were compared with 'no treatment', therefore ICERs for denosumab versus other active drugs not reported.	Direção Geral da Saúde and Amgen.
Parthan, 2013[23]	US	Postmenopausal women *Base case:* Population characteristics as per the FREEDOM trial	Denosumab (Prolia®)	- Alendronate - Risedronate - Ibandronate	Third-party payer or potential inclusion of government payment	ICER for denosumab vs. generic alendronate was USD $85,060. Branded risedronate & branded ibandronate were both dominated by denosumab.	Amgen Inc.

Study	Country	Patient population	Intervention	Comparator(s)	Perspective	Results (Primary analysis)	Funding source
Parthan, 2014[24]	Sweden	Men aged over 75 years of age *Base case:* - Mean age of 78 years - Mean femoral neck T-score: –2.12 SD - 23% prevalence of vertebral fracture	Denosumab (Prolia®)	- Alendronate - Risedronate - Ibandronate - Zoledronate - Strontium ranelate - Teriparatide	Government payer	Denosumab had lower costs and higher QALYs than all other anti-osteoporotic drug alternatives, therefore was dominate over all other alternatives.	NR
Silverman, 2015[25]	US	Men aged over 75 years of age *Base case:* - Mean age of 78 years - Mean femoral neck T-score of –2.12 - 23% prevalence of vertebral fracture	Denosumab (Prolia®)	- Alendronate - Risedronate - Ibandronate - Teriparatide - Zoledronate	Third-party payer or potential inclusion of government payment	The ICER of denosumab versus generic alendronate was USD $16,888. Zoledronate, risedronate, ibandronate, and teriparatide were all dominated by denosumab.	Amgen Inc.
Ström, 2013[26]	UK	Postmenopausal women age ≥50 years *Base case:* 70-year-old women with a prior fragility fracture and unknown BMD	Denosumab (Prolia®)	- Alendronate - Risedronate - Strontium ranelate - No treatment	Government payer	The ICER, for denosumab vs. - No treatment: £25,376 - Generic alendronate: £46,915 - Risedronate: £23,609 - Strontium ranelate: £14,790	Amgen Inc.

Abbreviations
BMD: bone mineral density; **ICER**: incremental cost-effectiveness ratio; **MOF**: major osteoporotic fracture; **NR:** not reported; **QALY**: quality-adjusted life year; **UK**: United Kingdom; **US:** United States; **WTP**: willingness-to-pay
Notes:

The FREEDOM RCT recruited women with a mean age of 72 years (range 60–90 years), mean BMD T-score at the femoral neck of –2.15, and with 24% of women having experienced a previous fracture.

7 Additional methodological details on the economic evaluation

Section 7 is intended to supplement the economic evaluation methods and results sections of the health technology assessment (HTA).

Firstly, the role of probabilistic sensitivity analysis (PSA) is discussed, and methods and results from the descriptive analyses performed on the 200,000 patient-level cost and quality-adjusted life year (QALY) outputs are presented (***Section 7.1***).

Secondly, the methodology used to generate the time-to-fracture survival curves, including the choice of Weibull model and the examination of model fit, is discussed (***Section 7.2***).

Finally, issues arising from the translation of the clinical results to the economic model are discussed, and justifications for the choice of a discrete event simulation (DES) model are provided (***Section 7.3***).

7.1 The use of probabilistic sensitivity analyses to address uncertainties in the model

PSA was not a focus of the sensitivity analyses conducted for this HTA. It was considered that there might be limited value to the overall outcome, and that the uncertainties could be sufficiently addressed by deterministic sensitivity analyses (DSAs) and scenario analyses. While we acknowledge that PSA is preferred by the EUnetHTA Guideline, the adoption of this approach in addressing uncertainties remains a methodological choice. The DES model is a simulation by nature, and the uncertainties are innate to the probabilistic simulation process. Also, performing PSA on top of the simulation can be computationally expensive.

