Report on Bayesian Analysis of Secukinumab

STA421 Foundations of Bayesian Methodology

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Contents

Chapter 1

Introduction

1.1 Ankylosing spondylitis and the antagonist: secukinumab

Ankylosing spondylitis is a chronic immune-mediated inflammatory disease characterized by spinal inflammation, progressive spinal rigidity, and peripheral arthritis. The worldwide estimated prevalence of this genetic solid associated with antigen (HLA)-B27 disease is 0.2-0.5% (Dougados and Baeten, 2011)

Interleukin 17 (IL-17) is assumed to be a critical inflammatory cytokine in the development of ankylosing spondylitis. Therefore, secukinumab, a fully human anti-IL-17A monoclonal antibody, has attracted people's attention. However, the essential role of secukinumab in clinical practice remains to be confirmed.

1.2 Summary

In 2013, published proof-of-concept research confirmed secukinumab's utility (Baeten *et al.*, 2013), which assessed the efficacy anf safety in treating patients with active ankylosing spondylitis from a Bayesian perspective.

This report justifies this study based on sample size design, prior elicitation, and data analysis.

Chapter 2

Results

2.1 Methods

Besides conventional analyses such as the χ^2-test (Pearson, 1900) and Fisher's exact test (Fisher, 1992), Bayesian analysis comes into play here due to the relatively small sample size. With Monte Carlo Simulation (Metropolis and Ulam, 1949) and JAGS (Plummer, 2003), the priors are elicitated, and whether the proof of concept (POC) or posterior probability of superiority (PPS) is proved to be supported by the evidence.

2.2 Study design and sample size computation

2.2.1 Sample size computation

The optimal sample size for a 1:1 design for comparing 60% (Secukinumab) and 25% (Placebo) with a power of 80% and significance level of 5% is 31 and is computed by the function 'power.prop.test' from package 'stats'.

```
##
##      Two-sample comparison of proportions power calculation
##
##               n = 30.10887
##              p1 = 0.6
##              p2 = 0.25
##       sig.level = 0.05
##           power = 0.8
##     alternative = two.sided
##
## NOTE: n is number in *each* group
```

The proof of concept (POC) in the study requires that the ASAS20 response rate on secukinumab is more significant than placebo. With data from 20 patients on secukinumab and 5 patients on placebo, the study should be able to show that POC $> 90\%$, for actual response rates of 25% on placebo and 60% on secukinumab.

POC shown in Figure 2.1 is the proportion when the difference between two estimated response rates of each iteration is greater than 0; in other words, the estimated response rate of each iteration for the secukinumab group is more significant than the placebo group. To justify the above information, assume a Monte Carlo simulation of response rates on secukinumab and placebo to compute the POC.

Secukinumab:

$$
\begin{aligned}
p_s &= 0.6 \\
n_s &= 20 \\
X_s^{(i)} &\sim Bin(n_s,\ p_s),\ \ i = 1, \ldots, m \\
\hat{p_s}^{(i)} &= \frac{x_s^{(i)}}{n_s}
\end{aligned}
$$

Placebo:

$$
\begin{aligned}
p_p &= 0.25 \\
n_p &= 5 \\
X_p^{(i)} &\sim Bin(n_p,\ p_p),\ \ i = 1, \ldots, m \\
\hat{p_p}^{(i)} &= \frac{x_p^{(i)}}{n_p}
\end{aligned}
$$

Each simulation iteration, whether secukinumab or place group, follows a binomial distribution with a sample size of 20 or 5 and a response rate of 0.6 or 0.25. With the help of this simulation, each iteration's estimated response rate for both groups is generated.

