Lecanemab Phase III

Vahan Aslanyan

```
set.seed(219)
source("bayesian_ssr.R")
```

```
-- Attaching packages --------------------------------------- tidyverse 1.3.2 --
v ggplot2 3.5.0      v purrr   1.0.1
v tibble  3.1.8      v dplyr   1.0.10
v tidyr   1.2.1      v stringr 1.5.0
v readr   2.1.3      v forcats 0.5.2

Warning: package 'ggplot2' was built under R version 4.2.3

-- Conflicts ------------------------------------------ tidyverse_conflicts() --
x dplyr::filter() masks stats::filter()
x dplyr::lag()    masks stats::lag()
```

Lecanemab

From study protocol:

"The sample size for this study is estimated based on comparison of BAN2401 versus placebo with respect to the primary efficacy endpoint, the change from baseline in CDR-SB at 18 months. Based on data from BAN2401 Phase 2 study BAN2401-G000-201, an estimated standard deviation of the change from baseline CDR-SB at 18 months in placebo is 2.031 and an estimated treatment difference is 0.373 in all subjects. Therefore, assuming an estimated 20% dropout rate at 18 months in this study, a total sample size of 1566 subjects, including 783 subjects in placebo and 783 subjects in BAN2401, will have 90% power to detect the treatment difference between BAN2401 and placebo in all subjects using a 2-sample t-test at a significance level of 2-sided alpha = 0.05."

From sample size rationale: sd=2.031 variance is 4.124961, so nu_prior is 0.2424265 , so alpha/beta is 0.2424265

From collected data: SE=0.1122449 N=1795 , so SD=4.755529 (SE*sqrt(N)), Mean Change=0.45, so treatment effect size is 0.0946267