Besides limitations for running PSAs, we still explored the propagation of uncertainties via PSA. Two approaches have been undertaken:

1. Individual simulations were exported, where descriptive and comparative analyses were undertaken to evaluate the uncertainty propagations. Descriptive analyses against cost and QALY outcomes are presented here. In the HTA report, incremental cost-effect pairs for the denosumab versus intravenous (IV) ibandronate comparison were plotted on the cost-effectiveness (CE) plane. We focused on the denosumab versus IV ibandronate comparison because IV ibandronate was shown to be the most cost-effective treatment option at a hypothetical willingness-to-pay (WTP) threshold of Swiss Francs (CHF) 100,000 in the base case. Denosumab was the only treatment option that was not dominated by IV ibandronate.

2. PSA was undertaken under the base-case model, only against costs and utility multipliers. The analysis against these variables is computationally feasible. The output of the PSA has been used to produce a cost-effectiveness acceptability (CEAC) curve and interpreted to guide the decision making. Methods and results for this PSA are discussed in the HTA report.

The detailed supplementary analyses for the descriptive analyses against cost and QALY outcomes are presented below:

7.1.1 Analysis of the simulation output from the base case DES model

The individual Monte Carlo patient-level simulations have been obtained from TreeAge output for the DES model base-case result. Across all treatment options, 200,000 iterations were simulated, and it added up to be 2.4 million data points (200,000 individuals × 7 drugs × 2 quantities of interests (cost and QALY) = 2,400,000). Costs and QALY outcomes were analysed separately to investigate differences across the seven treatment options. All the data are plotted using boxplots for visualisations. Due to the extreme right-skewed distribution (see below), non-parametric analysis of variance (ANOVA) has been used. Kruskal-Wallis rank-sum tests were conducted accompanied by pairwise Wilcoxon rank-sum test to run the post-hoc comparison for treatment of each pair.

Cost results from different treatment options

The cost of different treatment options was extremely volatile due to the high costs of fracture events. A significant proportion of the data is considered to be outliers, and those extreme values produced significantly skewed distribution which interfered with how the plot could be generated. All outliers have been removed from the boxplot for graphical clarity. The mean costs for each treatment option have also been added to the plot as reference points. The box plots against each treatment option have been provided in ***Figure 19***.

It appears the cost of no treatment option was much more significantly greater than others. This may be explained by the high medical costs involved due to fracture onset.

The non-parametric comparison using the Kruskal-Wallis rank-sum test returned highly significant p values ($p < 0.001$). Post-hoc pairwise comparisons using the Wilcoxon rank-sum test also confirmed that all treatment options are also significantly different from each other. These differences were not apparent from the boxplot as the y-axis has been distorted due to the outliers. The R codes and outputs can be found in ***Exhibit 1***, where significant p values were highlighted in grey.