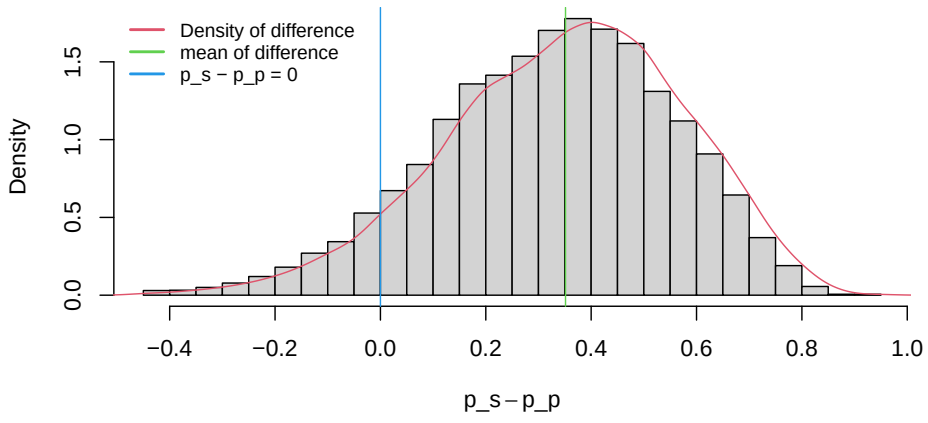
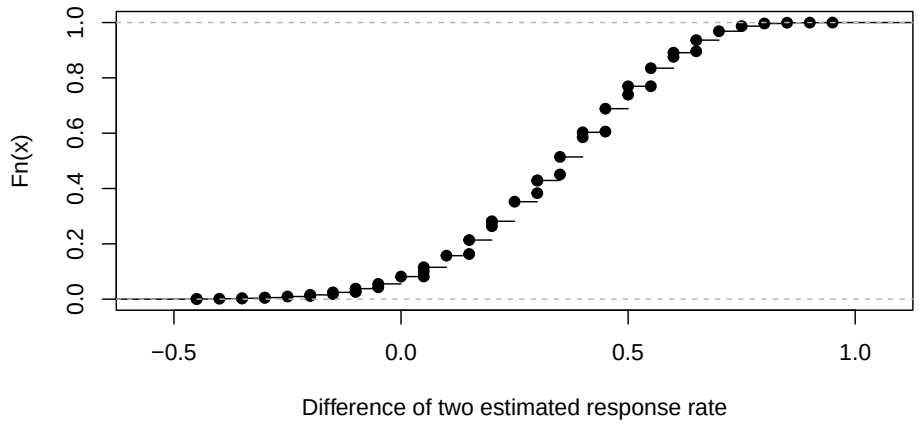


Figure 2.1: Histogram of difference between two estimated response rate




```
## [1] 0.9184
## [1] 0.9184
## [1] 0.0027
```

Figure 2.2: Empirical cumulative distribution function of difference

After computation, POC is 91.84% with a Monte Carlo standard error of 0.0027, close to 0.

2.2.2 Study design

The research designed a multicentre, randomized, double-blind, placebo-controlled study, screened 37 patients, and finally analyzed 23 patients for the primary outcome of treatment and 6 patients for the primary outcome of placebo.(Baeten *et al.*, 2013)

Ten simulations for a 4:1 study design with 1 to 10 folds sample sizes are implemented using a for-loop.

```
## [[1]]
##  [1] 0.7297 0.7817 0.8507 0.8884 0.9184 0.9402 0.9535 0.9630 0.9716 0.9802
##
## [[2]]
##  [1] 0.00444 0.00413 0.00356 0.00315 0.00274 0.00237 0.00211 0.00189 0.00166
## [10] 0.00139
```