Scenario 16

```
alpha<-runif(5000,0,1000)
beta<-alpha/0.2424265
df_sample_size<-tibble()

df_q_andmu_posteriors_50<-tibble()
df_alpha_beta_posteriors_50<-tibble()
df_D_posteriors_50<-tibble()
interim_allocation_50<-tibble()

df_q_andmu_posteriors_25<-tibble()
df_alpha_beta_posteriors_25<-tibble()
df_D_posteriors_25<-tibble()
interim_allocation_25<-tibble()

df_q_andmu_posteriors_125<-tibble()
df_alpha_beta_posteriors_125<-tibble()
df_D_posteriors_125<-tibble()
interim_allocation_125<-tibble()

for(i in 1:length(alpha)){
  aux<-sample_size_calculation(alpha_prior = alpha[i],beta_prior = beta[i], eta=0.95, zeta
  if(any(is.na(aux)))next
  df_sample_size<-rbind(df_sample_size,aux)
  #Scenario 1
  length1<-round(aux$treatment1/2)
  y1_aux=rnorm(length1,mean=0.45, sd=4.755529)
  length2<-round(aux$treatment2/2)
  y2_aux=rnorm(length2,mean=0, sd=4.755529)


  y=c(y1_aux,y2_aux)
  treatment_assignment<-c(rep(1,length1),rep(2,length2))
  df_50=tibble(treatment_assignment,y)
```

```
aux_post_50<-posterior_calculations(alpha_prior=alpha[i],beta_prior=beta[i],q_prior=c(1,
                                    N_treat = c(length1,length2),
                                    y_treatment = df_50)

df_q_andmu_posteriors_50<-rbind(df_q_andmu_posteriors_50,aux_post_50$q_andmu_posteriors)
df_alpha_beta_posteriors_50<-rbind(df_alpha_beta_posteriors_50,aux_post_50$alpha_beta_pa
df_D_posteriors_50<-rbind(df_D_posteriors_50,aux_post_50$D)

treatment_differences_50<-get_treatment_difference(aux_post_50$q_andmu_posteriors,aux_po
new_r<-allocation_calculation(treatment_differences_50)
interim_allocation_50<-rbind(interim_allocation_50,new_r)

#Scenario 2

length1<-round(aux$treatment1/4)
y1_aux=rnorm(length1,mean=0.45, sd=4.755529)
length2<-round(aux$treatment2/4)
y2_aux=rnorm(length2,mean=0, sd=4.755529)


y=c(y1_aux,y2_aux)
treatment_assignment<-c(rep(1,length1),rep(2,length2))

df_25=tibble(treatment_assignment,y)

aux_post_25<-posterior_calculations(alpha_prior=alpha[i],beta_prior=beta[i],q_prior=c(1,
                                    N_treat = c(length1,length2),
                                    y_treatment = df_25)

df_q_andmu_posteriors_25<-rbind(df_q_andmu_posteriors_25,aux_post_25$q_andmu_posteriors)
df_alpha_beta_posteriors_25<-rbind(df_alpha_beta_posteriors_25,aux_post_25$alpha_beta_pa
df_D_posteriors_25<-rbind(df_D_posteriors_25,aux_post_25$D)

treatment_differences_25<-get_treatment_difference(aux_post_25$q_andmu_posteriors,aux_po
new_r<-allocation_calculation(treatment_differences_25)
interim_allocation_25<-rbind(interim_allocation_25,new_r)


#Scenario 3

length1<-round(aux$treatment1/8)
```

```
  y1_aux=rnorm(length1,mean=0.45, sd=4.755529)
  length2<-round(aux$treatment2/8)
  y2_aux=rnorm(length2,mean=0, sd=4.755529)


  y=c(y1_aux,y2_aux)
  treatment_assignment<-c(rep(1,length1),rep(2,length2))

  df_125=tibble(treatment_assignment,y)

  aux_post_125<-posterior_calculations(alpha_prior=alpha[i],beta_prior=beta[i],q_prior=c(1
                                       N_treat = c(length1,length2),
                                       y_treatment = df_125)

  df_q_andmu_posteriors_125<-rbind(df_q_andmu_posteriors_125,aux_post_125$q_andmu_posterio
  df_alpha_beta_posteriors_125<-rbind(df_alpha_beta_posteriors_125,aux_post_125$alpha_beta
  df_D_posteriors_125<-rbind(df_D_posteriors_125,aux_post_125$D)

  treatment_differences_125<-get_treatment_difference(aux_post_125$q_andmu_posteriors,aux_
  new_r<-allocation_calculation(treatment_differences_125)
  interim_allocation_125<-rbind(interim_allocation_125,new_r)

}
colMeans(df_sample_size)
```

```
treatment1 treatment2
  569.1589   569.1589
```

Scenario 16 no RAR

```
#no RAR
interim_ss50<-tibble()
for(i in 1:nrow(df_alpha_beta_posteriors_50)){
  interim_aux<-sample_size_calculation(alpha_prior=df_alpha_beta_posteriors_50$alpha_poste
                                       xi=0.95,r=c(1/2,1/2),q_prior =as.numeric( df_q_andm
                                       delta_star=0.373)
  interim_ss50<-rbind(interim_ss50,interim_aux)
}

colMeans(interim_ss50)
```

```
treatment1 treatment2
   1263.04    1263.04
```

Scenario 16 RAR

```
interim_ss_rar50<-tibble()
for(i in 1:nrow(df_alpha_beta_posteriors_50)){
  interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors_50$alpha_post
                                       xi=0.95,r=as.numeric(interim_allocation_50[i,]),q_p
                                       delta_star=0.373)
  interim_ss_rar50<-rbind(interim_ss_rar50,interim_aux)
}

colMeans(interim_ss_rar50,na.rm = T)
```

```
treatment1 treatment2
10204.6596   834.5773
```

Scenario 17 no rar

```
#no RAR
interim_ss25<-tibble()
for(i in 1:nrow(df_alpha_beta_posteriors_25)){
  interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors_25$alpha_post
                                       xi=0.95,r=c(1/2,1/2),q_prior =as.numeric( df_q_andm
                                       delta_star=0.373)
  interim_ss25<-rbind(interim_ss25,interim_aux)
}

colMeans(interim_ss25)
```

```
treatment1 treatment2
  1106.523   1106.523
```

