Comparative effectiveness of neutralizing monoclonal antibodies in high risk COVID-19 patients: a Bayesian network-meta-analyses.

Supplementary Material: full details of NMA methodology, code, extracted data, results, and sensitivity analysis.

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1 Methods

1.1 Overview

Where feasible, formal evidence synthesis in the form of network meta-analysis (NMA) will be carried out. All outcomes extracted as part of the rapid review will be synthesised where possible.

1.2 Identification of Evidence Networks

Since the included studies are expected to report different outcomes, separate outcome-specific evidence networks will be constructed. Studies enrolling outpatients infected with or exposed to Covid-19 will be considered, while studies enrolling patients already hospitalised as a result of Covid-19 will not be included for the following reasons:

- Patient characteristics are likely to differ considerably, thus there is a high risk of effect modification if trials involving hospitalised patients are synthesised with those enrolling only outpatients
- The timing of the interventions relative to symptom onset is likely to differ considerably (hospitalised patients will receive treatment much later on average)

Different doses of the same mAB therapy will be treated as a single intervention in the base case. This decision was made in advance due to the expectation that the number of included studies would be small, and that certain event types (e.g. deaths, ICU admissions) were expected to be rare. This approach increases statistical power at the potential cost of additional heterogeneity (the latter will be accounted for via the use of random-effects models where possible).

Subgroup analysis may be carried out for the following groups if data is available:

- Immunocompromised patients
- Seronegative patients

The feasibility of including each study in the relevant evidence network will be then be assessed according to the following criteria:
• Comparability of baseline patient characteristics and inclusion criteria across trials in the network
• Consistency in the definitions and reporting of outcomes
• For dichotomous outcomes: at least one event reported across treatment arms

1.3 Extraction of outcome data

All available outcome data for studies meeting the PICO criteria will be extracted (including subgroup data). Separate outcome data for each treatment arm will be extracted where available, which is expected to consist of:

• Dichotomous outcomes: number of events and sample size by treatment arm
• Continuous outcomes: mean and standard error by treatment arm. Where standard error is not reported, this will be estimated from published confidence intervals or similar.

It is not anticipated that any other types of data (e.g. time to event, count data) will arise. For publications reporting only summary measures of treatment effect, these will also be extracted, together with the associated measures of uncertainty (e.g. standard errors and/or confidence intervals) for comparison purposes.

1.4 Statistical analysis

The following treatment effects will be synthesised:

• Relative risks for dichotomous outcomes
• Mean differences and/or mean ratios for continuous outcomes (the preferred measure of treatment effect will be context-specific)

Bayesian network meta-analysis will be used to synthesise treatment effects (Dias et al., 2013a). For dichotomous outcomes, a GLM with a binomial likelihood and a log link function will be used (Warn et al., 2002), while for continuous outcomes a normal likelihood and an identity link will be used. It anticipated that for the base case, random-effects meta-analysis will be used, except where there is only a single trial contributing to each comparison and no closed loops.

It is anticipated that the NMAs will include a small number of studies and that event counts will be low within each study. Therefore, for dichotomous outcomes, a normal distribution with mean 0 and standard deviation 2.82 will be used as a prior distribution for the treatment effect parameters. This is the weakly informative prior distribution recommended in (Günhan et al., 2020) for meta analysis of few studies of rare events, which is symmetric about the null (i.e. neither benefit nor harm is regarded as more likely a priori) and has 95% of the density between 1/250 and 250 (i.e. a 95% prior belief that no relative risk exceeds 250).
Due to the small number of studies in the network, weakly informative priors will be used for the heterogeneity parameters (HN(0.5) for relative risks) as discussed in (Röver et al., 2021) and elsewhere. Sensitivity analysis will be carried out on prior distributions.

Analysis will be carried out in R, primarily using the package BUGSnet (Béliveau et al., 2019) (which implements MCMC sampling in JAGS). MCMC sampling will be conducted using 100,000 iterations of which 50,000 are burn-in iterations, and 5,000 adaptation iterations, and 3 chains.

Convergence and model plausibility will be assessed by checking:

- Trace plots
- Density plots of the posterior distributions for treatment effect and heterogeneity parameters
- Convergence diagnostics such as Gelman-Rubin diagnostics, Geweke's statistic etc. output by the BUGSnet package

If the anticipated base case model exhibits poor convergence or implausible posterior distributions, MCMC parameters may be adjusted to improve convergence.

Heterogeneity will primarily be assessed qualitatively via comparisons of the characteristics of the included studies (patients, outcomes etc.). Where differences in patient characteristics exist across studies, the potential for effect-modification will be assessed by examining subgroup analysis if included in the identified studies.

Consistency will be assessed by comparing direct and indirect estimates of treatment effects.

Estimated treatment effects will also be compared with estimates of the between-trial standard deviation parameter tau (where random-effects models have been used). As the evidence networks are not anticipated to contain a large number of comparisons, formal statistical methods to assess inconsistency and heterogeneity will not be carried out.

1.5 Calculation of absolute effects

In the case of dichotomous outcomes, baseline natural history models will also be fitted to the event rates in the SoC arms of the included studies. Again a GLM with a binomial likelihood and log link function will be used, with a preference for random-effects models where possible. These will be used to estimate the absolute event rates and risk reductions versus SoC for each treatment and each outcome.

1.6 Sensitivity analysis

The following sensitivity analysis will be carried out:

1. Calculation of a ‘pooled mAB versus SoC effect’ for each outcome
2. Inclusion of data from (Eom et al., 2021) (regdanvimab versus placebo) in the relevant evidence networks, allowing consideration of regdanvimab as a comparator
3. For the relative-effects parameter, the following alternatives will be explored:
   - More informative prior $N(0, [\log(10)/1.96]^2)$
   - Less informative prior $N(0, [\log(10000)/1.96]^2)$

4. Where random effects models have been used in the base case, the following alternative priors will be used for the heterogeneity parameter:
   - Informative priors from (Turner et al., 2012) $[\log\text{-normal}(-4.06, 1.45^2)$ for mortality and $\log\text{-normal}(-3.02, 1.85^2)$ for other outcomes]
   - Non-informative prior $U(0,5)$
   - Alternative weakly informative prior Half-Cauchy(0.5) (Röver et al., 2021)

Fixed-effects models will also be fitted.

2 NMA code

2.1 Required packages

```r
# Packages for data processing
library(readxl)
library(dplyr)
library(tidyr)
library(stringr)

# Package to run NMAs
library(BUGSnet)

# Packages to produce plots
library(ggplot2)
library(grid)
library(gridExtra)
```

2.2 Data preparation

Note: data can be found in the attached spreadsheet and is also presented here under ‘Compete Tabulation of Study-level Inputs.’

```r
## Create a data frame of outcomes for looping over
# This is used repeatedly for running the same analysis for each outcome
outcomes_full<- data.frame("Outcome"=c("Mortality",
  "Hospitalisation",
  "Invasive Ventilation",
  "ICU Admission",
  "Infusion-related AEs"),
  stringsAsFactors=FALSE)
```
"Serious AEs"),
# This is basically the 'short name' for each outcome
"model"=c("mort",
"hosp",
"inv",
"icu",
"iae",
"sae"
),
# Name of the R object used to store the processed NMA input data for each outcome
"data"=c("mort_data",
"hosp_data",
"inv_data",
"icu_data",
"iae_data",
"sae_data"),
# Specify fixed or random for base case
"type"=c("re",
"re",
"re",
"re",
"re",
"re")
## Load data from spreadsheets
# Vector of sheet names to extract from excel
outcomes=names(outcomes_full$model)
## Loop over sheets (outcomes), shorten treatment names for convenient plotting, and assign a data frame to each
for (i in outcomes) {

  # Load the excel sheet
  tmp_df<-read_excel("data_short.xlsx",
                      sheet=i)

  # Replace treatment names with short names
  tmp_df$tx<-str_replace_all(tmp_df$treatment,
                             c("Bamlanivimab_etesevimab"="bam_ete",
                               "Bamlanivimab"="bam",
                               "Etesevimab"="ete",
                               "Etesevimab"="ete",
                               "Etesevimab"="ete",
                               "Etesevimab"="ete",
                               "Etesevimab"="ete",
                               "Etesevimab"="ete")
  }
}


```r
# Save a copy of the full data frame for later use (in scenarios etc)
assign(paste0(i,"_df"),tmp_df)

# Now remove the excluded studies and process the data for the base case NMA

tmp_df<-filter(tmp_df,
    Exclude != "Y" | is.na(Exclude)
)

# Process the data for use in BUGSnet

nma_data<-data.prep(tmp_df,
    varname.s = "study",
    varname.t="tx"
)

assign(paste0(i,"_data"),
    nma_data)

rm(tmp_df,nma_data)
}

### Base Case NMA

```
```r
outcome="events",
N="sampleSize",
reference="pbo",
family="binomial",
link="log",
effects=ifelse(type="fe",
"fixed",
"random"
),
prior.d=eff_prior,
prior.sigma = ifelse(type="re",
het_prior,
"DEFAULT")
}
invisible(
results<-nma.run(model,n.adapt = 5000, n.iter = 100000)
)
return(results)
}
# This code loops over all outcomes and runs the base case NMAs
# Output (i.e. including simulations) are saved in .RDS files
# Note that even if the cache is invalidated, the NMAs will only be re-run if
# the .RDS files are deleted
# If changing any base case options you need to delete these files!
for(i in seq_along(outcomes))
{
  nma_file<-paste0("./output_data/",outcomes[i],"_NMA.RDS")
  if(!(!file.exists(nma_file)))
  {
    saveRDS(nma_binary(get(outcomes_full$data[i]),
      type=outcomes_full$type[i]),
    file=nma_file
  }
}
## This is a wrapper for a couple of BUGSnet functions to extract NMA results
## It takes the ouput of nma.run as input and returns a list consisting of:
# $sucraplot, $heatplot, $forestplot
get_nma_results<-function(results,
  Title="" # Outcome name, if needed
  )
```

{  
  nma_results<-list()

  sucra.out <- nma.rank(results, largerbetter=FALSE, sucra.palette= "Set1")

  sucraplot<-sucre.out$sucraplot+labs(title=paste0("Ranking: ",Title))

  nma_results$sucraplot<-sucraplot

  # Heatplot with treatments ordered by estimated superiority
  league.out <- nma.league(results,
                            central.tdcy="median",
                            #order = sucra.out$order,
                            digits=2)

  heatplot<-league.out$heatplot#+labs(title=paste0("Pairwise comparisons (Relative Risks)"))

  nma_results$heatplot<-heatplot

  # Extract the tables so that we can save these if needed
  nma_results$table<-league.out$table
  nma_results$longtable<-league.out$longtable

  # Forest plot relative to placebo
  forestplot<-nma.forest(results,
                          central.tdcy="median",
                          comparator = "pbo",
                          x.trans = "log")#+labs(title=paste0("Relative Risks versus Placebo "))

  nma_results$forestplot<-forestplot
  return(nma_results)
}

# Loops over the outcomes, load the NMA simulations/output, extract the results and save to an appropriate file

for(i in seq_along(outcomes))
{
  nma_file<-paste0("./output_data/",outcomes[i],"_NMA.RDS")
  nma_results_file<-paste0("./output_data/",outcomes[i],"_NMA_results.RDS")

  if(!file.exists(nma_results_file))
  {
    # Load NMA sims
    nma_outputs<-readRDS(nma_file)
  }  
}
# Generate NMA results
nma_results <- get_nma_results(nma_outputs, Title = outcomes_full$Outcome[i])

# Save NMA results as file
saveRDS(nma_results, nma_results_file)

# Save tables for article plots
saveRDS(list("table" = nma_results$table, "longtable" = nma_results$longtable),
file = paste0("./plotting_data/", outcomes[i], "_NMA_tables.RDS"))

rm(nma_outputs, nma_results)
gc()
}

2.4 Pooled mAB pairwise meta-analysis

We estimated the pooled mAB versus placebo effect by reclassifying all mAB therapies as a single intervention and carrying out the corresponding pairwise meta-analysis as before.