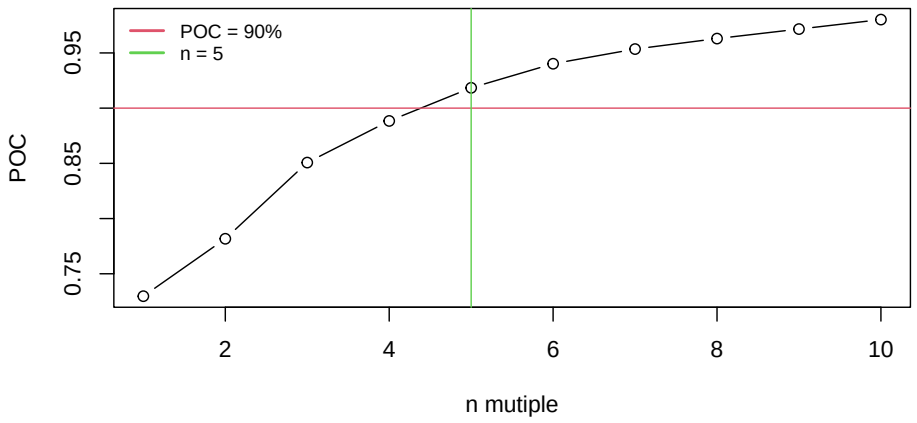


Figure 2.3: POC in 4:1 study design

As shown in the plot of POC (figure 2.3), POC increases when multiple increases. When n is 5, that is 20 patients on secukinumab and 5 patients on placebo, POC is greater than 90%. In addition, the Monte Carlo standard error (figure 2.4) decreases when multiple increases indicating that a larger n provides a better study design.

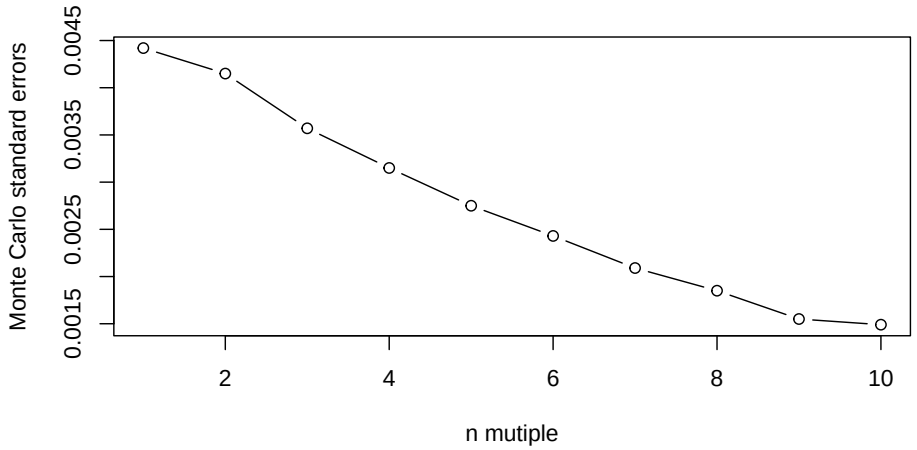


Figure 2.4: MCse(POC) in 4:1 study design

Therefore, the 4:1 study design based on 20 patients on secukinumab and 5 patients on

placebo considers the smallest number of patients for response rates (25% on placebo and 60% on secukinumab) and the condition POC $>$ 90%.

2.3 Prior elicitation

2.3.1 Placebo group

Elicitation of the prior distribution for placebo is described in the study(Baeten *et al.*, 2013) in the following way:

From a review of antitumor necrosis factor (TNF)-α treatment in ankylosing spondylitis, historical data were available from eight randomized placebo controlled clinical trials in ankylosing spondylitis patients. The earliest time point assessed in this review was 12 weeks after doing. Assuming a stable placebo response rate between weeks 6 and 12, these data were used in the derivation of the historical data prior.

A random effects meta-analysis of the 8 historical trials was performed assuming exchangeable placebo response rates on the logit scale. Using this model, the predictive distribution for the proportion of responders on placebo in a new study was derived, leading to an estimated response rate of 25% (and a 95% credible interval of 13% to 48%). For ease of use and interpretation, this predictive distribution was approximated by a Beta density with matching mean and standard deviation.

The data for 8 historical studies subject to placebo are as follows:

- Total number of observations n_i in each study subject to placebo $i = 1, \ldots, 8$:
  pl_{total} = c(107, 44, 51, 39, 139, 20, 78, 35)

- Number of cases x_i in each study subject to placebo $i = 1, \ldots, 8$:
  pl_{case} = c(23, 12, 19, 9, 39, 6, 9, 10)

The placebo response rate p_i is first transformed into logit scale y_i;

$$
\begin{aligned}
p_i &= x_i/n_i \\
y_i &= logit(p_i) = log(\frac{p_i}{1-p_i}) = log(\frac{x_i}{n_i - x_i}) \\
se(logit(p_i)) &= \sqrt{\frac{1}{x_i} + \frac{1}{n_i - x_i}}
\end{aligned}
$$