Figure 19 Boxplots for simulation results on costs for the seven therapies

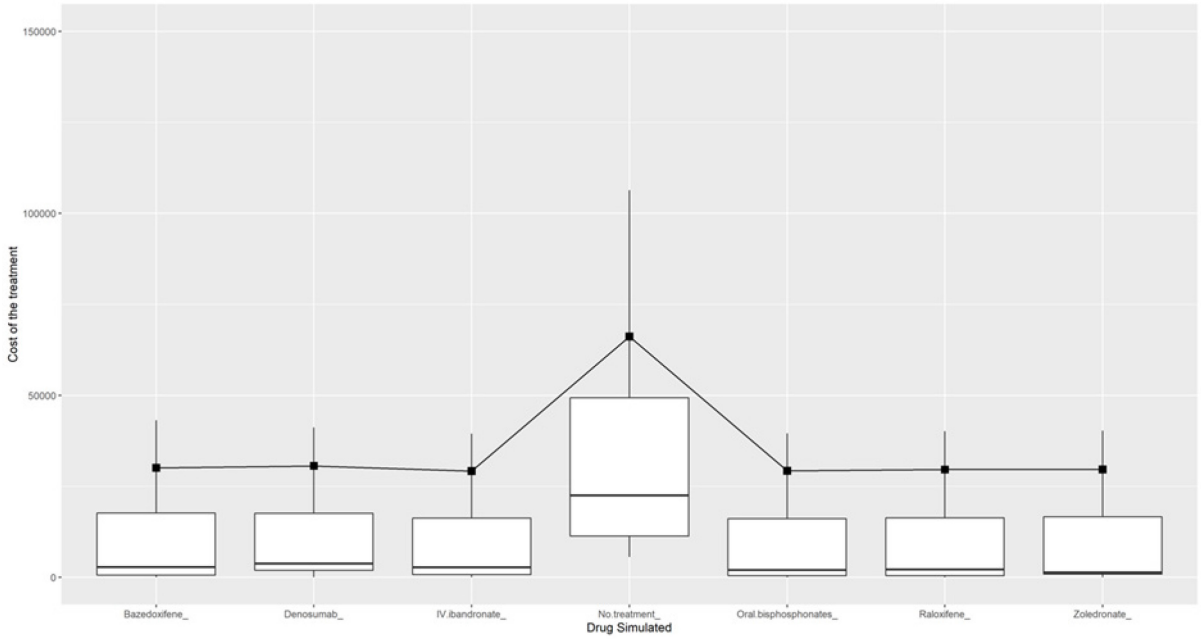


Exhibit 1 Test outputs for the cost comparison between treatment options

```
> kruskal.test(data = all.long, effectiveness~Drugs)

        Kruskal-Wallis rank sum test

data:  effectiveness by Drugs
Kruskal-Wallis chi-squared = 29.388, df = 6, p-value = 5.137e-05


> pairwise.wilcox.test(all.long$cost, all.long$Drugs,p.adjust.method = "BH")

        Pairwise comparisons using Wilcoxon rank sum test with continuity correction

data:  all.long$cost and all.long$Drugs

                     Bazedoxifene_ Denosumab_ IV.ibandronate_ No.treatment_ Oral.bisphosphonates_ Raloxifene_
Denosumab_           < 2e-16       -          -               -             -                     -
IV.ibandronate_      8.5e-15       < 2e-16    -               -             -                     -
No.treatment_        < 2e-16       < 2e-16    < 2e-16         -             -                     -
Oral.bisphosphonates_ < 2e-16      < 2e-16    < 2e-16         < 2e-16       -                     -
Raloxifene_          < 2e-16       < 2e-16    < 2e-16         < 2e-16       < 2e-16               -
Zoledronate_         < 2e-16       < 2e-16    < 2e-16         < 2e-16       < 2e-16               < 2e-16

P value adjustment method: BH
```