Scenario 17 RAR

```
interim_ss_rar25<-tibble()
for(i in 1:nrow(df_alpha_beta_posteriors_25)){
  interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors_25$alpha_post
                                       xi=0.95,r=as.numeric(interim_allocation_25[i,]),q_p
                                       delta_star=0.373)
  interim_ss_rar25<-rbind(interim_ss_rar25,interim_aux)
}

colMeans(interim_ss_rar25,na.rm = T)
```

```
treatment1 treatment2
 8177.8716   824.9518
```

Scenario 18 no RAR

```
#no RAR
interim_ss125<-tibble()
for(i in 1:nrow(df_alpha_beta_posteriors_125)){
  interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors_125$alpha_pos
                                       xi=0.95,r=c(1/2,1/2),q_prior =as.numeric( df_q_andm
                                       delta_star=0.373)
  interim_ss125<-rbind(interim_ss125,interim_aux)
}

colMeans(interim_ss125)
```

```
treatment1 treatment2
  945.1239   945.1239
```

Scenario 18 RAR

```
interim_ss_rar125<-tibble()
for(i in 1:nrow(df_alpha_beta_posteriors_125)){
  interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors_125$alpha_pos
                                       xi=0.95,r=as.numeric(interim_allocation_125[i,]),q_
                                       delta_star=0.373)
  interim_ss_rar125<-rbind(interim_ss_rar125,interim_aux)
```

```
}

colMeans(interim_ss_rar125,na.rm = T)
```

```
treatment1 treatment2
 6106.1610   760.0187
```

Scenario 19 RAR

```
interim_ss_rar25<-tibble()
df_sample_size<-tibble()
interim_ss_rar50<-tibble()
df_q_andmu_posteriors_50<-tibble()
df_alpha_beta_posteriors_50<-tibble()
df_D_posteriors_50<-tibble()
interim_allocation_50<-tibble()

df_q_andmu_posteriors_25<-tibble()
df_alpha_beta_posteriors_25<-tibble()
df_D_posteriors_25<-tibble()
interim_allocation_25<-tibble()



for(i in 1:length(alpha)){
  aux<-sample_size_calculation(alpha_prior = alpha[i],beta_prior = beta[i], eta=0.95, zeta
  if(any(is.na(aux)))next
  df_sample_size<-rbind(df_sample_size,aux)
  #Scenario 4
  length1<-round(aux$treatment1/4)
  y1_aux=rnorm(length1,mean=0, sd=4.755529)
  length2<-round(aux$treatment2/4)
  y2_aux=rnorm(length2,mean=0.45, sd=4.755529)

  y=c(y1_aux,y2_aux)

  treatment_assignment<-c(rep(1,length1),rep(2,length2))
  df_25=tibble(treatment_assignment,y)

  aux_post_25<-posterior_calculations(alpha_prior=alpha[i],beta_prior=beta[i],q_prior=c(1,
```

```
                                    N_treat = c(length1,length2),
                                    y_treatment = df_25)

df_q_andmu_posteriors_25<-aux_post_25$q_andmu_posteriors
df_alpha_beta_posteriors_25<-aux_post_25$alpha_beta_params
df_D_posteriors_25<-aux_post_25$D

treatment_differences_25<-get_treatment_difference(aux_post_25$q_andmu_posteriors,aux_po
new_r<-allocation_calculation(treatment_differences_25)
interim_allocation_25<-rbind(interim_allocation_25,new_r)

interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors_25$alpha_post
                                     xi=0.95,r=as.numeric(new_r),q_prior =as.numeric( df
                                     delta_star=0.373)
if(any(is.na(interim_aux)))next
interim_ss_rar25<-rbind(interim_ss_rar25,interim_aux)


#Scenario 4
length1<-max(0,round(interim_aux$treatment1/2-aux$treatment1/4))
y1_aux=rnorm(length1,mean=0, sd=4.755529)
length2<-max(0,round(interim_aux$treatment2/2-aux$treatment2/4))
y2_aux=rnorm(length2,mean=0.45, sd=4.755529)


y=c(y1_aux,y2_aux)
treatment_assignment<-c(rep(1,length1),rep(2,length2))
df_50=tibble(treatment_assignment,y)
df<-rbind(df_25,df_50)
aux_post_50<-posterior_calculations(alpha_prior=alpha[i],beta_prior=beta[i],q_prior=c(1,
                                    N_treat = c(max(round(aux$treatment1/4),round(interim_a
                                                max(round(aux$treatment2/4),round(interim_a
                                    y_treatment = df)

df_q_andmu_posteriors_50<-aux_post_50$q_andmu_posteriors
df_alpha_beta_posteriors_50<-aux_post_50$alpha_beta_params
df_D_posteriors_50<-aux_post_50$D
treatment_differences_50<-get_treatment_difference(aux_post_50$q_andmu_posteriors,aux_po
new_r<-allocation_calculation(treatment_differences_50)
interim_allocation_50<-rbind(interim_allocation_50,new_r)
interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors_50$alpha_post
```

```
                                        xi=0.95,r=as.numeric(new_r),q_prior =as.numeric( df
                                        delta_star=0.373)
     if(any(is.na(interim_aux)))next
    interim_ss_rar50<-rbind(interim_ss_rar50,interim_aux)


}
colMeans(interim_ss_rar50)
```

```
treatment1 treatment2
  1260.010   1450.872
```