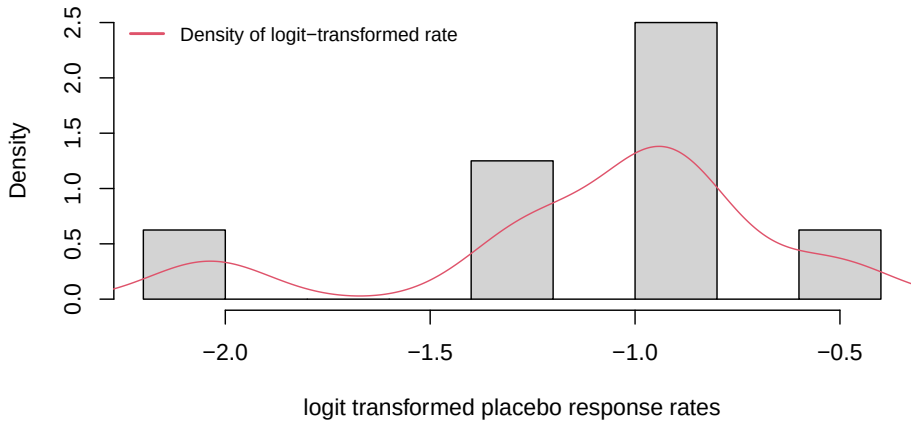


Figure 2.5: Histogram of logit transformed placebo response rates

from this logit transformation, we can quickly get the standard error $se(y_i) = \sqrt{\frac{1}{x_i} + \frac{1}{n_i - x_i}}$ by observed data x_i and n_i. In addition, y_i approximately follows a normal distribution with parameters of θ_i and precision (figure 2.5), where precision can be computed from standard error ($\frac{1}{se(y_i)^2}$), and θ_i also follows a normal distribution with parameters of μ and precision τ.

Prior: assume that mu follows a normal distribution $N(0, 10^{-4})$ and τ follows a gamma distribution $G(10^{-3}, 10^{-3})$.

The above model is implemented in an MCMC sampling engine called JAGS.

```
## Compiling model graph
##    Resolving undeclared variables
##    Allocating nodes
## Graph information:
##    Observed stochastic nodes: 8
##    Unobserved stochastic nodes: 11
##    Total graph size: 34
##
## Initializing model
##
## Iterations = 10010:110000
## Thinning interval = 10
## Number of chains = 4
## Sample size per chain = 10000
##
## 1. Empirical mean and standard deviation for each variable,
##    plus standard error of the mean:
##
##              Mean      SD  Naive SE Time-series SE
## p_new      0.2588 0.06374 0.0003187      0.0003234
## theta_new -1.0783 0.34384 0.0017192      0.0017249
##
## 2. Quantiles for each variable:
##
##              2.5%    25%     50%     75%   97.5%
## p_new      0.1405  0.226  0.2547  0.2848  0.4058
## theta_new -1.8114 -1.231 -1.0739 -0.9210 -0.3814
```