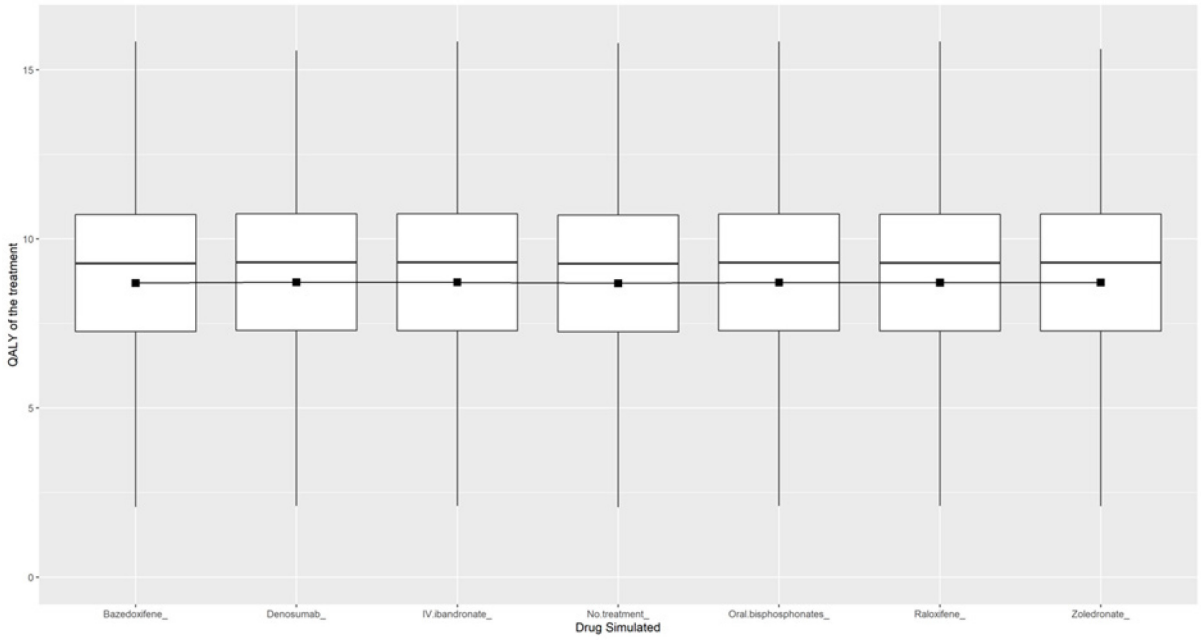
Abbreviations:
IV: intravenous

QALY results from different treatment options

The simulated QALY results are much more homogeneous, and this is largely in line with the clinical findings. There are still outliers also. However, the outliers are less influential to the boxplot without impacting the scale of the y-axis. For consistency, outliers are omitted from the plot for better presentation. The mean QALY values are also presented alongside the boxplot for references. See ***Figure 20*** for more detail.

Non-parametric comparisons were undertaken to investigate the differences of QALY against each treatment option. The test results were still significant ($p < 0.001$). However, post-hoc tests showed that the results were only driven by one or two treatment options. It appears that no treatment option had the most significant p values across the board. This is explainable, as patients would suffer from fractures most severely when treatment was not applied. Also, it appears bazedoxifene also showed some inferior outcomes, particularly compared to denosumab and IV ibandronate, although it was not as inferior as no treatment option. The outputs can be found in ***Exhibit 2***, where significant p values were highlighted in grey.

Figure 20 Boxplots for simulation results on QALY for the seven therapies



Abbreviations:
QALY: quality-adjusted life year

Exhibit 2 Test outputs for the QALY comparison between treatment options

```
> kruskal.test(data = all.long, cost~Drugs)

        Kruskal-Wallis rank sum test

data:  cost by Drugs
Kruskal-Wallis chi-squared = 93028, df = 6, p-value < 2.2e-16


> pairwise.wilcox.test(all.long$effectiveness, all.long$Drugs,p.adjust.method = "BH")

        Pairwise comparisons using Wilcoxon rank sum test with continuity correction

data:  all.long$effectiveness and all.long$Drugs

                     Bazedoxifene_ Denosumab_ IV.ibandronate_ No.treatment_ Oral.bisphosphonates_ Raloxifene_
Denosumab_           0.00678       -          -               -             -                     -
IV.ibandronate_      0.01041       0.78371    -               -             -                     -
No.treatment_        0.44555       0.00037    0.00076         -             -                     -
Oral.bisphosphonates_ 0.07285      0.38557    0.51631         0.00678       -                     -
Raloxifene_          0.19881       0.19887    0.33839         0.02271       0.69517               -
Zoledronate_         0.07285       0.38557    0.51631         0.00678       0.99419               0.69517

P value adjustment method: BH
```

Abbreviations:
IV: intravenous; **QALY**: quality-adjusted life year

7.2 Methodologies related to the survival analysis

The survival analysis in the HTA was pragmatically conducted to provide time-to-event parameters for the DES model on fracture events.