# This loop creates the data frame for the meta-analysis of pooled mABs versus placebo
# Load data from spreadsheets
# Exclude Eom21 (does not meet criteria) and McCreary 2021 (as it only contributes to mAB-mAB comparisons)
# Replace each intervention name with 'mAB'

for (i in outcomes)
{
  tmp_df <- get(paste0(i, "_df")) %>%
    # Exclude study of regdanvimab, and McCreary 2021 which had no placebo arm
    filter(Exclude != "Y" | is.na(Exclude),
    study != "Mc Creary 2021")

  # Replace all mAB short names with 'mAB'
  tmp_df$tx <- str_replace_all(tmp_df$tx,
    c("bam_ete" = "mAB",
    "bam" = "mAB",
    "cas_imd" = "mAB",
    "sot" = "mAB")
  )

  nma_data <- data.prep(tmp_df,
    varname.s = "study",
    varname.t = "tx")

  assign(paste0(i, "_pooled_data"),
    nma_data)
# This code runs the pooled mABs meta-analysis for each outcome and saves the results
# All model inputs are unchanged from the base case

for(i in seq_along(outcomes))
{
    nma_pooled_file<-paste0("./output_data/",outcomes[i],"_pooled_MA.RDS")
    if(!(file.exists(nma_pooled_file)))
    {
        saveRDS(nma_binary(get(paste0(outcomes[i],"_pooled_data")), type=outcomes_full$type[i]),
                 file=nma_pooled_file
    }
}

2.5 Estimation of absolute treatment effects

# This function generates an estimate of the baseline event risk pooled across placebo arms of the included studies
# It takes as input the event numbers and sample sizes from the trials, using the data that has been processed by BUGSnet for the main NMAs.
# These baseline risks are then pooled using a random effects logistic regression model to estimate the posterior predictive distribution for baseline risks
# The function returns a data frame of samples from this distribution

calculate_risk<-function(base_list)
{
    base_df<-base_list$arm.data %>%
        filter(tx="pbo")

    # Create data frame for use in JAGS
    base_model_df<-list(
        "ns"=nrow(base_df),
        "r"=base_df$events,
        "n"=base_df$sampleSize
    )

    # JAGS code for baseline mode (adapted from NICE TSD5)
    sink("model.txt")
    cat(
        # JAGS code below
# Binomial likelihood, logit link
# Baseline random effects model

```r
model{# *** PROGRAM STARTS
  for (i in 1:ns){# LOOP THROUGH STUDIES
    r[i] ~ dbin(p[i],n[i]) # Likelihood
    logit(p[i]) <- mu[i] # Log-odds of response
    mu[i] ~ dnorm(m,tau.m) # Random effects model
  }
  mu.new ~ dnorm(m,tau.m) # predictive dist. (log-odds)
  m ~ dnorm(0,.0001) # vague prior for mean
  var.m <- 1/tau.m # between-trial variance
  tau.m <- pow(sd.m,-2) # between-trial precision = (1/between-trial variance)
  sd.m ~ dnorm(0,4)T(0,)# weakly-informative prior for between-trial SD
  logit(R) <- m # posterior probability of response
  logit(R.new) <- mu.new # predictive probability of response
  logR.new<-log(R.new)
}
"
}
sink()

out <- jags.model(file="model.txt",
  data=base_model_df,
  n.adapt=5000,
  n.chains = 3
)

jagssamples <- coda.samples(out,
  variable.names=c("R","R.new","logR.new","mu.new"),
  n.iter=100000,
  thin=1)

jagssamples_df<-do.call(rbind.data.frame,jagssamples)
names(jagssamples_df)<-c("R","R.new","logR.new","logitR.new")

return(jagssamples_df)
}
```

# This function takes the output of a BUGSnet model run and extracts the posterior simulations of the treatment effects

```r
extract_effects<-function(nma_out)
{
  out_df<-do.call(rbind.data.frame,nma_out$samples) %>%
    select(1:length(nma_out$trt.key))
  names(out_df)<-nma_out$trt.key
  return(out_df)
}
```
# This function takes as input the posterior simulations of the baseline risks and treatment effects and generates estimated absolute risks, and risk differences versus placebo, for each treatment in the network

```r
create_rd_samples <- function(n_iter = 10000, baseline_risks, trt_effects) {
  base_samples <- sample(baseline_risks$logR.new, n_iter)
  trt_samples <- sample_n(trt_effects, n_iter)
  abs_risks <- exp(base_samples + trt_samples)
  risk_diff <- exp(base_samples + trt_samples) - exp(base_samples)
  names(risk_diff) <- paste0(names(abs_risks), "_vs_pbo")
  return(list("abs" = abs_risks,
                "rd" = risk_diff))
}

for (i in outcomes) {
  nma_sims <- readRDS(paste0("./output_data/", i, "_NMA.RDS"))
  pooled_ma_sims <- readRDS(paste0("./output_data/", i, "_pooled_MA.RDS"))

  effects <- cbind(extract_effects(nma_sims),
                   extract_effects(pooled_ma_sims)[-1])

  # Include regdanvimab effects if these have been calculated
  reg_sims_file <- paste0("./output_data/", i, "_NMA_reg.RDS")
  if (file.exists(reg_sims_file)) {
    reg_sims <- readRDS(reg_sims_file)
    effects <- cbind(effects, extract_effects(reg_sims)"reg")
  }

  names(effects) <- str_replace_all(names(effects), c("mAB" = "pooled_mABs", "reg" = "*reg"))

  invisible(samples <- create_rd_samples(n_iter = 10000, calculate_risk(get(paste0(i,"_data")))))
}


```r
effects
)

saveRDS(samples,
  file=paste0("./output_data/",i,"_ARR.RDS")
)
rm(samples,nma_sims)
gc()
}

2.6 Sensitivity Analysis

2.6.1 Prior distributions for relative treatment effects.

For all outcomes we investigate the following alternative priors for the treatment effect parameters:

1. More informative prior: \(N(0,1.175^2)\). This distribution gives a 95\% prior probability that no relative risk between any pair of treatments in the network exceeds 10 (note that 0.175=\log(10)/1.96).

2. Less informative prior: \(N(0,4.700^2)\). This distribution gives a 95\% prior probability that no relative risk between any pair of treatments in the network exceeds 10,000 (note that 4.700=\log(10000)/1.96).

# This code runs sensitivity analysis on the prior distributions for the relative treatment effects and saves the results.

eff_SA_file<-../output_data/eff_sa.RDS

# Scenarios: upper limits of 95\% prior HDIs on the RR scale (base case=250)
eff_bounds<-c(10,250,10000)

# Calculate prior distribution parameters for passing to JAGS
precisions<-(log(eff_bounds)/1.96)^{-2}
eff_priors<-paste0("dnorm(0,"#,precisions,",")

# Prior distributions formatted for table captions
printdists<-paste0("Efficacy prior  N(0,"#,format(precisions^{1/2},digits=2 ),"^2),",
c(" (more informative)",
  " (base case)",
  " (less informative)"
)
```
# Short versions for plot captions

plotdists <- paste0("N(0,", format(precisions^{-1/2}, "^2")")

# Vector of figure captions (note that we use grid.arrange so there is only
# a single figure for each outcome)

eff_SA_captions <- paste0("Sensitivity analysis using alternative prior distr
ibutions for the treatment effect parameter (log relative risk), for the outc
ome of ",

outcomes_full$Outcome,
". Top: ",
printdists[1],
", middle: ",
printdists[2],
", bottom: ",
printdists[3])

if (!(file.exists(eff_SA_file)))
{
effsaresults <- list()

# Loop over outcomes and run SA

for (i in seq_along(outcomes))
{
  plots <- list()
  tables <- list()
  effsaresults[[i]] <- list()
  for (j in seq_along(eff_priors))
  {
    ## Run NMA scenario: outcome i, effecicay prior j
    invisible(
      modelrun <- nma_binary(get(outcomes_full$data[i]),
      type = outcomes_full$type[i],
      eff_prior = eff_priors[j])
    )

    # Save results as a list (nested within a list)

    effsaresults[[i]][[j]] <- list()
    effsaresults[[i]][[j]][["league"]]<-nma.league(modelrun,
    central.tdcy="median",
    digits=2)

    # Store the name of the distribution here
2.6.2 Comparison of fixed and random effects.

# Sensitivity analysis to compare fixed versus random effects.
# Run alternative NMA model (typically fixed effects, where base case is random effects) and save NMA output
# Note that model is only run if output file does not exist already (delete to re-run)

for (i in seq_along(outcomes)) {
  # Character string for alternative model type
  alt_type<-ifelse(outcomes_full$data[i]=="re","fe","re")

  # File path to save NMA output
  alt_file<-paste0("./output_data/",outcomes[i],"_NMA_",alt_type,".RDS")

  # Run only if the output file does not exist
  if (!(file.exists(alt_file))){
    invisible(saveRDS(nma_binary(get(outcomes_full$data[i]),
                                 type=alt_type
                              ),
                         file=alt_file)
  )
}
2.6.3 Heterogeneity parameter prior sensitivity analysis

For all outcomes we examined the sensitivity of the results to the choice of prior distribution for the heterogeneity parameter (between trial standard deviation). The following distributions were examined:

1. Base case: half-normal(0.5)
2. Uniform(0,5)
3. Informative priors from Turner et al. (2012) for the between trial variance: log-normal(-4.06,1.45^2) for mortality and log-normal(-3.02, 1.85^2) for other outcomes
4. Alternative weakly-informative prior: Half-Cauchy(0.5) Röver et al. (2021)

Turner et al. (2012) gives prior for sigma^2, therefore it is necessary to edit the JAGS code produced by BUGSnet to implement these in a scenario analysis. This is done in the following code chunk.