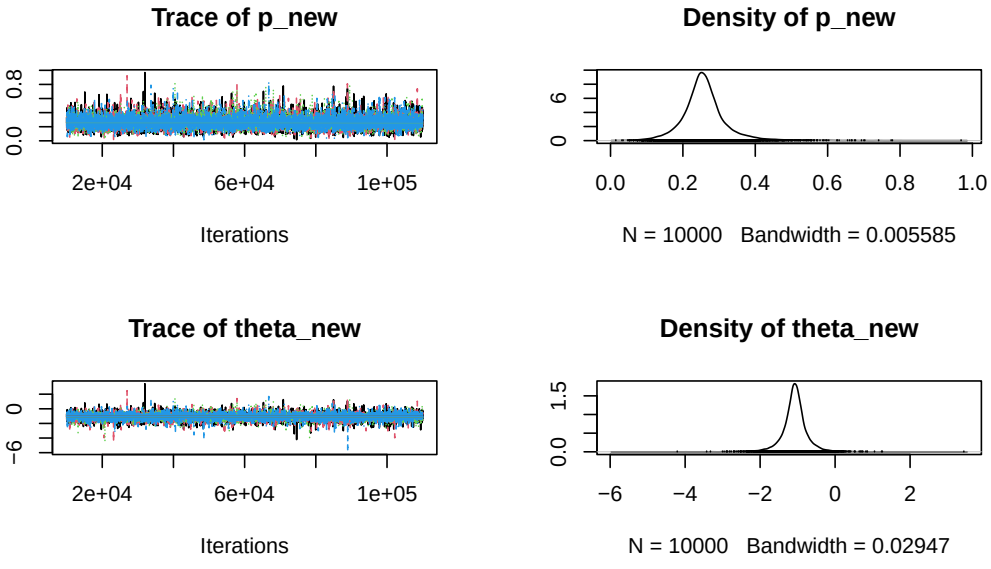


Figure 2.6: Trace plots and density plots of posterior predictive placebo response rate

Under the JAGS frame, firstly, 10000 iterations are run for warming up, then another 100000 iterations are run for sampling posterior predictive placebo response rate θ_{new} and back-transformed p_{new}. The summarization of p_{new} is shown in the following table 2.1.

	mean	sd	median	equi-tailed 95% interval
p_new	0.2588	0.06374	0.2543	[0.1405, 0.4058]
Baeten et al.	0.25	-	-	[0.13, 0.40]

Table 2.1: Summarisation of posterior predictive distribution for p contained in p_new

$$
\begin{aligned}
X \sim Beta(\alpha, \beta) & \\
E(X) &= \frac{\alpha}{\alpha+\beta} \\
\alpha &= E(X)(\alpha+\beta) \\
&= E(X)\alpha + E(X)\beta \\
\alpha(1-E(X)) &= E(X)\beta \\
\alpha &= \frac{E(X)\beta}{1-E(X)} \\
Var(X) &= \frac{\alpha\beta}{(\alpha+\beta)^2(\alpha+\beta+1)} = \frac{E(X)(1-E(X))}{\alpha+\beta+1} \\
&= \frac{E(x)(1-E(X))}{\frac{E(X)\beta}{1-E(X)}+\beta+1} \\
&= \frac{E(x)(1-E(X))^2}{E(X)\beta+\beta(1-E(X))+(1-E(x))} \\
&= \frac{E(x)(1-E(X))^2}{\beta+1-E(x)} \\
Var(x)\cdot(\beta+1-E(x)) &= E(x)(1-E(X))^2 \\
Var(X)\beta &= E(x)(1-E(X))^2 - Var(X) + E(X)Var(X) \\
\beta &= \frac{E(x)(1-E(X))^2 - Var(X) + E(X)Var(X)}{Var(X)} \\
\alpha &= \frac{E(X)}{1-E(X)} \cdot \frac{E(x)(1-E(X))^2 - Var(X) + E(X)Var(X)}{Var(X)} \\
&= \frac{E(X)^2}{Var(X)(1-E(X))} \cdot ((1-E(X))^2 - \frac{Var(X)}{E(X)} + Var(X)) \\
&= E(X)^2(\frac{1-E(X)}{Var(X)} - (\frac{1}{E(X)(1-E(X))} - \frac{E(X)}{E(X)(1-E(X))})) \\
&= E(X)^2(\frac{1-E(X)}{Var(x)} - \frac{1}{E(X)})
\end{aligned}
$$

```
## $alpha
## [1] 11.96032
##
## $beta
```