Scenario 20 RAR

```
interim_ss_rar25<-tibble()
df_sample_size<-tibble()
interim_ss_rar75<-tibble()
df_q_andmu_posteriors_75<-tibble()
df_alpha_beta_posteriors_75<-tibble()
df_D_posteriors_75<-tibble()
interim_allocation_75<-tibble()

df_q_andmu_posteriors_25<-tibble()
df_alpha_beta_posteriors_25<-tibble()
df_D_posteriors_25<-tibble()
interim_allocation_25<-tibble()



for(i in 3:length(alpha)){
  aux<-sample_size_calculation(alpha_prior = alpha[i],beta_prior = beta[i], eta=0.95, zeta
  if(any(is.na(aux)))next
  df_sample_size<-rbind(df_sample_size,aux)
  #Scenario 4
  length1<-round(aux$treatment1/4)
  y1_aux=rnorm(length1,mean=0, sd=4.755529)
  length2<-round(aux$treatment2/4)
  y2_aux=rnorm(length2,mean=0.45, sd=4.755529)
  y=c(y1_aux,y2_aux)
```

```
treatment_assignment<-c(rep(1,length1),rep(2,length2))
df_25=tibble(treatment_assignment,y)

aux_post_25<-posterior_calculations(alpha_prior=alpha[i],beta_prior=beta[i],q_prior=c(1,
                                    N_treat = c(length1,length2),
                                    y_treatment = df_25)

df_q_andmu_posteriors_25<-aux_post_25$q_andmu_posteriors
df_alpha_beta_posteriors_25<-aux_post_25$alpha_beta_params
df_D_posteriors_25<-aux_post_25$D

treatment_differences_25<-get_treatment_difference(aux_post_25$q_andmu_posteriors,aux_po
new_r<-allocation_calculation(treatment_differences_25)
interim_allocation_25<-rbind(interim_allocation_25,new_r)

interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors_25$alpha_post
                                     xi=0.95,r=as.numeric(new_r),q_prior =as.numeric( df
                                     delta_star=0.373)
if(any(is.na(interim_aux)))next
interim_ss_rar25<-rbind(interim_ss_rar25,interim_aux)


#Scenario 5
length1<-max(0,round(interim_aux$treatment1*0.75-aux$treatment1/4))
y1_aux=rnorm(length1,mean=0, sd=4.755529)
length2<-max(0,round(interim_aux$treatment2*0.75-aux$treatment2/4))
y2_aux=rnorm(length2,mean=0.45, sd=4.755529)

y=c(y1_aux,y2_aux)
treatment_assignment<-c(rep(1,length1),rep(2,length2))
df_75=tibble(treatment_assignment,y)
df<-rbind(df_25,df_75)
aux_post_75<-posterior_calculations(alpha_prior=alpha[i],beta_prior=beta[i],q_prior=c(1,
                                    N_treat = c(max(round(aux$treatment1/4),round(interim_a
                                                max(round(aux$treatment2/4),round(interim_a
                                    y_treatment = df)

df_q_andmu_posteriors_75<-aux_post_75$q_andmu_posteriors
df_alpha_beta_posteriors_75<-aux_post_75$alpha_beta_params
df_D_posteriors_75<-aux_post_75$D
treatment_differences_75<-get_treatment_difference(aux_post_75$q_andmu_posteriors,aux_po
```

```
  new_r<-allocation_calculation(treatment_differences_75)
  interim_allocation_75<-rbind(interim_allocation_75,new_r)
  interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors_75$alpha_post
                                       xi=0.95,r=as.numeric(new_r),q_prior =as.numeric( df
                                       delta_star=0.373)
  if(any(is.na(interim_aux)))next

   interim_ss_rar75<-rbind(interim_ss_rar75,interim_aux)


}
colMeans(interim_ss_rar75)
```

```
treatment1 treatment2
  1036.160   1336.333
```