7.2.1 The choice of using the Weibull model over others

The survival models did not consider other curves except Weibull. There are three reasons.

a) The implementation of different survival curves could be highly complex to be implemented using TreeAge. Some weights or probabilities would have to be assigned to different choices of parametric survival curves, and an additional process would have to be designed for the DES model to sample the survival time from different curves. A separate set of algorithms would be required to cater for such needs, and such complexity may convey very little benefits.
b) Further, we consider that the stochastic uncertainties from the simulation (i.e. the first-order uncertainty) may be more influential and relevant to the model outcome than the choice of survival curves and precisions around parameter estimates (i.e. second-order uncertainties, reflected by both survival models and its standard errors of point estimates). Therefore, it was considered sufficient to only use the simulation to represent patients' random time-to-fracture events. Despite the sole use of Weibull distribution, a range of different modelling parameters was still incorporated in the survival models. A total of 918 sets of parameters were derived to allow the DES model to take up relevant parameter inputs given patients' individual circumstances (see the Excel file – available upon request – for more detail).

c) Lastly, the Weibull models appeared to be a good choice given their relatively good fit. Among the 18 models, the fitting outcome were all over 95% (R^2 values from the regression outputs) at the baseline level. There were no strong motivations at that time to seek alternative survival models to fit the data. More discussion is provided below surrounding the examination of the model fitting.

It should be particularly noted that the parametric survival models in this HTA independently regressed the survival probabilities against the (log-transformed) time for individual fracture sites and treatment options. The estimates of regression coefficients did not require any consideration to choose either proportional hazards (PH) or accelerated failure time (AFT) model parameterisation. The treatment effect (as in relative risks) was directly applied to the simulation cohort rather than estimated via regression techniques. The use of the Weibull model reconciled the two approaches and alleviated the need to weigh up the benefits of PH and AFT.

7.2.2 Model fit examinations (residuals and prediction accuracy)

Using relative risks produced from the Bayesian network meta-analyses (BNMA), fracture rates at different sites were calculated from the baseline then converted to annual fracture probabilities. The detailed calculation procedures are available from the Excel model (available upon request). Then a cohort of 1,000 patients were simulated to experience fracture events. Hazards were then derived, and then the annual survival probabilities were calculated. The complementary log-log (c-log-log) transformation was undertaken for the survival probabilities. The time was also log-transformed. This allowed a simple linear regression to be conducted over the data under the Weibull assumption. The model fitting was examined by the linear model diagnostic statistics, including F-statistic, R^2 and coefficient significance. The fitting was also inspected by the observed versus fitted plots. Advanced diagnostics such as leverages, Cook's distance, and other information criteria were not performed due to project time constraints.

All the models returned with relatively high levels of fitting, evident from the significant coefficients and R^2 values. There appeared to be no evidence of violations of any regression assumptions either. Therefore, the use of more advanced diagnostics was not motivated at the time. While we acknowledge that the modelling diagnostics might not be comprehensive from an academic point of view, the use of more advanced diagnostics would not yield the best alternatives either. For example, it would not be reasonable to remove leverage points given the data was simulated using a consistent algorithm rather than collected from observations.

7.2.3 Issues around the starting age

The model starting age was a point of interest during the modelling. When patients grow older, they are more likely to experience fracture events in general. Therefore, the time-to-fracture parameters would need to reflect the change and allow the DES model to implement it accordingly. More specifically, the DES model did allow the fracture to happen multiple times (via resampling of the survival distributions). When patients experience more than one fracture event, subsequent events (its time-to-fracture parameters) would need to be parameterised at the appropriate age at the time. Therefore, a family of Weibull models was generated at individual ages. They were incorporated into the TreeAge as a table to allow the DES model to take up appropriate inputs for resampling.