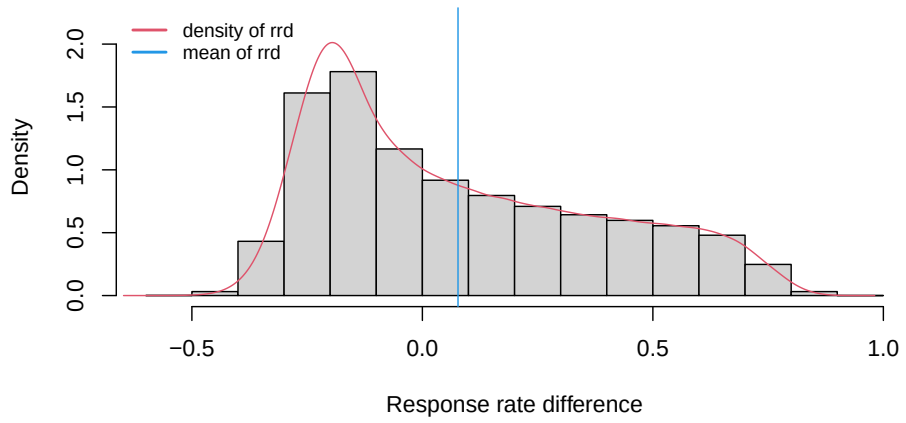
```
## [1] 34.2542
```

A Beta density $B(11.96, 34.25)$ derived using moments matching for ease of use and interpretation approximated this predictive distribution.

2.3.2 Treatment group

Elicitation of the prior distribution for treatment is described in the study in the following way: "The prior distribution for the proportion of responders in the active group was also a Beta distribution. One of the parameters was set to 1. The other parameter was chosen such that there was an approximately 50:50 chance that the responder rate on active treatment would be greater than the responder rate on placebo (based on the prior distributions only). Thus a Beta(shape1=0.5, shape2=1) distribution was chosen." (Baeten *et al.*, 2013)

Another Monte Carlo simulation based on a Beta(shape1=11, shape2=32) prior distribution for the placebo group is implemented to justify the parameter choice for the treatment group.




```
## [1] 0.497798
## [1] 0.0004999954
```

Figure 2.7: Historgram of response rate difference

1000000 response rates of treatment and 1000000 response rates of placebo are generated by the function 'rbeta' applying corresponding parameters. Because the two response rates are assumed to follow the beta distribution, the simulated treatment rate to the simulated placebo rate is subtracted to get the response rate difference. If the difference between the two response rates is greater than 0, the treatment response rate is greater than that of the placebo, that is, 'above <- diffR $>$ 0' in codes, where 'above' is a logic variable (TRUE or FALSE). Therefore, the mean of 'above' is the proportion of how many response rates of treatment is more significant than that of placebo in 1000000 samples. This proportion is 0.497976 (with a Monte Carlo

standard error of 0.0004999962) and is close to a 50:50 chance (50%). To sum up, the choice of beta parameters of 0.5 and 1 is correct.

2.4 Data analysis

2.4.1 Classical analyses

Group	n	Responders x (%)
Secukinumab	23	14 (60.9%)
Placebo	6	1 (16.7%)

Table 2.2: ASAS20 responders at week 6: data provided explicitly and implicitly in Table 2 of Baeten et al. (2013).

The commonly used statistical tests to compare two proportions are the χ^2 test and Fisher's exact test. However, the χ^2 test assumes that the total number of patients is fixed, while the assumption of Fisher's exact test is a fixed margin. Therefore, Fisher's exact test is more suitable for our case.

To conveniently apply the functions of both tests, firstly, table 2.2 is rearranged into table 2.3.

	non-Responders	Responders
Secukinumab	9	14
Placebo	5	1

Table 2.3: Rerranged table

Chi square test

The χ^2-test investigates whether rows and columns of a contingency table are statistically significantly associated. In other words, the χ^2-test examines the association between treatments and outcomes.

- H_0: the treatment variables and the outcomes variables of the contingency table are independent.
- H_1: the treatment and outcomes variables are dependent

```
##
##  Pearson's Chi-squared test with Yates' continuity correction
##
## data:  dfDACA
## X-squared = 2.1637, df = 1, p-value = 0.1413
```

The p-value is significantly more significant than 0.05. Hence there is not enough evidence to reject the null hypothesis.

Fisher's exact test

Fisher's exact test investigates the same as the χ^2-test. Their hypothesis is also the same.

```
##
##  Fisher's Exact Test for Count Data
##
## data:  dfDACA
## p-value = 0.08008
## alternative hypothesis: true odds ratio is not equal to 1
## 95 percent confidence interval:
##  0.002547579 1.522031658
## sample estimates:
## odds ratio
##  0.1377534
```

Once again, the p-value is more extensive than 0.05. There is not enough evidence to reject the null hypothesis.