```r
hty_priors <- c("dnorm(0,4)T(0,)",
    "dunif(0,5) ",
    "dlnorm(-3.02, 0.2921841) ",
    "dt(0, pow(0.5,-2), 1)T(0,)"
)
prior_names <- c("HN(0.5) (base case)",
    "Unif(0,5)",
    "from Turner et al.",
    "Half-Cauchy(0.5)"
)
```

# Captions for the figures (note one plot per outcome again)
hty_prior_captions <- paste0("Estimated treatment effects for each mAB versus placebo obtained from varying the prior distribution on the heterogeneity parameter sigma, for the outcome of ",
    outcomes_full$Outcome)

#het_sa_file<-.output_data/het_prior_sa.RDS
for (i in seq_along(outcomes))
{
    het_sa_file<-paste0("./output_data/het_prior_sa_",outcomes[i],".RDS")
    if (!file.exists(het_sa_file))
    {
        hetsaresults<-list()
        hetsaresults[[i]]<-list()

        # Temporarily change Turner et al prior if outcome is mortality
        hty_priors[3]<- ifelse(outcomes[i]=="mort",
            "dlnorm(-4.06,0.4756243)",
            "dlnorm(-3.02, 0.2921841)"
        )

        for (j in seq_along(hty_priors))
        {
            # If we are not using Turner et al priors, can proceed as normal specifying priors for the standard deviation
            if(j!=3){
                invisible(
                modelrun<-nma_binary(get(outcomes_full$data[i]),
                    type="re",
                    het_prior=hty_priors[j]
                )
            )
        }

        # Hack to specify prior between-trial variance rather than standard deviation in BUGSnet when Turner et al is used
        if (j==3)
        {
            sca_model<-nma.model(data=get(outcomes_full$data[i]),
                outcome="events",
                N="sampleSize",
                reference="pbo",
                family="binomial",
                link="log",
                effects="random",
                prior.d="dnorm(0,0.1260097)",
                prior.sigma = hty_priors[j])

            # Edit the JAGS code created by nma.model
            sca_model$bugs<-str_replace(sca_model$bugs,
                "sigma ~ dlnorm",
                "sigma2 ~ dlnorm"
            )
        }
    }
sca_model$bugs <- str_replace(sca_model$bugs,
  "sigma2 <- sigma[^2]",
  "sigma <- pow(sigma2,0.5)"")

invisible(
  modelrun <- nma.run(sca_model, n.adapt = 5000, n.iter = 100000)
)
rm(sca_model)

hetsaresults[[i]][[j]] <- list()

leagueplot <- nma.league(modelrun,
  central.tdcy = "median",
  digits = 2)

# Delete the plot environment to save memory
leagueplot$plot_env <- rlang::new_environment()

hetsaresults[[i]][[j]][["league"]]<-leagueplot
hetsaresults[[i]][[j]][["tablecaption"]]<-prior_names[j]

fplot <- nma.forest(modelrun,
  central.tdcy = "median",
  comparator = "pbo") +
  labs(title = prior_names[j])

fplot$plot_env <- rlang::new_environment()

hetsaresults[[i]][[j]][["plot"]]<-fplot

} saveRDS(hetsaresults, file = het_sa_file)
rm(modelrun, hetsaresults)
gc()


2.6.4 Investigation of consistency

The only closed loops in the evidence networks arise from the direct comparison between bamlanivimab/etesevimab and casirivimab/imdevimab carried out in (McCreary et al., 2021).
The outcomes affected are mortality, hospitalisation, infusion-related AEs and serious AEs. Consistency was assessed by comparing the direct estimate of relative effects of bamlanivimab/etesevimab versus casirivimab/imdevimab from (McCreary et al., 2021), and the indirect estimate of the same effect obtained re-running an NMA of all studies evaluating bamlanivimab/etesevimab and casirivimab/imdevimab with (McCreary et al., 2021) excluded (note that the latter does not contribute to the indirect estimate as there is no placebo arm).

# This code carries out the investigation of consistency for the relevant outcomes
outcomes_c<-c("mort","hosp","sae")

filename_consistency<-.output_data/check_consistency.RDS"

if(!(file.exists(filename_consistency)))
{
  consistency<-list()
  for (i in outcomes_c)
  {
    # Get only those studies producing an indirect estimate of the effect of bamlanivimab/etesevimab versus casirivimab/imdevimab
    tmp_df<-get(paste0(i,"_df"))
    tmp_df_indirect<-filter(tmp_df, 
      Exclude != "Y" | is.na(Exclude),
      study != "McCreary 2021" &
      study != "Gupta 2021" &
      tx %in% c("bam_ete","cas_imd","pbo"))

    nma_data_indirect<-data.prep(tmp_df_indirect, 
      varname.s = "study",
      varname.t="tx")

    invisible(
      modelrun_indirect<-nma_binary(nma_data_indirect,type="fe")
    )

    consistency[[paste0(i,"_indirect")]]<-nma.league(modelrun_indirect, 
      central.tdcy="median",
      digits=2)$longtable

    rm(tmp_df_indirect,nma_data_indirect,modelrun_indirect)

    tmp_df_direct<-filter(tmp_df, 
      study="McCreary 2021",
      tx %in% c("bam_ete","cas_imd","pbo") &
      exclude != "Y" | is.na(exclude)
    )

    nma_data_direct<-data.prep(tmp_df_direct, 
      varname.s = "study",
      varname.t="tx")

    invisible(
      modelrun_direct<-nma_binary(nma_data_direct, type="fe")
    )

    consistency[[paste0(i,"_direct")]]<-nma.league(modelrun_direct, 
      central.tdcy="median",
      digits=2)$longtable

    rm(tmp_df_direct,nma_data_direct,modelrun_direct)
  
  consistency[[paste0(i,"_indirect")]]<-nma.league(modelrun_indirect, 
    central.tdcy="median",
    digits=2)$longtable
  
  consistency[[paste0(i,"_direct")]]<-nma.league(modelrun_direct, 
    central.tdcy="median",
    digits=2)$longtable
  
  consistency[[paste0(i,"_indirect")]]<-nma.league(modelrun_indirect, 
    central.tdcy="median",
    digits=2)$longtable
  
  consistency[[paste0(i,"_direct")]]<-nma.league(modelrun_direct, 
    central.tdcy="median",
    digits=2)$longtable

  # Add indirect estimate to list
  consistency[[i]]<-data.frame(
    estimate=consistency$indirect$estimate, 
    lci=consistency$indirect$lci, 
    uci=consistency$indirect$uci, 
    study=consistency$indirect$study, 
    tx=consistency$indirect$tx, 
    exclude=consistency$indirect$exclude 
  )
  consistency[[i]]<-data.frame(
    estimate=consistency$direct$estimate, 
    lci=consistency$direct$lci, 
    uci=consistency$direct$uci, 
    study=consistency$direct$study, 
    tx=consistency$direct$tx, 
    exclude=consistency$direct$exclude 
  )

  # Add direct estimate to list
}

 write_csv(filename_consistency,consistency,sep="\t")
tx!="bam")

nma_data_direct<-data.prep(tmp_df_direct,
    varname.s = "study",
    varname.t="tx")

invisible(
    model_direct<-nma.model(data=nma_data_direct,
        outcome="events",
        N="sampleSize",
        reference="bam_ete",
        family="binomial",
        link="log",
        effects="fixed"
    )
)
invisible(modelrun_direct<-nma.run(model_direct,n.adapt = 5000, n.iter = 100000))

consistency[[paste0(i,"_direct")]]<-nma.league(modelrun_direct,
    central.tdcy="median",
    digits=2)$longtable

rm(tmp_df,nma_data_direct,modelrun_direct)
}
saveRDS(consistency,filename_consistency)
}

3 Complete tabulation of study-level data extracted.

3.1 Notes on the extracted data

Treatments:

- **bam** bamlanivimab
- **bam_ete** bamlanivimab/etesevimab
- **cas_imd** casirivimab/imdevimab
- **pbo** placebo
- **reg** regdanvimab (note: included in scenario analyses only)
- **sot** sotrovimab

Studies:
1. (Weinreich et al., 2021) consisted of two stages, investigating casirivimab 1200mg/imdevimab 1200mg vs placebo, and casirivimab 2800mg/imdevimab 2800mg versus placebo. Each stage has a separate concurrent placebo arm, and results were reported for each stage. It is therefore treated as two separate studies in the NMA for efficacy outcomes. However, for safety outcomes, only pooled placebo event numbers are reported - for this reason, pooled casirivimab/imdevimab event numbers are also used for these outcomes, treating Weinreich 2021 as a single study.

2. (Scenario analysis only) (Eom et al., 2021) contained three parallel arms, regdanvimab 40mg/kg, regdanvimab 80mg/kg, and placebo. Event numbers in the regdanvimab arms have been pooled in the NMA scenario where this study is included.

3. For the ‘Hospitalisation’ outcome, all studies reported all-cause hospitalisation except (Dougan et al., 2021b), which only included COVID-related hospitalisation.

4. Hospital Length-of-Stay was reported in three publications. Due to time-constraints and model complexity (i.e. the need to account for zero-inflated data) an NMA for this outcome has not been carried out.

5. For the supplemental oxygen outcome, only one study (Gupta et al., 2021) reported results in the base case ((Eom et al., 2021) also reported results but this study did not meet the inclusion criteria of the Review). This outcome has not been included in the analysis.

### 3.2 Extracted data for NMA

#### Table 2.1: Mortality, extracted data

| study         | treatment                     | dose    | events | sampleSize | Notes | Outcome    |
|---------------|-------------------------------|---------|--------|------------|-------|------------|
| McCreary 2021 | Bamlanivimab                  | NR      | 1      | 128        | NA    | Mortality  |
| McCreary 2021 | Bamlanivimab_etesevimab       | NR      | 7      | 885        | NA    | Mortality  |
| McCreary 2021 | Casirivimab_imdevimab         | NR      | 6      | 922        | NA    | Mortality  |
| study          | treatment                        | dose               | events | sampleSize | Notes         | Outcome                  |
|---------------|----------------------------------|--------------------|--------|------------|---------------|--------------------------|
| Dougan 2021   | Bamlanivimab_etesevimab          | 2800mg_2800mg      | 0      | 518        | NA            | Mortality               |
| Dougan 2021   | Placebo                          | PBO                | 10     | 517        | NA            | Mortality               |
| Weinreich 2021a | Casirivimab_imdevimab          | 1200mg             | 1      | 736        | NA            | Mortality               |
| Weinreich 2021a | Placebo                          | PBO                | 1      | 748        | NA            | Mortality               |
| Weinreich 2021a | Casirivimab_imdevimab          | 2400mg             | 1      | 1355       | NA            | Mortality               |
| Weinreich 2021b | Placebo                          | PBO                | 3      | 1341       | NA            | Mortality               |
| Gupta 2021    | Sotrovimab                       | 500mg              | 0      | 528        | NA            | Mortality               |
| Gupta 2021    | Placebo                          | PBO                | 2      | 529        | NA            | Mortality               |
| Dougan 2021b  | Bamlanivimab_etesevimab          | 700mg_1400mg       | 0      | 511        | NA            | Mortality               |
| Dougan 2021b  | Placebo                          | PBO                | 4      | 258        | NA            | Mortality               |
| Eom 2021      | Regdanvimab                      | all                | 0      | 103        | Excluded from analysis as no events observed | Mortality |
| Eom 2021      | Placebo                          | PBO                | 0      | 103        | Excluded from analysis as no events observed | Mortality |

Table 2.2: Hospitalisation, extracted data

| study          | treatment                        | dose               | events | sampleSize | Notes         | Outcome                  |
|---------------|----------------------------------|--------------------|--------|------------|---------------|--------------------------|
| McCreary 2021 | Bamlanivimab                     | NR                 | 16     | 128        | NA            | All cause hospitalisation |
| McCreary 2021 | Bamlanivimab_etesevimab          | NR                 | 130    | 885        | NA            | All cause hospitalisation |
| McCreary 2021 | Casirivimab_imdevimab            | NR                 | 132    | 922        | NA            | All cause hospitalisation |
| Dougan 2021   | Bamlanivimab_etesevimab          | 2800mg_2800mg      | 11     | 518        | NA            | Covid-related hospitalisation only |
| Dougan 2021   | Placebo                          | PBO                | 33     | 517        | NA            | Covid-related hospitalisation only |
| study        | treatment                  | dose     | events | sampleSize | Notes | Outcome                          |
|-------------|----------------------------|----------|--------|------------|-------|-----------------------------------|
| Weinreich 2021a | Casirivimab_imdevimab     | 1200mg   | 7      | 736        | NA    | All-cause hospitalisation        |
| Weinreich 2021a | Placebo                  | PBO      | 26     | 748        | NA    | All-cause hospitalisation        |
| Weinreich 2021b | Casirivimab_imdevimab     | 2400mg   | 20     | 1355       | NA    | All-cause hospitalisation        |
| Weinreich 2021b | Placebo                  | PBO      | 66     | 1341       | NA    | All-cause hospitalisation        |
| Gupta 2021    | Sotrovimab                | 500mg    | 6      | 528        | NA    | All-cause hospitalisation        |
| Gupta 2021    | Placebo                   | PBO      | 29     | 529        | NA    | All-cause hospitalisation        |
| Eom 2021      | Placebo                   | PBO      | 9      | 103        | NA    | All-cause hospitalisation        |
| Eom 2021      | Regdanvimab               | all      | 9      | 204        | NA    | All-cause hospitalisation        |
| Dougan 2021b  | Bamlanivimab_etesevimab   | 700mg_1400mg | 4 | 511        | Event numbers reported in Kaplan Meier plot only | Covid-related hospitalisation only |
| Dougan 2021b  | Placebo                   | PBO      | 14     | 258        | Event numbers reported in Kaplan Meier plot only | Covid-related hospitalisation only |

Table 2.3: Invasive Ventilation, extracted data
| study             | treatment         | dose         | events | sampleSize | Notes | Outcome                        |
|-------------------|-------------------|--------------|--------|------------|-------|--------------------------------|
| Gupta 2021        | Placebo           | PBO          | 4      | 529        | NA    | Mechanical ventilation or ECMO |
| Eom 2021          | Placebo           | PBO          | 0      | 103        | NA    | Invasive ventilation          |
| Eom 2021          | Regdanvimab       | all          | 1      | 204        | NA    | Invasive ventilation          |

**Table 2.4: ICU Admission, extracted data**

| study             | treatment         | dose         | events | sampleSize | Notes | Outcome                        |
|-------------------|-------------------|--------------|--------|------------|-------|--------------------------------|
| Weinreich 2021a   | Casirivimab_imdevimab | 1200mg      | 3      | 736        | NA    | ICU Admission                  |
| Weinreich 2021a   | Placebo           | PBO          | 7      | 748        | NA    | ICU Admission                  |
| Weinreich 2021b   | Casirivimab_imdevimab | 2400mg      | 6      | 1355       | NA    | ICU Admission                  |