Scenario 19 no RAR

```
interim_ss_25<-tibble()
df_sample_size<-tibble()
interim_ss_50<-tibble()
df_q_andmu_posteriors_50<-tibble()
df_alpha_beta_posteriors_50<-tibble()
df_D_posteriors_50<-tibble()
interim_allocation_50<-tibble()

df_q_andmu_posteriors_25<-tibble()
df_alpha_beta_posteriors_25<-tibble()
df_D_posteriors_25<-tibble()
interim_allocation_25<-tibble()



for(i in 1:length(alpha)){
  aux<-sample_size_calculation(alpha_prior = alpha[i],beta_prior = beta[i], eta=0.95, zeta
  if(any(is.na(aux)))next
  df_sample_size<-rbind(df_sample_size,aux)
  #Scenario 4
  length1<-round(aux$treatment1/4)
  y1_aux=rnorm(length1,mean=0, sd=4.755529)
```

```
length2<-round(aux$treatment2/4)
y2_aux=rnorm(length2,mean=0.45, sd=4.755529)

y=c(y1_aux,y2_aux)

treatment_assignment<-c(rep(1,length1),rep(2,length2))
df_25=tibble(treatment_assignment,y)

aux_post_25<-posterior_calculations(alpha_prior=alpha[i],beta_prior=beta[i],q_prior=c(1,
                                    N_treat = c(length1,length2),
                                    y_treatment = df_25)

df_q_andmu_posteriors_25<-aux_post_25$q_andmu_posteriors
df_alpha_beta_posteriors_25<-aux_post_25$alpha_beta_params
df_D_posteriors_25<-aux_post_25$D


interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors_25$alpha_post
                                     xi=0.95,r=c(0.5,0.5),q_prior =as.numeric( df_q_andm
                                     delta_star=0.373)
if(any(is.na(interim_aux)))next
interim_ss_25<-rbind(interim_ss_25,interim_aux)


#Scenario 4
length1<-max(0,round(interim_aux$treatment1/2-aux$treatment1/4))
y1_aux=rnorm(length1,mean=0, sd=4.755529)
length2<-max(0,round(interim_aux$treatment2/2-aux$treatment2/4))
y2_aux=rnorm(length2,mean=0.45, sd=4.755529)


y=c(y1_aux,y2_aux)
treatment_assignment<-c(rep(1,length1),rep(2,length2))
df_50=tibble(treatment_assignment,y)
df<-rbind(df_25,df_50)
aux_post_50<-posterior_calculations(alpha_prior=alpha[i],beta_prior=beta[i],q_prior=c(1,
                                    N_treat = c(max(round(aux$treatment1/4),round(interim_a
                                                max(round(aux$treatment2/4),round(interim_a
                                    y_treatment = df)

df_q_andmu_posteriors_50<-aux_post_50$q_andmu_posteriors
```

```
  df_alpha_beta_posteriors_50<-aux_post_50$alpha_beta_params
  df_D_posteriors_50<-aux_post_50$D
  interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors_50$alpha_post
                                       xi=0.95,r=c(0.5,0.5),q_prior =as.numeric( df_q_andm
                                       delta_star=0.373)
    if(any(is.na(interim_aux)))next
   interim_ss_50<-rbind(interim_ss_50,interim_aux)


}
colMeans(interim_ss_50)
```

```
treatment1 treatment2
  1235.128   1235.128
```