It needs to be acknowledged that the model fitting for older ages was not as good as for younger patients. This was most likely due to the smaller number of data points available for the regression (50 data points to 100 years when a patient starts at age 50 compared to 20 data points when starting from the age 80). The mechanics around repeated fractures for the DES model were considered essential. However, the number of fractures patients experienced in the simulation was relatively small. Therefore, the model fitting issue may not be substantial enough to have an impact on the veracity of the DES model.

7.2.4 Issues around censoring

The survival analyses were performed on a simulated cohort rather than observed from experiments or trials. Therefore, information censoring was not relevant.

7.3 The choice of using the DES model over conventional state-transition models

The choice of DES model was based the merit of using such modelling approach, the relative PICO criteria in this HTA, and the data analysis from the clinical section.

7.3.1 Translational issues from clinical findings to the parameterisation of the DES model

In the clinical section, the relative fracture risks were estimated using Bayesian network meta-analyses (BNMA). The BNMA approach allows the relative risk and its credible intervals to be generated directly instead of producing relative risk point estimates and associated 95% confidence intervals. In other words, the relative risks from the BNMA were the “true value”, and the associated credible intervals were not their precision measures but their dispersion in distributional forms (normally distributed). In this situation, it removes the need to reflect “parameter uncertainties” of those relative risks in the

survival modelling and the subsequent DES model. The survival and the DES model could directly rely on the estimates produced from the BNMA and investigate the impact of stochastic uncertainties. This is the greatest advantage of using BNMA over frequentists approaches.

Secondly, stochastic uncertainties are considered more relevant and important. Simulations carried out by the DES model had enabled stochastic uncertainties to be fully captured via individual patient-level simulations. Credible limits of the BNMA-estimated relative risks could be used to produce another two sets of survival analysis parameters and feed them into the TreeAge model. However, this would result in a multiplicity in its propagation, which would cause a significant overestimation of the uncertainty.

We would argue that the use of BNMA had avoided the need to consider parameter uncertainties for the survival and the DES model. This was an advantage to mitigate translational issues from clinical findings to the health economic evaluations. Nevertheless, DSAs and different scenarios were still conducted to test the clinical findings.

7.3.2 The advantage of DES over conventional state-transition models

The choice using the DES model in this HTA over conventional Markov cohort models under either expected cohort or microsimulation scenarios was driven by several reasons.

Firstly, the flexibility in time management allowed fracture events to occur at any time of the disease course. This avoided the use of specific and short cycle length and associated transition probabilities under the conventional Markov model scenarios.

Secondly, the use of the DES model can incorporate complex patient characteristics conveniently. Patients in this HTA appeared to be highly heterogeneous, and fracture risks could be associated with a range of clinical factors. To use the Markov model to handle these complex situations would result in highly complex model setups, strong structural assumptions and significantly many input parameters, which may or may not be available from clinical investigations. Therefore, the DES model was considered a more straightforward choice for this HTA. The use of DES model was considered and implemented while the clinical data analysis was still being worked on. In the absence the concrete results from the clinical section, the DES model appeared to be the best option at the time given the complexities expected from the literature and data extraction.

Lastly, the outputs from the BNMA could be directly taken up by the DES model to address stochastic uncertainties via individual simulations. This is not possible via expected cohort Markov models and is likely to be highly convoluted via microsimulations. Uncertainties from conventional meta-analyses via

frequentists approaches (addressed by point estimates and associated confident intervals) carry intrinsic limitations (i.e. second-order uncertainties on model inputs) to inform economic evaluations. Consequently, those intrinsic limitations created a gap in how clinical findings are translated to economic model inputs. Consequently, these limitations ought to be reflected in the economic modelling processes by investigating parameter uncertainties. Under such scenarios, stochastic uncertainties are often underplayed. We consider patients' individual variabilities in how they respond to different treatment options are more relevant to decision-making. The BNMA offered the opportunity to close such a gap and to address stochastic uncertainties more adequately. Therefore, the DES model was chosen as the approach for this HTA.

8 Reference list

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