| Weinreich 2021b   | Placebo           | PBO          | 18     | 1341       | NA    | ICU Admission                  |
| Gupta 2021        | Sotrovimab        | 500mg        | 0      | 528        | NA    | ICU Admission                  |
| Gupta 2021        | Placebo           | PBO          | 10     | 529        | NA    | ICU Admission                  |
| Eom 2021          | Regdanvimab       | all          | 0      | 101        | NA    | ICU Admission                  |
| Eom 2021          | Regdanvimab       | 80mg_kg      | 0      | 103        | NA    | ICU Admission                  |
| Eom 2021          | Placebo           | PBO          | 0      | 103        | NA    | ICU Admission                  |

**Table 2.5: Infusion-related AEs, extracted data**

| study             | treatment         | dose         | events | sampleSize | Notes | Outcome                        |
|-------------------|-------------------|--------------|--------|------------|-------|--------------------------------|
| McCreary 2021     | Bamlanivimab      | NR           | 0      | 128        | NA    | NA                             |
| McCreary 2021     | Bamlanivimab_etelevimab | NR          | 12     | 885        | NA    | NA                             |
| McCreary 2021     | Casirivimab_imdevimab | NR          | 9      | 922        | NA    | NA                             |
| Weinreich 2021    | Placebo           | PBO          | 0      | 1843       | NA    | Grade 2+ within 4 days. Concurrent placebo not reported. |
| Weinreich 2021    | Casirivimab_imdevimab | all         | 3      | 2676       | NA    | Grade 2+ within 4 days. Concurrent placebo not reported. |
| Gupta 2021b       | Sotrovimab        | 500mg        | 6      | 523        | NA    | Infusion reactions             |
| Gupta 2021b       | Placebo           | PBO          | 6      | 526        | NA    | Infusion reactions             |
| Eom 2021          | Placebo           | PBO          | 2      | 110        | NA    | NA                             |
| Eom 2021          | Regdanvimab       | all          | 1      | 215        | NA    | NA                             |
| study          | treatment                        | dose            | events | sampleSize | Notes                  | Outcome |
|---------------|----------------------------------|-----------------|--------|------------|------------------------|---------|
| McCreary 2021 | Bamlanivimab                     | NR              | 0      | 128        | NA                     | NA      |
| McCreary 2021 | Bamlanivimab_etesevimab          | NR              | 1      | 885        | NA                     | NA      |
| McCreary 2021 | Casirivimab_imdevimab            | NR              | 4      | 922        | NA                     | NA      |
| Dougan 2021   | Bamlanivimab_etesevimab          | 2800mg_2800mg   | 7      | 518        | NA                     | NA      |
| Dougan 2021   | Placebo                          | PBO             | 5      | 517        | NA                     | NA      |
| Weinreich 2021| Placebo                          | PBO             | 74     | 1843       | Concurrent placebo arm results not reported. | NA      |
| Weinreich 2021| Casirivimab_imdevimab            | all             | 33     | 2676       | Concurrent placebo arm results not reported. | NA      |
| Gupta 2021    | Sotrovimab                       | 500mg           | 11     | 523        | NA                     | NA      |
| Gupta 2021    | Placebo                          | PBO             | 32     | 526        | NA                     | NA      |
| Dougan 2021b  | Bamlanivimab_etesevimab          | 700mg_1400mg    | 6      | 511        | NA                     | NA      |
| Dougan 2021b  | Bamlanivimab_etesevimab          | PBO             | 2      | 258        | NA                     | NA      |
| Eom 2021      | Placebo                          | PBO             | 0      | 110        | Excluded as no events  | NA      |
| Eom 2021      | Regdanvimab                      | all             | 0      | 215        | Excluded as no events  | NA      |

4 Results

4.1 Mortality

Summary of Evidence Network
Table 4.1: Summary of evidence network, Mortality

| Characteristic                                      | Value       |
|-----------------------------------------------------|-------------|
| Number of Interventions                            | 5           |
| Number of Studies                                  | 6           |
| Total Number of Patients in Network                | 8976        |
| Total Possible Pairwise Comparisons                | 10          |
| Total Number of Pairwise Comparisons With Direct Data| 6           |
| Is the network connected?                          | TRUE        |
| Number of Two-arm Studies                          | 5           |
| Number of Multi-Arms Studies                       | 1           |
| Total Number of Events in Network                  | 36          |
| Number of Studies With No Zero Events              | 3           |
| Number of Studies With At Least One Zero Event      | 3           |
| Number of Studies with All Zero Events             | 0           |

Table 4.1: Summary of comparison data, Mortality

| comparison            | n.studies | n.patients | n.outcomes | proportion |
|-----------------------|-----------|------------|------------|------------|
| bam vs. bam_ete       | 1         | 1013       | 8          | 0.0078973  |
| bam vs. cas_imd       | 1         | 1050       | 7          | 0.0066667  |
| bam_ete vs. cas_imd   | 1         | 1807       | 13         | 0.0071942  |
| bam_ete vs. pbo       | 2         | 1804       | 14         | 0.0077605  |
| comparison    | n.studies | n.patients | n.outcomes | proportion  |
|---------------|-----------|------------|------------|-------------|
| cas_imd vs. pbo | 2         | 4180       | 6          | 0.0014354   |
| pbo vs. sot    | 1         | 1057       | 2          | 0.0018921   |

Figure 4.2: Pairwise comparisons: estimates of relative risk (posterior median and 95% CrI) for the outcome of Mortality

Figure 4.3: Estimates of relative risk for each mAB versus placebo (posterior median and 95% CrI) for the outcome of Mortality
4.2 Hospitalisation

Summary of Evidence Network

Table 4.2: Summary of evidence network, Hospitalisation

| Characteristic                                      | Value     |
|----------------------------------------------------|-----------|
| Number of Interventions                            | 5         |
| Number of Studies                                  | 6         |
| Total Number of Patients in Network                | 8976      |
| Total Possible Pairwise Comparisons                | 10        |
| Total Number of Pairwise Comparisons With Direct Data | 6         |
| Is the network connected?                          | TRUE      |
| Number of Two-arm Studies                          | 5         |
| Number of Multi-Arms Studies                       | 1         |
| Total Number of Events in Network                  | 494       |
| Number of Studies With No Zero Events              | 6         |
| Number of Studies With At Least One Zero Event      | 0         |
| Number of Studies with All Zero Events             | 0         |

Table 4.2: Summary of comparison data, Hospitalisation

| comparison      | n.studies | n.patients | n.outcomes | proportion  |
|-----------------|-----------|------------|------------|-------------|
| bam vs. bam_ete | 1         | 1013       | 146        | 0.1441264   |
| comparison          | n.studies | n.patients | n.outcomes | proportion     |
|---------------------|-----------|------------|------------|----------------|
| bam vs. cas_imd     | 1         | 1050       | 148        | 0.1409524      |
| bam_ete vs. cas_imd | 1         | 1807       | 262        | 0.1449917      |
| bam_ete vs. pbo     | 2         | 1804       | 62         | 0.0343681      |
| cas_imd vs. pbo     | 2         | 4180       | 119        | 0.0284689      |
| pbo vs. sot         | 1         | 1057       | 35         | 0.0331126      |

Figure 4.5: Pairwise comparisons: estimates of relative risk (posterior median and 95% CrI) for the outcome of Hospitalisation
Figure 4.6: Estimates of relative risk for each mAB versus placebo (posterior median and 95% CrI) for the outcome of Hospitalisation

4.3 Invasive Ventilation

Summary of Evidence Network

Figure 4.7: Network diagram, Invasive Ventilation

Table 4.3: Summary of evidence network, Invasive Ventilation

| Characteristic                                      | Value   |
|-----------------------------------------------------|---------|
| Number of Interventions                            | 3       |
| Number of Studies                                  | 3       |
| Total Number of Patients in Network                 | 5237    |
| Total Possible Pairwise Comparisons                 | 3       |
| Total Number of Pairwise Comparisons With Direct Data| 2       |
| Is the network connected?                           | TRUE    |
| Number of Two-arm Studies                           | 3       |
| Number of Multi-Arms Studies                        | 0       |
| Total Number of Events in Network                   | 14      |
| Number of Studies With No Zero Events               | 2       |
| Number of Studies With At Least One Zero Event       | 1       |
| Number of Studies with All Zero Events              | 0       |
Table 4.3: Summary of comparison data, Invasive Ventilation

| comparison         | n.studies | n.patients | n.outcomes | proportion |
|--------------------|-----------|------------|------------|------------|
| cas_imd vs. pbo    | 2         | 4180       | 10         | 0.0023923  |
| pbo vs. sot        | 1         | 1057       | 4          | 0.0037843  |

Figure 4.8: Pairwise comparisons: estimates of relative risk (posterior median and 95% CrI) for the outcome of Invasive Ventilation

Figure 4.9: Estimates of relative risk for each mAB versus placebo (posterior median and 95% CrI) for the outcome of Invasive Ventilation
4.4 ICU Admission

Summary of Evidence Network

Figure 4.10: Network diagram, ICU Admission

Table 4.4: Summary of evidence network, ICU Admission

| Characteristic                                           | Value     |
|----------------------------------------------------------|-----------|
| Number of Interventions                                | 3         |
| Number of Studies                                      | 3         |
| Total Number of Patients in Network                     | 5237      |
| Total Possible Pairwise Comparisons                    | 3         |
| Total Number of Pairwise Comparisons With Direct Data   | 2         |
| Is the network connected?                              | TRUE      |
| Number of Two-arm Studies                              | 3         |
| Number of Multi-Arms Studies                            | 0         |
| Total Number of Events in Network                       | 44        |
| Number of Studies With No Zero Events                   | 2         |
| Number of Studies With At Least One Zero Event          | 1         |
| Number of Studies with All Zero Events                  | 0         |

Table 4.4: Summary of comparison data, ICU Admission

| comparison       | n.studies | n.patients | n.outcomes | proportion   |
|------------------|-----------|------------|------------|--------------|
| cas_imd vs. pbo  | 2         | 4180       | 34         | 0.0081340    |
| comparison  | n.studies | n.patients | n.outcomes | proportion |
|------------|-----------|------------|------------|------------|
| pbo vs. sot| 1         | 1057       | 10         | 0.0094607  |

Figure 4.11: Pairwise comparisons: estimates of relative risk (posterior median and 95% CrI) for the outcome of ICU Admission

Figure 4.12: Estimates of relative risk for each mAB versus placebo (posterior median and 95% CrI) for the outcome of ICU Admission
4.5 Infusion-related AEs

Summary of Evidence Network

Figure 4.13: Network diagram, Infusion-related AEs

Table 4.5: Summary of evidence network, Infusion-related AEs

| Characteristic                                      | Value       |
|-----------------------------------------------------|-------------|
| Number of Interventions                            | 5           |
| Number of Studies                                  | 3           |
| Total Number of Patients in Network                 | 7503        |
| Total Possible Pairwise Comparisons                 | 10          |
| Total Number of Pairwise Comparisons With Direct Data| 5           |
| Is the network connected?                          | TRUE        |
| Number of Two-arm Studies                          | 2           |
| Number of Multi-Arms Studies                       | 1           |
| Total Number of Events in Network                   | 36          |
| Number of Studies With No Zero Events               | 1           |
| Number of Studies With At Least One Zero Event      | 2           |
| Number of Studies with All Zero Events              | 0           |

Table 4.5: Summary of comparison data, Infusion-related AEs

| comparison          | n.studies | n.patients | n.outcomes | proportion |
|---------------------|-----------|------------|------------|------------|
| bam vs. bam_ete     | 1         | 1013       | 12         | 0.0118460  |
| comparison          | n.studies | n.patients | n.outcomes | proportion |
|---------------------|-----------|------------|------------|------------|
| bam vs. cas_imd     | 1         | 1050       | 9          | 0.0085714  |
| bam_ete vs. cas_imd | 1         | 1807       | 21         | 0.0116215  |
| cas_imd vs. pbo     | 1         | 4519       | 3          | 0.0006639  |
| pbo vs. sot         | 1         | 1049       | 12         | 0.0114395  |

Figure 4.14: Pairwise comparisons: estimates of relative risk (posterior median and 95% CrI) for the outcome of Infusion-related AEs

Figure 4.15: Estimates of relative risk for each mAB versus placebo (posterior median and 95% CrI) for the outcome of Infusion-related AEs
4.6 Serious AEs

Summary of Evidence Network

Figure 4.16: Network diagram, Serious AEs

Table 4.6: Summary of evidence network, Serious AEs

| Characteristic                                      | Value          |
|----------------------------------------------------|----------------|
| Number of Interventions                            | 5              |
| Number of Studies                                  | 5              |
| Total Number of Patients in Network                | 9307           |
| Total Possible Pairwise Comparisons                | 10             |
| Total Number of Pairwise Comparisons With Direct Data | 7              |
| Is the network connected?                          | TRUE           |
| Number of Two-arm Studies                          | 4              |
| Number of Multi-Arms Studies                        | 1              |
| Total Number of Events in Network                  | 175            |