Scenario 20 no RAR

```
interim_ss_25<-tibble()
df_sample_size<-tibble()
interim_ss_75<-tibble()
df_q_andmu_posteriors_75<-tibble()
df_alpha_beta_posteriors_75<-tibble()
df_D_posteriors_75<-tibble()
interim_allocation_75<-tibble()

df_q_andmu_posteriors_25<-tibble()
df_alpha_beta_posteriors_25<-tibble()
df_D_posteriors_25<-tibble()
interim_allocation_25<-tibble()



for(i in 3:length(alpha)){
  aux<-sample_size_calculation(alpha_prior = alpha[i],beta_prior = beta[i], eta=0.95, zeta
  if(any(is.na(aux)))next
  df_sample_size<-rbind(df_sample_size,aux)
  #Scenario 4
  length1<-round(aux$treatment1/4)
  y1_aux=rnorm(length1,mean=0, sd=4.755529)
  length2<-round(aux$treatment2/4)
```

```
y2_aux=rnorm(length2,mean=0.45, sd=4.755529)
y=c(y1_aux,y2_aux)

treatment_assignment<-c(rep(1,length1),rep(2,length2))
df_25=tibble(treatment_assignment,y)

aux_post_25<-posterior_calculations(alpha_prior=alpha[i],beta_prior=beta[i],q_prior=c(1,
                                    N_treat = c(length1,length2),
                                    y_treatment = df_25)

df_q_andmu_posteriors_25<-aux_post_25$q_andmu_posteriors
df_alpha_beta_posteriors_25<-aux_post_25$alpha_beta_params
df_D_posteriors_25<-aux_post_25$D

interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors_25$alpha_post
                                     xi=0.95,r=c(0.5,0.5),q_prior =as.numeric( df_q_andm
                                     delta_star=0.373)
if(any(is.na(interim_aux)))next
interim_ss_25<-rbind(interim_ss_25,interim_aux)


#Scenario 5
length1<-max(0,round(interim_aux$treatment1*0.75-aux$treatment1/4))
y1_aux=rnorm(length1,mean=0, sd=4.755529)
length2<-max(0,round(interim_aux$treatment2*0.75-aux$treatment2/4))
y2_aux=rnorm(length2,mean=0.45, sd=4.755529)

y=c(y1_aux,y2_aux)
treatment_assignment<-c(rep(1,length1),rep(2,length2))
df_75=tibble(treatment_assignment,y)
df<-rbind(df_25,df_75)
aux_post_75<-posterior_calculations(alpha_prior=alpha[i],beta_prior=beta[i],q_prior=c(1,
                                    N_treat = c(max(round(aux$treatment1/4),round(interim_a
                                                max(round(aux$treatment2/4),round(interim_a
                                    y_treatment = df)

df_q_andmu_posteriors_75<-aux_post_75$q_andmu_posteriors
df_alpha_beta_posteriors_75<-aux_post_75$alpha_beta_params
df_D_posteriors_75<-aux_post_75$D
interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors_75$alpha_post
                                     xi=0.95,r=c(0.5,0.5),q_prior =as.numeric( df_q_andm
```

```
                                          delta_star=0.373)
    if(any(is.na(interim_aux)))next

     interim_ss_75<-rbind(interim_ss_75,interim_aux)


  }
  colMeans(interim_ss_75)
```

```
treatment1 treatment2
  1132.362   1132.362
```