| Number of Studies With No Zero Events              | 4              |
| Number of Studies With At Least One Zero Event      | 1              |
| Number of Studies with All Zero Events              | 0              |

Table 4.6: Summary of comparison data, Serious AEs

| comparison     | n.studies | n.patients | n.outcomes | proportion  |
|----------------|-----------|------------|------------|-------------|
| bam vs. bam_ete| 1         | 1013       | 1          | 0.0009872   |
| comparison          | n.studies | n.patients | n.outcomes | proportion |
|---------------------|-----------|------------|------------|------------|
| bam vs. cas_imd     | 1         | 1050       | 4          | 0.0038095  |
| bam_ete vs. bam_ete | 4         | 3076       | 32         | 0.0104031  |
| bam_ete vs. cas_imd | 1         | 1807       | 5          | 0.0027670  |
| bam_ete vs. pbo     | 1         | 1035       | 12         | 0.0115942  |
| cas_imd vs. pbo     | 1         | 4519       | 107        | 0.0236778  |
| pbo vs. sot         | 1         | 1049       | 43         | 0.0409914  |

Figure 4.17: Pairwise comparisons: estimates of relative risk (posterior median and 95% CrI) for the outcome of Serious AEs
4.7 Pooled mAB effects

Table 4.7: Estimated pooled effects for mABs versus placebo, all outcomes

| Outcome               | RR..mABs.vs.Placebo |
|-----------------------|----------------------|
| Mortality             | 0.07 (0.01 to 0.25)  |
| Hospitalisation       | 0.26 (0.18 to 0.36)  |
| Invasive Ventilation  | 0.13 (0.02 to 0.51)  |
| ICU Admission         | 0.22 (0.08 to 0.54)  |
| Infusion-related AEs  | 1.08 (0.36 to 3.51)  |
| Serious AEs           | 0.39 (0.22 to 0.87)  |

Figure 4.19: Estimated pooled effects for mABs versus placebo, all outcomes

4.8 Inclusion of regdanvimab as intervention

In this section we explore the effect of including results from (Eom et al., 2021), which compared regdanvimab and placebo in a mixed-risk population, in the NMA. This study was excluded during the rapid review as results were not reported separately for the high-risk subpopulation. It has been included as a scenario analysis as it has been licensed in the EU for the population of interest to this review (adults with COVID-19 who are at increased risk of progressing to severe COVID-19). The study contained three arms: regdanvimab 40mg/kg, regdanvimab 80mg/kg, and placebo. For consistency with other comparisons in the network, outcomes for regdanvimab were pooled across 40mg/kg and 80mg/kg arms.

All relevant outcomes were considered for inclusion in this scenario analysis:
- Mortality: excluded as no events in either arm
- Hospitalisation: included
- Invasive ventilation: excluded as no events observed in placebo arm (1 event in treatment arm), therefore it was not possible to estimate a relative-risk for regdanvimab versus placebo for this outcome. While an RR for placebo versus regdanvimab could in theory be estimated this would be highly uncertain due to there being only a single event in the regdanvimab arm.
- ICU admission: excluded as no events in either arm
- Infusion-related AEs: included
- Serious AEs: excluded as no events in either arm

### 4.8.1 Hospitalisation

![Figure 4.20: Pairwise comparisons: estimates of relative risk (posterior median and 95% CrI) for the outcome of Hospitalisation, scenario analysis including regdanvimab data from (Eom et al., 2021)](image-url)
4.8.2 Infusion-related AEs

Figure 4.21: Relative risk estimates versus placebo (posterior median and 95% CrI) for the outcome of Hospitalisation, scenario analysis including reganvimab data from (Eom et al., 2021)

Figure 4.22: Pairwise comparisons: estimates of relative risk (posterior median and 95% CrI) for the outcome of Infusion-related AEs, scenario analysis including reganvimab data from (Eom et al., 2021)
4.9 Absolute Risk Reductions

For all dichotomous outcomes, baseline event rates under SoC have been estimated by pooling the rates from the SoC arms across trials using a Bayesian random-effects model, analogous to the model used for relative treatment effects but with a random intercept term only (see NICE TSD 5 (Dias et al., 2013b)). In all cases, event rates from (Eom et al., 2021) have been excluded from this calculation as this study included non-high-risk patients, who are likely to exhibit lower baseline event rates for most outcomes compared with the target population.

Absolute risks and risk differences for regdanvimab have therefore been estimated by applying the relative effects for regdanvimab versus placebo, to baseline event rates estimated from the remaining studies. This approaches assumes that the relative effect of regdanvimab versus placebo will generalise to the higher-risk populations of the other studies.

4.9.1 Mortality

Table 4.8: Absolute risks and risk difference per 1000 (posterior median and 95% CrI) for the outcome of Mortality

| Treatment | Absolute.risks.per.1.000 | Comparison | Risk.difference.per.1.000 |
|-----------|---------------------------|------------|---------------------------|
| pbo       | 5.57 (0.76, 31.99)        | pbo_vs_pbo | 0.00 (0.00, 0.00)         |
| bam       | 1.19 (0.06, 16.86)        | bam_vs_pbo | -3.66 (-23.21, 3.35)      |
| bam_ete   | 0.45 (0.04, 4.24)         | bam_ete_vs_pbo | -4.98 (-28.57, -0.66) |
| cas_imd   | 0.70 (0.06, 7.19)         | cas_imd_vs_pbo | -4.59 (-27.30, -0.52) |
| sot       | 0.39 (0.00, 12.94)        | sot_vs_pbo | -4.44 (-27.12, 1.85)      |
| Treatment       | Absolute.risks.per.1.000 | Comparison              | Risk.difference.per.1.000 |
|-----------------|--------------------------|-------------------------|---------------------------|
| pooled_mABs     | 0.37 (0.03, 3.26)        | pooled_mABs_vs_pbo      | -5.09 (-29.77, -0.68)     |

**Figure 4.24**: Absolute risks per 1000 for each treatment (top) and risk difference per 1000 patients for each treatment versus placebo (bottom) for the outcome of Mortality

### 4.9.2 Hospitalisation

**Table 4.8**: Absolute risks and risk difference per 1000 (posterior median and 95% CrI) for the outcome of Hospitalisation

| Treatment       | Absolute.risks.per.1.000 | Comparison              | Risk.difference.per.1.000 |
|-----------------|--------------------------|-------------------------|---------------------------|
| pbo             | 49.51 (26.79, 89.50)     | pbo_vs_pbo              | 0.00 (0.00, 0.00)         |
| bam             | 11.94 (4.37, 31.83)      | bam_vs_pbo              | -36.87 (-67.96, -16.06)   |
| bam_ete         | 13.18 (5.65, 28.29)      | bam_ete_vs_pbo          | -36.17 (-66.43, -17.95)   |
| cas_imd         | 13.39 (6.11, 28.84)      | cas_imd_vs_pbo          | -35.77 (-65.10, -18.09)   |
| sot             | 10.02 (2.98, 31.50)      | sot_vs_pbo              | -38.65 (-70.99, -16.54)   |
| pooled_mABs     | 12.59 (6.36, 24.56)      | pooled_mABs_vs_pbo      | -36.71 (-66.55, -19.63)   |
| *reg            | 23.27 (6.89, 75.05)      | *reg_vs_pbo             | -25.43 (-54.63, 17.01)    |
4.9.3 Invasive Ventilation

Table 4.8: Absolute risks and risk difference per 1000 (posterior median and 95% CrI) for the outcome of Invasive Ventilation

| Treatment   | Absolute.risks.per.1.000     | Comparison     | Risk.difference.per.1.000   |
|-------------|------------------------------|----------------|-----------------------------|
| pbo         | 4.37 (1.30, 13.92)           | pbo_vs_pbo     | 0.00 (0.00, 0.00)           |
| cas_imd     | 0.86 (0.10, 5.85)            | cas_imd_vs_pbo | -3.26 (-10.65, -0.17)       |
| sot         | 0.21 (0.00, 3.93)            | sot_vs_pbo     | -3.89 (-12.59, -0.60)       |
| pooled_mABs | 0.55 (0.07, 3.40)            | pooled_mABs_vs_pbo | -3.64 (-11.72, -0.92)     |
Figure 4.26: Absolute risks per 1000 for each treatment (top) and risk difference per 1000 patients for each treatment versus placebo (bottom) for the outcome of Invasive Ventilation.

4.9.4 ICU Admission

Table 4.8: Absolute risks and risk difference per 1000 (posterior median and 95% CrI) for the outcome of ICU Admission

| Treatment  | Absolute.risks.per.1.000 | Comparison       | Risk.difference.per.1.000 |
|------------|--------------------------|------------------|---------------------------|
| pbo        | 13.17 (5.06, 32.52)      | pbo_vs_pbo       | 0.00 (0.00, 0.00)         |
| cas_imd    | 4.39 (1.09, 16.13)       | cas_imd_vs_pbo   | -8.37 (-22.31, -0.87)     |
| sot        | 0.36 (0.01, 4.79)        | sot_vs_pbo       | -12.43 (-30.90, -4.28)    |
| pooled_mABs| 2.91 (0.75, 10.25)       | pooled_mABs_vs_pbo| -9.93 (-25.44, -3.24)     |
4.9.5 Infusion-related AEs

Table 4.8: Absolute risks and risk difference per 1000 (posterior median and 95% CrI) for the outcome of Infusion-related AEs

| Treatment      | Absolute.risks.per.1.000 | Comparison     | Risk.difference.per.1.000 |
|----------------|--------------------------|----------------|---------------------------|
| pbo            | 2.30 (0.13, 27.78)       | pbo_vs_pbo     | 0.00 (0.00, 0.00)         |
| bam            | 2.22 (0.04, 84.88)       | bam_vs_pbo     | -0.01 (-10.51, 67.84)     |
| bam_ete        | 5.57 (0.16, 157.93)      | bam_ete_vs_pbo | 2.61 (-3.75, 134.49)      |
| cas_imd        | 4.12 (0.12, 99.29)       | cas_imd_vs_pbo | 1.31 (-5.02, 83.63)       |
| sot            | 1.95 (0.09, 33.88)       | sot_vs_pbo     | -0.15 (-7.96, 13.83)      |
| pooled_mABs    | 2.43 (0.12, 37.50)       | pooled_mABs_vs_pbo | 0.08 (-5.06, 16.26) |
| *reg           | 0.45 (0.01, 12.23)       | *reg_vs_pbo    | -1.44 (-20.93, 2.06)      |
Figure 4.28: Absolute risks per 1000 for each treatment (top) and risk difference per 1000 patients for each treatment versus placebo (bottom) for the outcome of Infusion-related AEs

4.9.6 Serious AEs

Table 4.8: Absolute risks and risk difference per 1000 (posterior median and 95% CrI) for the outcome of Serious AEs

| Treatment      | Absolute.risks.per.1.000 | Comparison       | Risk.difference.per.1.000 |
|----------------|--------------------------|------------------|---------------------------|
| pbo            | 31.56 (4.74, 155.22)     | pbo_vs_pbo       | 0.00 (0.00, 0.00)         |
| bam            | 33.57 (1.19, 550.43)     | bam_vs_pbo       | 2.35 (-66.81, 461.39)     |
| bam_ete        | 17.87 (2.00, 133.37)     | bam_ete_vs_pbo   | -10.33 (-77.12, 44.18)    |
| cas_imd        | 13.45 (1.68, 108.51)     | cas_imd_vs_pbo   | -15.40 (-87.92, 26.03)    |
| sot            | 10.73 (1.15, 85.30)      | sot_vs_pbo       | -18.21 (-100.65, 8.31)    |
| pooled_mABs    | 12.31 (1.71, 70.08)      | pooled_mABs_vs_pbo| -18.07 (-93.31, -1.47)    |
5  Sensitivity Analysis

5.1  Treatment effects prior

For all outcomes we investigate the following alternative priors for the treatment effect parameters:

1. More informative prior: N(0,1.175^2). This distribution gives a 95% prior probability that no relative risk between any pair of treatments in the network exceeds 10 (note that 0.175=log(10)/1.96).

2. Less informative prior: N(0,4.700^2). This distribution gives a 95% prior probability that no relative risk between any pair of treatments in the network exceeds 10,000 (note that 4.700=log(10000)/1.96).

5.1.1  Mortality

Table 4.9: NMA sensitivity analysis results for the outcome of Mortality, using a prior distribution of N(0,1.2^2) for the treatment effect parameters.
|                      | pbo     | bam     | bam_ete  | cas_imd  | sot      |
|----------------------|---------|---------|----------|----------|----------|
| bam_ete              | 5.39 (1.81 to 16.42) | 3.22 (0.65 to 15.22) | bam_ete  | 1.53 (0.47 to 5.88) | 1.91 (0.22 to 15.60) |
| cas_imd              | 3.49 (1.01 to 10.91) | 2.09 (0.40 to 9.25) | 0.65 (0.17 to 2.13) | cas_imd  | 1.23 (0.13 to 10.08) |
| sot                  | 2.81 (0.47 to 18.61) | 1.68 (0.16 to 18.80) | 0.52 (0.06 to 4.53) | 0.82 (0.10 to 7.58) | sot      |

**Table 4.10: NMA sensitivity analysis results for the outcome of Mortality, using a prior distribution of \( N(0,2.8^2) \) for the treatment effect parameters.**

|                      | pbo     | bam     | bam_ete  | cas_imd  | sot      |
|----------------------|---------|---------|----------|----------|----------|
| pbo                  | pbo     | 0.22 (0.02 to 1.59) | 0.08 (0.02 to 0.31) | 0.13 (0.03 to 0.55) | 0.07 (0.00 to 1.29) |
| bam                  | 4.46 (0.63 to 40.91) | bam     | 0.36 (0.06 to 2.64) | 0.55 (0.11 to 4.18) | 0.32 (0.00 to 12.18) |
| bam_ete              | 11.98 (3.23 to 60.09) | 2.75 (0.38 to 16.83) | bam_ete  | 1.51 (0.43 to 6.84) | 0.87 (0.01 to 23.62) |
| cas_imd              | 7.81 (1.81 to 39.17) | 1.81 (0.24 to 9.49) | 0.66 (0.15 to 2.35) | cas_imd  | 0.56 (0.01 to 14.90) |
| sot                  | 13.96 (0.78 to 971.39) | 3.15 (0.08 to 309.82) | 1.15 (0.04 to 100.99) | 1.80 (0.07 to 156.69) | sot      |

**Table 4.11: NMA sensitivity analysis results for the outcome of Mortality, using a prior distribution of \( N(0,4.7^2) \) for the treatment effect parameters.**
5.1.2 Hospitalisation

Table 4.12: NMA sensitivity analysis results for the outcome of Hospitalisation, using a prior distribution of N(0,1.2^2) for the treatment effect parameters.

|     | pbo   | bam   | bam_ete | cas_imd | sot    |
|-----|-------|-------|---------|---------|--------|
| pbo | pbo   | 0.29  | 0.30    | 0.30    | 0.25   |
|     |       | (0.14 to 0.73) | (0.18 to 0.52) | (0.19 to 0.54) | (0.10 to 0.68) |
|     | pbo          | bam          | bam_ete       | cas_imd       | sot          |
|-----|--------------|--------------|---------------|---------------|--------------|
| bam | 3.48 (1.38 to 7.10) | bam | 1.03 (0.45 to 2.02) | 1.04 (0.47 to 2.07) | 0.85 (0.25 to 2.79) |
| bam_ete | 3.37 (1.91 to 5.64) | 0.97 (0.50 to 2.24) | bam_ete | 1.00 (0.60 to 1.82) | 0.83 (0.29 to 2.54) |
| cas_imd | 3.34 (1.86 to 5.32) | 0.96 (0.48 to 2.12) | 1.00 (0.55 to 1.66) | cas_imd | 0.82 (0.28 to 2.40) |
| sot | 4.03 (1.48 to 10.39) | 1.17 (0.36 to 4.08) | 1.20 (0.39 to 3.49) | 1.22 (0.42 to 3.54) | sot |

**Table 4.13**: NMA sensitivity analysis results for the outcome of Hospitalisation, using a prior distribution of N(0,2.8^2) for the treatment effect parameters.

|     | pbo          | bam          | bam_ete       | cas_imd       | sot          |
|-----|--------------|--------------|---------------|---------------|--------------|
| pbo | 0.24 (0.10 to 0.55) | 0.27 (0.15 to 0.45) | 0.27 (0.16 to 0.45) | 0.20 (0.07 to 0.56) |
| bam | 4.12 (1.83 to 9.67) | bam | 1.10 (0.51 to 2.30) | 1.11 (0.54 to 2.41) | 0.83 (0.21 to 3.13) |
| bam_ete | 3.75 (2.24 to 6.73) | 0.91 (0.43 to 1.96) | bam_ete | 1.01 (0.62 to 1.83) | 0.76 (0.23 to 2.46) |
| cas_imd | 3.69 (2.21 to 6.21) | 0.90 (0.42 to 1.85) | 0.99 (0.55 to 1.62) | cas_imd | 0.75 (0.22 to 2.31) |
| sot | 4.94 (1.80 to 15.04) | 1.20 (0.32 to 4.74) | 1.31 (0.41 to 4.42) | 1.34 (0.43 to 4.53) | sot |

**Table 4.14**: NMA sensitivity analysis results for the outcome of Hospitalisation, using a prior distribution of N(0,4.7^2) for the treatment effect parameters.

|     | pbo          | bam          | bam_ete       | cas_imd       | sot          |
|-----|--------------|--------------|---------------|---------------|--------------|
| pbo | 0.23 (0.10 to 0.53) | 0.26 (0.14 to 0.44) | 0.27 (0.15 to 0.45) | 0.19 (0.06 to 0.54) |
| bam | 4.26 (1.90 to 10.21) | bam | 1.11 (0.51 to 2.34) | 1.13 (0.55 to 2.49) | 0.82 (0.21 to 3.16) |
| bam_ete | 3.82 (2.29 to 7.09) | 0.90 (0.43 to 1.95) | bam_ete | 1.01 (0.61 to 1.85) | 0.74 (0.22 to 2.47) |
| cas_imd | 3.75 (2.25 to 6.46) | 0.88 (0.40 to 1.83) | 0.99 (0.54 to 1.63) | cas_imd | 0.72 (0.21 to 2.32) |
| sot | 5.17 (1.86 to 15.97) | 1.22 (0.32 to 4.81) | 1.35 (0.41 to 4.62) | 1.38 (0.43 to 4.73) | sot |
5.1.3 Invasive Ventilation

Table 4.15: NMA sensitivity analysis results for the outcome of Invasive Ventilation, using a prior distribution of $N(0,1.2^2)$ for the treatment effect parameters.

|       | pbo     | cas_imd | sot       |
|-------|---------|---------|-----------|
| pbo   | pbo     | 0.32 (0.08 to 1.14) | 0.26 (0.04 to 1.34) |
| cas_imd | 3.12 (0.88 to 12.41) | 0.81 (0.09 to 6.78) |
### Table 4.16: NMA sensitivity analysis results for the outcome of Invasive Ventilation, using a prior distribution of $N(0,2.8^2)$ for the treatment effect parameters.

|        | pbo                | cas_imd        | sot        |
|--------|--------------------|----------------|------------|
| sot    | 3.90 (0.74 to 22.99) | 1.24 (0.15 to 10.88) | sot        |

### Table 4.17: NMA sensitivity analysis results for the outcome of Invasive Ventilation, using a prior distribution of $N(0,4.7^2)$ for the treatment effect parameters.

|        | pbo                | cas_imd        | sot        |
|--------|--------------------|----------------|------------|
| pbo    | pbo                | 0.20 (0.03 to 0.89) | 0.05 (0.00 to 0.70) |
| cas_imd| 4.95 (1.13 to 31.27) | cas_imd       | 0.24 (0.00 to 6.34) |
| sot    | 20.33 (1.43 to 1015.15) | 4.13 (0.16 to 272.44) | sot        |
Figure 4.32: Sensitivity analysis using alternative prior distributions for the treatment effect parameter (log relative risk), for the outcome of Invasive Ventilation. Top: Efficacy prior $N(0,1.2^2)$ (more informative), middle: Efficacy prior $N(0,2.8^2)$ (base case), bottom: Efficacy prior $N(0,4.7^2)$ (less informative).

5.1.4 ICU Admission

Table 4.18: NMA sensitivity analysis results for the outcome of ICU Admission, using a prior distribution of $N(0,1.2^2)$ for the treatment effect parameters.

|     | pbo              | cas_imd            | sot               |
|-----|------------------|--------------------|-------------------|
| pbo | pbo              | 0.38 (0.15 to 1.02)| 0.16 (0.03 to 0.74)|
| cas_imd | 2.63 (0.98 to 6.46) | cas_imd           | 0.40 (0.06 to 2.42)|
Table 4.19: NMA sensitivity analysis results for the outcome of ICU Admission, using a prior distribution of N(0,2.8^2) for the treatment effect parameters.

|     | pbo      | cas_imd   | sot       |
|-----|----------|-----------|-----------|
| pbo | 6.41 (1.35 to 34.70) | 2.47 (0.41 to 16.37) | sot       |
| cas_imd | 2.99 (1.14 to 8.24) | cas_imd   | 0.08 (0.00 to 1.12) |
| sot  | 37.97 (3.37 to 1670.79) | 12.78 (0.89 to 628.92) | sot       |

Table 4.20: NMA sensitivity analysis results for the outcome of ICU Admission, using a prior distribution of N(0,4.7^2) for the treatment effect parameters.

|     | pbo      | cas_imd   | sot       |
|-----|----------|-----------|-----------|
| pbo | 0.33 (0.12 to 0.87)  | 0.03 (0.00 to 0.30)  | sot       |
| cas_imd | 3.04 (1.15 to 8.46) | cas_imd   | 0.02 (0.00 to 0.73) |
| sot  | 152.45 (5.02 to 101024.47) | 50.44 (1.37 to 34553.72) | sot       |
5.1.5 Infusion-related AEs

Table 4.21: NMA sensitivity analysis results for the outcome of Infusion-related AEs, using a prior distribution of $N(0,1.2^2)$ for the treatment effect parameters.

|     | pbo | bam     | bam_ete | cas_imd   | sot     |
|-----|-----|---------|---------|-----------|---------|
| pbo | pbo | 0.88 (0.14 to 4.42) | 1.63 (0.39 to 6.58) | 1.28 (0.36 to 4.65) | 0.90 (0.27 to 2.96) |

Figure 4.33: Sensitivity analysis using alternative prior distributions for the treatment effect parameter (log relative risk), for the outcome of ICU Admission. Top: Efficacy prior $N(0,1.2^2)$ (more informative), middle: Efficacy prior $N(0,2.8^2)$ (base case), bottom: Efficacy prior $N(0,4.7^2)$ (less informative).
Table 4.22: NMA sensitivity analysis results for the outcome of Infusion-related AEs, using a prior distribution of $N(0,2.8^2)$ for the treatment effect parameters.

|     | pbo       | bam       | bam_ete   | cas_imd    | sot       |
|-----|-----------|-----------|-----------|------------|-----------|
| pbo |           |           |           |            |           |
| bam | 1.14 (0.23 to 7.12) |        | 1.82 (0.36 to 12.59) | 1.44 (0.30 to 9.57) | 1.03 (0.14 to 8.94) |
| bam_ete | 0.62 (0.15 to 2.54) | 0.55 (0.08 to 2.80) | 0.78 (0.26 to 2.46) |          | 0.55 (0.09 to 3.52) |
| cas_imd | 0.78 (0.22 to 2.80) | 0.70 (0.10 to 3.38) | 1.28 (0.41 to 3.80) | cas_imd   | 0.70 (0.12 to 4.00) |
| sot  | 1.12 (0.34 to 3.69) | 0.97 (0.11 to 7.40) | 1.83 (0.28 to 11.31) | 1.44 (0.25 to 8.23) | sot       |

Table 4.23: NMA sensitivity analysis results for the outcome of Infusion-related AEs, using a prior distribution of $N(0,4.7^2)$ for the treatment effect parameters.

|     | pbo       | bam       | bam_ete   | cas_imd    | sot       |
|-----|-----------|-----------|-----------|------------|-----------|
| pbo |           |           |           |            |           |
| bam | 0.84 (0.03 to 28.90) |        | 2.36 (0.32 to 51.36) | 1.72 (0.23 to 37.83) | 0.72 (0.02 to 32.38) |
| bam_ete | 0.33 (0.02 to 4.06) | 0.42 (0.02 to 3.11) | 0.73 (0.20 to 2.69) |          | 0.28 (0.01 to 5.16) |
| cas_imd | 0.46 (0.03 to 4.12) | 0.58 (0.03 to 4.32) | 1.37 (0.37 to 4.94) | cas_imd   | 0.39 (0.02 to 5.59) |
| sot  | 1.16 (0.27 to 5.12) | 1.39 (0.03 to 50.31) | 3.53 (0.19 to 90.40) | 2.54 (0.18 to 55.10) | sot       |
Figure 4.34: Sensitivity analysis using alternative prior distributions for the treatment effect parameter (log relative risk), for the outcome of Infusion-related AEs. Top: Efficacy prior $N(0,1.2^2)$ (more informative), middle: Efficacy prior $N(0,2.8^2)$ (base case), bottom: Efficacy prior $N(0,4.7^2)$ (less informative)

5.1.6 Serious AEs

Table 4.24: NMA sensitivity analysis results for the outcome of Serious AEs, using a prior distribution of $N(0,1.2^2)$ for the treatment effect parameters.

|       | pbo   | bam   | bam_ete | cas_imd | sot   |
|-------|-------|-------|---------|---------|-------|
| pbo   | pbo   | 1.16 (0.19 to 6.11) | 0.64 (0.21 to 1.94) | 0.45 (0.21 to 1.58) | 0.40 (0.15 to 1.42) |
|      | pbo       | bam       | bam_ete    | cas_imd    | sot       |
|------|-----------|-----------|------------|------------|-----------|
| bam  | 0.86 (0.16 to 5.40) | bam       | 0.55 (0.09 to 4.12) | 0.41 (0.07 to 3.12) | 0.36 (0.05 to 3.15) |
| bam_ete | 1.56 (0.51 to 4.71) | 1.82 (0.24 to 11.39) | bam_ete    | 0.73 (0.21 to 3.35) | 0.63 (0.14 to 3.40) |
| cas_imd | 2.23 (0.63 to 4.70) | 2.45 (0.32 to 13.62) | 1.38 (0.30 to 4.66) | cas_imd    | 0.89 (0.19 to 3.35) |
| sot   | 2.48 (0.71 to 6.86) | 2.82 (0.32 to 19.73) | 1.58 (0.29 to 6.95) | 1.12 (0.30 to 5.40) | sot       |

**Table 4.25:** NMA sensitivity analysis results for the outcome of Serious AEs, using a prior distribution of $N(0,2.8^2)$ for the treatment effect parameters.

|      | pbo       | bam       | bam_ete    | cas_imd    | sot       |
|------|-----------|-----------|------------|------------|-----------|
| pbo  | 1.12 (0.07 to 10.86) | 0.58 (0.15 to 2.07) | 0.41 (0.17 to 1.69) | 0.34 (0.10 to 1.34) |
| bam  | 0.89 (0.09 to 13.92) | bam       | 0.51 (0.05 to 8.22) | 0.39 (0.04 to 6.60) | 0.31 (0.02 to 6.29) |
| bam_ete | 1.72 (0.48 to 6.64) | 1.96 (0.12 to 19.65) | bam_ete    | 0.74 (0.20 to 4.18) | 0.60 (0.10 to 4.09) |
| cas_imd | 2.44 (0.59 to 5.77) | 2.58 (0.15 to 22.58) | 1.36 (0.24 to 5.03) | cas_imd    | 0.83 (0.12 to 3.73) |
| sot   | 2.90 (0.75 to 10.51) | 3.19 (0.16 to 44.39) | 1.68 (0.24 to 9.98) | 1.20 (0.27 to 8.53) | sot       |

**Table 4.26:** NMA sensitivity analysis results for the outcome of Serious AEs, using a prior distribution of $N(0,4.7^2)$ for the treatment effect parameters.
Figure 4.35: Sensitivity analysis using alternative prior distributions for the treatment effect parameter (log relative risk), for the outcome of Serious AEs. Top: Efficacy prior $N(0, 1.2^2)$ (more informative), middle: Efficacy prior $N(0, 2.8^2)$ (base case), bottom: Efficacy prior $N(0, 4.7^2)$ (less informative).

| used (Mb) | gc trigger (Mb) | max used (Mb) |
|-----------|-----------------|--------------|
| Ncells    | 2753765 147.1   | 7652530 408.7| 7652530 408.7|
| Vcells    | 52963674 404.1  | 768366254 5862.2 | 5725313688 4368.1 |
5.2 Fixed versus random effects

5.2.1 Mortality

Figure 4.36: Comparison of the fit of fixed and random effects models for the outcome of Mortality

Figure 4.37: Comparison of estimated treatment effects (relative risks) versus placebo for the outcome of Mortality
5.2.2 Hospitalisation

Figure 4.38: Comparison of the fit of fixed and random effects models for the outcome of Hospitalisation

Figure 4.39: Comparison of estimated treatment effects (relative risks) versus placebo for the outcome of Hospitalisation
5.2.3 Invasive Ventilation

Figure 4.40: Comparison of the fit of fixed and random effects models for the outcome of Invasive Ventilation

Figure 4.41: Comparison of estimated treatment effects (relative risks) versus placebo for the outcome of Invasive Ventilation
5.2.4 ICU Admission

Figure 4.42: Comparison of the fit of fixed and random effects models for the outcome of ICU Admission

Figure 4.43: Comparison of estimated treatment effects (relative risks) versus placebo for the outcome of ICU Admission
5.2.5 Infusion-related AEs

Figure 4.44: Comparison of the fit of fixed and random effects models for the outcome of Infusion-related AEs

Figure 4.45: Comparison of estimated treatment effects (relative risks) versus placebo for the outcome of Infusion-related AEs
5.2.6 Serious AEs

Figure 4.46: Comparison of the fit of fixed and random effects models for the outcome of Serious AEs

Figure 4.47: Comparison of estimated treatment effects (relative risks) versus placebo for the outcome of Serious AEs
5.3  Heterogeneity Prior

For all outcomes we examined the sensitivity of the results to the choice of prior distribution for the heterogeneity parameter (between trial standard deviation). The following distributions were examined:

1. Base case: half-normal(0.5)
2. Uniform(0,5)
3. Informative priors from Turner et al. (2012) for the between trial variance: log-normal(-4.06,1.45^2) for mortality and log-normal(-3.02, 1.85^2) for other outcomes
4. Alternative weakly-informative prior: Half-Cauchy(0.5) Röver et al. (2021)

5.3.1 Mortality

Table 4.27: NMA sensitivity analysis results for the outcome of Mortality using the prior distribution HN(0.5) (base case) for the heterogeneity parameter

|      | pbo       | bam       | bam_ete    | cas_imd   | sot       |
|------|-----------|-----------|------------|-----------|-----------|
| pbo  | pbo       | 0.22 (0.02 to 1.63) | 0.08 (0.02 to 0.32) | 0.13 (0.02 to 0.57) | 0.07 (0.00 to 1.27) |
| bam  | 4.51 (0.61 to 42.04) | bam       | 0.37 (0.06 to 2.67) | 0.56 (0.11 to 4.24) | 0.31 (0.00 to 12.13) |
| bam_ete | 11.87 (3.15 to 61.90) | 2.73 (0.37 to 16.85) | bam_ete    | 1.51 (0.43 to 7.03) | 0.84 (0.01 to 23.80) |
| cas_imd | 7.73 (1.74 to 41.24) | 1.79 (0.24 to 9.48) | 0.66 (0.14 to 2.32) | cas_imd   | 0.55 (0.01 to 15.18) |
| sot  | 14.13 (0.79 to 890.81) | 3.24 (0.08 to 321.30) | 1.18 (0.04 to 95.47) | 1.83 (0.07 to 155.52) | sot       |

Table 4.28: NMA sensitivity analysis results for the outcome of Mortality using the prior distribution Unif(0,5) for the heterogeneity parameter

|      | pbo       | bam       | bam_ete    | cas_imd   | sot       |
|------|-----------|-----------|------------|-----------|-----------|
| pbo  | pbo       | 0.32 (0.01 to 16.04) | 0.08 (0.00 to 1.29) | 0.19 (0.02 to 4.30) | 0.10 (0.00 to 7.61) |
| bam  | 3.12 (0.06 to 78.58) | bam       | 0.25 (0.00 to 7.98) | 0.60 (0.01 to 27.17) | 0.30 (0.00 to 61.29) |
| bam_ete | 12.89 (0.77 to 228.23) | 4.08 (0.13 to 305.55) | bam_ete    | 2.39 (0.13 to 114.77) | 1.32 (0.01 to 247.11) |
| cas_imd | 5.18 (0.23 to 54.33) | 1.66 (0.04 to 72.25) | 0.42 (0.01 to 7.58) | cas_imd   | 0.50 (0.00 to 60.55) |
| sot  | 9.54 (0.13 to 804.06) | 3.29 (0.02 to 911.74) | 0.76 (0.00 to 121.18) | 2.00 (0.02 to 344.21) | sot       |
Table 4.29: NMA sensitivity analysis results for the outcome of Mortality using the prior distribution from Turner et al. for the heterogeneity parameter

|       | pbo    | bam    | bam_ete | cas_imd | sot    |
|-------|--------|--------|---------|---------|--------|
| pbo   | pbo    | 0.22 (0.02 to 1.27) | 0.09 (0.02 to 0.28) | 0.12 (0.02 to 0.44) | 0.07 (0.00 to 1.11) |
| bam   | 4.57 (0.79 to 40.33) | bam    | 0.40 (0.09 to 2.50) | 0.53 (0.13 to 3.57) | 0.29 (0.00 to 11.30) |
| bam_ete | 11.06 (3.52 to 49.67) | bam_ete | 2.51 (0.40 to 11.43) | 1.34 (0.46 to 4.26) | 0.74 (0.01 to 17.93) |
| cas_imd | 8.13 (2.25 to 41.30) | cas_imd | 0.75 (0.23 to 2.18) | 0.54 (0.01 to 14.82) |
| sot   | 14.69 (0.90 to 1174.07) | 3.41 (0.09 to 301.53) | 1.36 (0.06 to 108.70) | 1.84 (0.07 to 155.82) | sot    |

Table 4.30: NMA sensitivity analysis results for the outcome of Mortality using the prior distribution Half-Cauchy(0.5) for the heterogeneity parameter

|       | pbo    | bam    | bam_ete | cas_imd | sot    |
|-------|--------|--------|---------|---------|--------|
| pbo   | pbo    | 0.24 (0.02 to 3.32) | 0.08 (0.01 to 0.43) | 0.14 (0.02 to 1.09) | 0.08 (0.00 to 2.11) |
| bam   | 4.24 (0.30 to 50.13) | bam    | 0.35 (0.02 to 3.34) | 0.57 (0.06 to 7.26) | 0.31 (0.00 to 20.03) |
| bam_ete | 12.01 (2.31 to 90.09) | bam_ete | 2.86 (0.30 to 44.29) | 1.62 (0.35 to 19.19) | 0.92 (0.01 to 47.58) |
| cas_imd | 7.13 (0.92 to 42.81) | cas_imd | 1.74 (0.14 to 15.76) | 0.62 (0.05 to 2.85) | 0.53 (0.01 to 21.76) |
| sot   | 13.18 (0.47 to 863.46) | sot    | 3.22 (0.05 to 405.23) | 1.09 (0.02 to 99.07) | 1.90 (0.05 to 193.42) |
5.3.2 Hospitalisation

Table 4.31: NMA sensitivity analysis results for the outcome of Hospitalisation using the prior distribution HN(0.5) (base case) for the heterogeneity parameter

|      | pbo  | bam  | bam_ete | cas_imd | sot   |
|------|------|------|---------|---------|-------|
| pbo  | pbo  | 0.24 (0.10 to 0.56) | 0.27 (0.15 to 0.45) | 0.27 (0.16 to 0.45) | 0.20 (0.07 to 0.55) |
| bam  | 4.13 (1.80 to 9.55) | bam  | 1.10 (0.50 to 2.27) | 1.11 (0.53 to 2.37) | 0.83 (0.21 to 3.09) |
|        | pbo       | bam     | bam_ete  | cas_imd  | sot       |
|--------|-----------|---------|----------|----------|-----------|
| pbo    | 3.75 (2.24 to 6.76) | 0.91 (0.44 to 1.99) | bam_ete | 1.01 (0.61 to 1.83) | 0.76 (0.23 to 2.47) |
| bam    | 3.69 (2.20 to 6.25) | 0.90 (0.42 to 1.87) | 0.99 (0.55 to 1.63) | cas_imd | 0.74 (0.22 to 2.32) |
| sot    | 4.97 (1.81 to 14.99) | 1.21 (0.32 to 4.71) | 1.32 (0.40 to 4.41) | 1.34 (0.43 to 4.50) | sot |

**Table 4.32: NMA sensitivity analysis results for the outcome of Hospitalisation using the prior distribution Unif(0,5) for the heterogeneity parameter**

|        | pbo       | bam     | bam_ete  | cas_imd  | sot       |
|--------|-----------|---------|----------|----------|-----------|
| pbo    | 0.25 (0.08 to 0.92) | 0.27 (0.12 to 0.58) | bam_ete | 0.27 (0.13 to 0.62) | 0.21 (0.06 to 0.84) |
| bam    | 4.08 (1.09 to 12.52) | bam | 1.08 (0.31 to 3.04) | 1.11 (0.34 to 3.30) | 0.84 (0.14 to 4.93) |
| bam_ete | 3.76 (1.72 to 8.34) | 0.92 (0.33 to 3.24) | bam_ete | 1.02 (0.46 to 2.62) | 0.77 (0.18 to 3.95) |
| cas_imd | 3.67 (1.61 to 7.48) | 0.90 (0.30 to 2.94) | 0.98 (0.38 to 2.18) | cas_imd | 0.75 (0.17 to 3.57) |
| sot    | 4.87 (1.18 to 17.59) | 1.20 (0.20 to 7.06) | 1.30 (0.25 to 5.60) | 1.33 (0.28 to 5.94) | sot |

**Table 4.33: NMA sensitivity analysis results for the outcome of Hospitalisation using the prior distribution from Turner et al. for the heterogeneity parameter**

|        | pbo       | bam     | bam_ete  | cas_imd  | sot       |
|--------|-----------|---------|----------|----------|-----------|
| pbo    | 0.24 (0.11 to 0.50) | 0.27 (0.16 to 0.43) | 0.27 (0.17 to 0.43) | 0.20 (0.07 to 0.51) |
| bam    | 4.14 (2.00 to 8.99) | bam | 1.11 (0.57 to 2.15) | 1.12 (0.59 to 2.22) | 0.83 (0.24 to 2.80) |
| bam_ete | 3.73 (2.33 to 6.31) | 0.90 (0.47 to 1.75) | bam_ete | 1.01 (0.66 to 1.64) | 0.75 (0.24 to 2.20) |
| cas_imd | 3.69 (2.33 to 5.91) | 0.89 (0.45 to 1.69) | 0.99 (0.61 to 1.51) | cas_imd | 0.74 (0.24 to 2.11) |
| sot    | 4.99 (1.96 to 14.12) | 1.21 (0.36 to 4.25) | 1.34 (0.45 to 4.13) | 1.35 (0.47 to 4.18) | sot |
Table 4.34: NMA sensitivity analysis results for the outcome of Hospitalisation using the prior distribution Half-Cauchy(0.5) for the heterogeneity parameter

|       | pbo  | bam  | bam_ete | cas_imd | sot  |
|-------|------|------|---------|---------|------|
| pbo   | pbo  | 0.24 (0.10 to 0.57) | 0.27 (0.15 to 0.45) | 0.27 (0.16 to 0.46) | 0.20 (0.07 to 0.57) |
| bam   | 4.11 (1.75 to 9.71) | bam  | 1.09 (0.49 to 2.29) | 1.11 (0.52 to 2.40) | 0.83 (0.20 to 3.15) |
| bam_ete | 3.74 (2.21 to 6.82) | 0.91 (0.44 to 2.05) | bam_ete | 1.01 (0.61 to 1.86) | 0.76 (0.22 to 2.52) |
| cas_imd | 3.69 (2.17 to 6.29) | 0.90 (0.42 to 1.92) | 0.99 (0.54 to 1.64) | cas_imd | 0.75 (0.22 to 2.37) |
| sot   | 4.91 (1.77 to 15.09) | 1.20 (0.32 to 4.92) | 1.31 (0.40 to 4.48) | 1.33 (0.42 to 4.60) | sot  |
Figure 4.49: Estimated treatment effects for each mAB versus placebo obtained from varying the prior distribution on the heterogeneity parameter sigma, for the outcome of Hospitalisation.

5.3.3 Invasive Ventilation
Table 4.35: NMA sensitivity analysis results for the outcome of Invasive Ventilation using the prior distribution HN(0.5) (base case) for the heterogeneity parameter

|        | pbo  | cas_imd       | sot            |
|--------|------|---------------|----------------|
| pbo    | pbo  | 0.20 (0.03 to 0.90) | 0.05 (0.00 to 0.71) |
| cas_imd| 4.96 (1.11 to 31.58) | cas_imd        | 0.25 (0.00 to 6.29) |
| sot    | 19.97 (1.42 to 1038.79) | 4.08 (0.16 to 268.81) | sot |
**Table 4.36: NMA sensitivity analysis results for the outcome of Invasive Ventilation using the prior distribution Unif(0,5) for the heterogeneity parameter**

|       | pbo      | cas_imd   | sot       |
|-------|----------|-----------|-----------|
| pbo   | pbo      | 0.24 (0.01 to 6.71) | 0.08 (0.00 to 6.18) |
| cas_imd | 4.18 (0.15 to 68.02) | cas_imd | 0.30 (0.00 to 52.17) |
| sot   | 12.89 (0.16 to 961.18) | 3.29 (0.02 to 551.16) | sot       |

**Table 4.37: NMA sensitivity analysis results for the outcome of Invasive Ventilation using the prior distribution from Turner et al. for the heterogeneity parameter**

|       | pbo      | cas_imd   | sot       |
|-------|----------|-----------|-----------|
| pbo   | pbo      | 0.20 (0.03 to 0.86) | 0.04 (0.00 to 0.66) |
| cas_imd | 4.92 (1.17 to 29.93) | cas_imd | 0.22 (0.00 to 5.54) |
| sot   | 22.90 (1.53 to 1327.10) | 4.62 (0.18 to 329.12) | sot       |

**Table 4.38: NMA sensitivity analysis results for the outcome of Invasive Ventilation using the prior distribution Half-Cauchy(0.5) for the heterogeneity parameter**

|       | pbo      | cas_imd   | sot       |
|-------|----------|-----------|-----------|
| pbo   | pbo      | 0.20 (0.03 to 1.37) | 0.05 (0.00 to 1.11) |
| cas_imd | 4.89 (0.73 to 35.43) | cas_imd | 0.25 (0.00 to 9.88) |
| sot   | 19.05 (0.90 to 979.67) | 3.96 (0.10 to 298.83) | sot       |
Figure 4.50: Estimated treatment effects for each mAB versus placebo obtained from varying the prior distribution on the heterogeneity parameter sigma, for the outcome of Invasive Ventilation

5.3.4 ICU Admission

Table 4.39: NMA sensitivity analysis results for the outcome of ICU Admission using the prior distribution HN(0.5) (base case) for the heterogeneity parameter

|          | pbo   | cas_imd       | sot            |
|----------|-------|---------------|----------------|
| pbo      | pbo   | 0.33 (0.12 to 0.88) | 0.03 (0.00 to 0.29) |
| cas_imd  | 2.99 (1.14 to 8.24) | cas_imd       | 0.08 (0.00 to 1.08) |
Table 4.40: NMA sensitivity analysis results for the outcome of ICU Admission using the prior distribution Unif(0,5) for the heterogeneity parameter

|       | pbo     | cas_imd | sot      |
|-------|---------|---------|----------|
| sot   | 36.92 (3.44 to 1930.94) | 12.43 (0.92 to 691.76) | sot |

|       | pbo     | cas_imd | sot      |
|-------|---------|---------|----------|
| pbo   | 0.36 (0.03 to 7.11) | 0.04 (0.00 to 3.61) | sot |
| cas_imd | 2.75 (0.14 to 29.44) | 0.11 (0.00 to 17.89) | sot |
| sot   | 23.66 (0.28 to 1321.68) | 9.40 (0.06 to 912.95) | sot |

Table 4.41: NMA sensitivity analysis results for the outcome of ICU Admission using the prior distribution from Turner et al. for the heterogeneity parameter

|       | pbo     | cas_imd | sot      |
|-------|---------|---------|----------|
| pbo   | 0.33 (0.13 to 0.79) | 0.03 (0.00 to 0.27) | sot |
| cas_imd | 3.01 (1.27 to 7.56) | 0.08 (0.00 to 0.99) | sot |
| sot   | 38.76 (3.67 to 1643.79) | 12.92 (1.01 to 598.15) | sot |

Table 4.42: NMA sensitivity analysis results for the outcome of ICU Admission using the prior distribution Half-Cauchy(0.5) for the heterogeneity parameter

|       | pbo     | cas_imd | sot      |
|-------|---------|---------|----------|
| pbo   | 0.34 (0.10 to 1.26) | 0.03 (0.00 to 0.44) | sot |
| cas_imd | 2.95 (0.79 to 9.75) | 0.08 (0.00 to 1.66) | sot |
| sot   | 35.46 (2.29 to 1510.59) | 12.28 (0.60 to 613.12) | sot |
Figure 4.51: Estimated treatment effects for each mAB versus placebo obtained from varying the prior distribution on the heterogeneity parameter sigma, for the outcome of ICU Admission

### 5.3.5 Infusion-related AEs

Table 4.43: NMA sensitivity analysis results for the outcome of Infusion-related AEs using the prior distribution HN(0.5) (base case) for the heterogeneity parameter

|       | pbo   | bam   | bam_ete | cas_imd | sot    |
|-------|-------|-------|---------|---------|--------|
| pbo   |       | 1.06  | (0.05 to 14.74) | 2.49 (0.27 to 26.21) | 1.82 (0.26 to 16.62) | 0.86 (0.21 to 3.54) |
| bam   | 0.95  | (0.07 to 19.21) |     bam   | 2.24 (0.32 to 39.83) | 1.67 (0.25 to 28.08) | 0.82 (0.04 to 22.78) |
|     | pbo   | bam   | bam_ete | cas_imd | sot    |
|-----|-------|-------|---------|---------|--------|
| pbo | pbo   | 0.92 (0.02 to 27.44) | 2.09 (0.06 to 47.30) | 1.67 (0.10 to 26.63) | 0.88 (0.04 to 18.97) |
| bam | 1.09 (0.04 to 43.84) | bam   | 2.20 (0.05 to 101.66) | 1.77 (0.05 to 78.65) | 0.95 (0.01 to 117.23) |
| bam_ete | 0.48 (0.02 to 15.99) | 0.45 (0.01 to 21.04) | bam_ete | 0.79 (0.03 to 26.08) | 0.41 (0.01 to 49.42) |
| cas_imd | 0.60 (0.04 to 10.50) | 0.56 (0.01 to 18.48) | 1.27 (0.04 to 29.04) | cas_imd | 0.51 (0.01 to 37.16) |
| sot | 1.14 (0.05 to 23.09) | 1.05 (0.01 to 89.78) | 2.43 (0.02 to 162.64) | 1.94 (0.03 to 104.35) | sot    |

**Table 4.44: NMA sensitivity analysis results for the outcome of Infusion-related AEs using the prior distribution Unif(0,5) for the heterogeneity parameter**

|     | pbo   | bam   | bam_ete | cas_imd | sot    |
|-----|-------|-------|---------|---------|--------|
| pbo | pbo   | 1.03 (0.05 to 14.65) | 2.58 (0.31 to 24.71) | 1.88 (0.28 to 15.42) | 0.86 (0.23 to 3.25) |
| bam | 0.97 (0.07 to 19.93) | bam   | 2.38 (0.35 to 43.23) | 1.76 (0.27 to 30.06) | 0.86 (0.04 to 22.28) |
| bam_ete | 0.39 (0.04 to 3.20) | 0.42 (0.02 to 2.83) | bam_ete | 0.74 (0.24 to 2.36) | 0.34 (0.02 to 4.08) |
| cas_imd | 0.53 (0.06 to 3.54) | 0.57 (0.03 to 3.76) | 1.36 (0.42 to 4.18) | cas_imd | 0.46 (0.04 to 4.54) |
| sot | 1.16 (0.31 to 4.39) | 1.16 (0.04 to 23.44) | 2.98 (0.24 to 41.48) | 2.19 (0.22 to 26.60) | sot    |

**Table 4.45: NMA sensitivity analysis results for the outcome of Infusion-related AEs using the prior distribution from Turner et al. for the heterogeneity parameter**
Table 4.46: NMA sensitivity analysis results for the outcome of Infusion-related AEs using the prior distribution Half-Cauchy(0.5) for the heterogeneity parameter

|     | pbo   | bam   | bam_ete | cas_imd | sot   |
|-----|-------|-------|---------|---------|-------|
| pbo | pbo   | 0.98 (0.04 to 16.76) | 2.45 (0.21 to 28.19) | 1.82 (0.23 to 17.08) | 0.86 (0.15 to 4.90) |
| bam | 1.02 (0.06 to 22.54) | bam   | 2.37 (0.24 to 44.67) | 1.79 (0.19 to 32.82) | 0.88 (0.03 to 31.04) |
| bam_ete | 0.41 (0.04 to 4.69) | 0.42 (0.02 to 4.18) | bam_ete | 0.75 (0.15 to 4.36) | 0.35 (0.02 to 7.27) |
| cas_imd | 0.55 (0.06 to 4.34) | 0.56 (0.03 to 5.18) | 1.34 (0.23 to 6.54) | cas_imd | 0.46 (0.03 to 7.10) |
| sot  | 1.16 (0.20 to 6.56) | 1.14 (0.03 to 31.36) | 2.88 (0.14 to 54.82) | 2.16 (0.14 to 34.46) | sot   |
5.3.6 Serious AEs

Table 4.47: NMA sensitivity analysis results for the outcome of Serious AEs using the prior distribution HN(0.5) (base case) for the heterogeneity parameter

|     | pbo | bam  | bam_ete | cas_imd | sot   |
|-----|-----|------|---------|---------|-------|
| pbo | pbo | 1.10 (0.06 to 11.20) | 0.58 (0.15 to 2.06) | 0.41 (0.17 to 1.70) | 0.34 (0.09 to 1.35) |
Table 4.48: NMA sensitivity analysis results for the outcome of Serious AEs using the prior distribution $\text{Unif}(0,5)$ for the heterogeneity parameter

|     | pbo          | bam          | bam_ete       | cas_imd       | sot          |
|-----|--------------|--------------|---------------|---------------|--------------|
| pbo | 1.26 (0.04 to 31.77) | 0.56 (0.05 to 6.02) | 0.56 (0.08 to 8.17) | 0.38 (0.03 to 7.97) |
| bam | 0.79 (0.03 to 23.96) | 0.45 (0.01 to 16.80) | 0.47 (0.02 to 19.94) | 0.32 (0.01 to 27.62) |
| bam | 1.77 (0.17 to 19.21) | 2.24 (0.06 to 74.02) | 1.02 (0.08 to 24.81) | 0.68 (0.02 to 34.42) |
| cas_imd | 1.78 (0.12 to 12.70) | 2.11 (0.05 to 47.15) | 0.98 (0.04 to 11.88) | 0.70 (0.02 to 22.64) |
| sot | 2.61 (0.13 to 32.15) | 3.14 (0.04 to 187.89) | 1.46 (0.03 to 43.60) | 1.43 (0.04 to 58.10) |

Table 4.49: NMA sensitivity analysis results for the outcome of Serious AEs using the prior distribution from Turner et al. for the heterogeneity parameter

|     | pbo          | bam          | bam_ete       | cas_imd       | sot          |
|-----|--------------|--------------|---------------|---------------|--------------|
| pbo | 1.10 (0.07 to 10.17) | 0.58 (0.16 to 1.91) | 0.38 (0.19 to 1.50) | 0.34 (0.11 to 1.17) |
| bam | 0.91 (0.10 to 14.47) | 0.52 (0.06 to 8.64) | 0.37 (0.04 to 6.19) | 0.31 (0.03 to 6.29) |
| bam | 1.72 (0.52 to 6.10) | 1.94 (0.12 to 18.14) | 0.68 (0.20 to 3.61) | 0.59 (0.11 to 3.50) |
| cas_imd | 2.63 (0.67 to 5.40) | 2.71 (0.16 to 23.33) | 1.47 (0.28 to 4.92) | 0.88 (0.14 to 3.26) |
| sot | 2.93 (0.85 to 9.39) | 3.19 (0.16 to 39.54) | 1.70 (0.29 to 8.79) | 1.13 (0.31 to 7.13) |
Table 4.50: NMA sensitivity analysis results for the outcome of Serious AEs using the prior distribution Half-Cauchy(0.5) for the heterogeneity parameter

|       | pbo  | bam  | bam_ete | cas_imd | sot   |
|-------|------|------|---------|--------|-------|
| pbo   | pbo  | 1.16 | 0.57    | 0.43   | 0.35  |
| bam   | 0.86 | bam  | 0.49    | 0.40   | 0.31  |
| bam_ete | 1.74 | 2.03 | bam_ete | 0.78   | 0.61  |
| cas_imd | 2.35 | 2.49 | 1.29    | cas_imd | 0.80 |
| sot   | 2.88 | 3.24 | 1.65    | 1.25   | sot   |
5.4 Appendix: Investigation of consistency

The only closed loops in the evidence networks arise from the direct comparison between bamlanivimab/etesevimab and casirivimab/imdevimab carried out in (McCreary et al., 2021). The outcomes affected are mortality, hospitalisation, infusion-related AEs and serious AEs. Consistency was assessed by comparing the direct estimate of relative effects of bamlanivimab/etesevimab versus casirivimab/imdevimab from (McCreary et al., 2021), and the indirect estimate of the same effect obtained re-running an NMA of all studies evaluating...
bamlanivimab/etesevimab and casirivimab/imdevimab with (McCreary et al., 2021) excluded (note that the latter does not contribute to the indirect estimate as there is no placebo arm).

Table 4.51: Direct and Indirect Estimates, casirivimab/imdevimab versus bamlanivimab/etesevimab

| Outcome    | Direct       | Indirect    |
|------------|--------------|-------------|
| Mortality  | 0.72 (0.24, 2.06) | 21.42 (1.25, 958.02) |
| Hospitalisation | 0.97 (0.78, 1.20) | 1.17 (0.58, 2.43) |
| Serious AEs | 2.09 (0.38, 16.62) | 0.26 (0.08, 0.84) |

For all three outcomes, 95% credible intervals for the direct and indirect relative treatment effect estimates overlap, indicating that there is no statistically significant inconsistency in the networks. The results show a numerical difference between the direct and indirect effect estimates for the mortality outcome, which could potentially indicate a violation of the assumption of consistency which was not detected due to low statistical power. Upon examining the raw event counts, there were no deaths in the bamlanivimab/etesevimab arms of Dougan et al. (2021a), compared with one death in each casirivimab/imdevimab arm of (Weinreich et al., 2021). When combined with the weakly informative prior, this results in a very high point estimate of the RR of mortality for casirivimab/imdevimab versus bamlanivimab/etesevimab, although this estimate is highly uncertain due to extremely small event numbers. By contrast, mortality rates observed in (McCreary et al., 2021) were similar for both treatments, giving a relative risk that is close to 1. Due to the low event numbers it is not possible to determine whether this discrepancy has arisen by chance, or indicates a genuine violation of the consistency assumption. This situation is similar for the SAE outcome.

The results for hospitalisation do not indicate any violation of the consistency assumption.

5.5 Appendix: Model diagnostics

```r
##
## ### Mortality
```
## $gelman.rubin
## $psrf
##       Point est. Upper C.I.
## d[2]    1.000540   1.001812
## d[3]    1.000333   1.001190
## d[4]    1.000270   1.000427
## d[5]    1.000742   1.001911
## sigma   1.000175   1.000627

## $mpsrf
## [1] 1.000964

## attr(,"class")

```r
## $gelman.rubin
## $psrf
##       Point est. Upper C.I.
## d[2]    1.000540   1.001812
## d[3]    1.000333   1.001190
## d[4]    1.000270   1.000427
## d[5]    1.000742   1.001911
## sigma   1.000175   1.000627

## $mpsrf
## [1] 1.000964

## attr(,"class")
```
## gelman.rubin.results

### $geweke

### $stats

|          | Chain 1    | Chain 2    | Chain 3     |
|----------|------------|------------|-------------|
| d[2]     | 0.76744920 | -0.3772772 | 0.06006038  |
| d[3]     | -1.08528266 | 0.6057266  | 0.29232265  |
| d[4]     | 0.06156129  | -0.4630726 | 0.26234962  |
| d[5]     | 0.81839348  | 0.8409934  | 0.79983817  |
| sigma    | 1.69986347  | -0.5039221 | 0.19475546  |

### $frac1

[1] 0.1

### $frac2

[1] 0.5

### attr(,"class")

[1] "geweke.results"

### Hospitalisation
## $gelman.rubin
## $psrf
### Point est. Upper C.I.

|    |      |      |
|----|------|------|
| d[2]| 1.000375 | 1.000878 |
| d[3]| 1.000162 | 1.000455 |
| d[4]| 1.000201 | 1.000533 |
| d[5]| 1.000224 | 1.000618 |
| sigma | 1.000475 | 1.001760 |

## $mpsrf
### [1] 1.001056

## attr(,"class")
# Invasive Ventilation

## gelman.rubin.results

```r
## $geweke
## $stats
##          Chain 1    Chain 2    Chain 3
## d[2]   0.7896875  1.1819564  1.3795317
## d[3]   0.7353951  0.5454311 -0.7832502
## d[4]   0.9172696  1.0722359 -0.7812157
## d[5]  -0.5033228 -0.1167988  2.6646940
## sigma -0.5039929  0.3088583  0.5573365
##
## $frac1
## [1] 0.1
##
## $frac2
## [1] 0.5
##
## attr(,"class")
## [1] "geweke.results"
```

### gelman.rubin

### psrf

### Point est. Upper C.I.

### d[2]  1.000188  1.000657

---

![Graphs](image-url)
### ICU Admission

#### $\text{mpsrf}$

|    | Chain 1 | Chain 2 | Chain 3 |
|----|---------|---------|---------|
| $d[2]$ | -0.5798184 | 0.3931644 | 1.3349431 |
| $d[3]$ | 0.5637790 | -0.4126955 | -1.2926784 |
| $\sigma$ | 0.6745141 | -1.4093452 | -0.5052508 |

#### $\text{geweke}$

|    | Chain 1 | Chain 2 | Chain 3 |
|----|---------|---------|---------|
| $d[2]$ | -0.5798184 | 0.3931644 | 1.3349431 |
| $d[3]$ | 0.5637790 | -0.4126955 | -1.2926784 |
| $\sigma$ | 0.6745141 | -1.4093452 | -0.5052508 |

### $\text{frac1}$

|    | 0.1 |

### $\text{frac2}$

|    | 0.5 |

#### ICU Admission

---

### ICU Admission

#### $d[2]$ and $d[3]$ Trace Plots

---

#### $\sigma$ Trace Plot

---

#### $d[2]$ and $d[3]$ Density Plots

---

#### $\sigma$ Density Plot

---
### Infusion-related AEs
# $gelman.rubin
# $psrf
# Point est. Upper C.I.
## d[2]  1.000711  1.002006
## d[3]  1.000102  1.000263
## d[4]  1.000127  1.000396
## d[5]  1.000350  1.001296
## sigma 1.000243  1.000499
#
# $mpsrf
# [1] 1.00099
#
# attr(,"class")
## [1] "gelman.rubin.results"
##
## $geweke
## $stats
##
##           Chain 1     Chain 2     Chain 3
## d[2]  0.26330992  0.18629910  1.38429119
## d[3]  0.28380474  0.89430631 -0.17529491
## d[4] -0.07028057  0.67089110  0.05830988
## d[5]  0.11504257 -0.55033827  0.93321909
## sigma -0.23224453 -0.31519715 -0.35377794
##
## $frac1
## [1] 0.1
##
## $frac2
## [1] 0.5
##
## attr(,"class")
## [1] "geweke.results"
##
## ### Serious AEs
```r
## $gelman.rubin
## $psrf
##       Point est. Upper C.I.
## d[2]    1.003796   1.012137
## d[3]    1.000086   1.000301
## d[4]    1.000047   1.000167
## d[5]    1.000041   1.000154
## sigma   1.000027   1.000090
##
## $mpsrf
## [1] 1.003435
##
## attr("class")
```
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