Odds ratio and relative risk

```
## 2 by 2 table analysis:
## ------------------------------------------------------
## Outcome   : Non_resp
## Comparing : Placebo vs. Secukinumab
##
##             Non_resp Resp    P(Non_resp) 95% conf. interval
## Placebo            5    1         0.8333    0.3687   0.9772
## Secukinumab        9   14         0.3913    0.2177   0.5976
##
##                                    95% conf. interval
##              Relative Risk: 2.1296    1.1424   3.9699
##          Sample Odds Ratio: 7.7778    0.7762  77.9311
## Conditional MLE Odds Ratio: 7.2593    0.6570 392.5295
##     Probability difference: 0.4420   -0.0027   0.6599
##
##               Exact P-value: 0.0801
##         Asymptotic P-value: 0.0811
## ------------------------------------------------------
```

According to the results of 'twoby2', the risk of non-response for placebo is 0.8333, and the risk of non-response for Secukinumab is 0.3913. Therefore, the relative risk is 2.1296 with the 95%-CI from 1.1424 to 3.9699. The odds ratio for non-response is 7.7778 with the 95%-CI from 0.7762 to 77.9311.

2.4.2 Bayesian analyses

The 95% confidence intervals for the true probability of response in the Secukinumab and the placebo groups for the data provided in Table 2.2 are computed by the 'BinomCI' from package 'DescTools'.

Group	95% confidence interval
Secukinumab	[0.408 , 0.778]
Placebo	[0.03 , 0.564]

Table 2.4: 95%CI for the true probability of response in the Secukinumab and placebo groups

The results in table 2.4 mean that for repeated samples from a distribution with unknown parameter p, the 95% confidence interval will cover the true probability p in 95% of the cases.

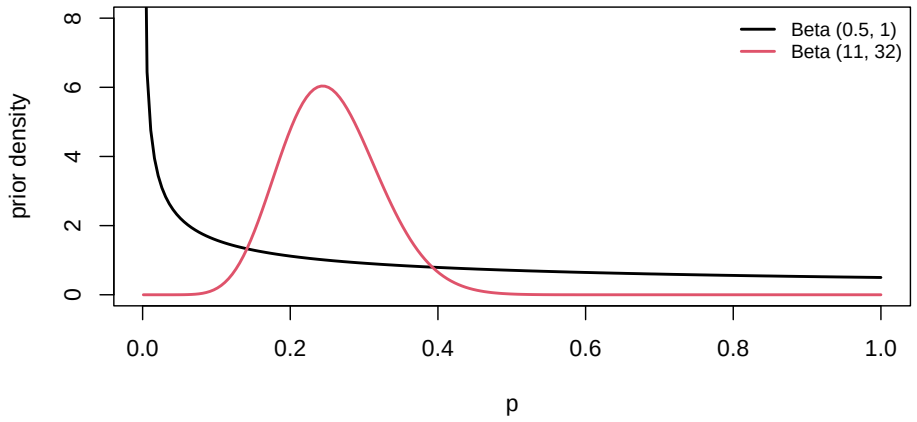


Figure 2.8: Beta(0.5, 1) and Beta(11, 32) priors

Group	Prior	mean ($\frac{\alpha}{\alpha+\beta}$)	median	equi-tailed 95% interval
Secukinumab	Beta(0.5, 1)	0.333	0.25	[0.001 , 0.951]
placebo	Beta(11.32)	0.256	0.252	[0.139 , 0.395]

Table 2.5: Summarisation of two priors

The plot of both Beta(0.5, 1) and Beta(11, 32) priors are shown in the figure 2.8, and their summarization of mean, median, and the equi-tailed 95% interval is in the table 2.5.

Prior: $X \sim Beta(\alpha, \beta)$

Posterior: $p \mid y_1, \ldots, y_n \sim Beta(\alpha + n\bar{y}, \beta + n - n\bar{y})$

Posterior distribution of the response rate for Secukinumab group:

$$\begin{aligned} p \mid y_1, \ldots, y_n &\sim Beta(0.5 + 14, 1 + 23 - 14) \\ &\sim Beta(14.5, 10) \end{aligned}$$

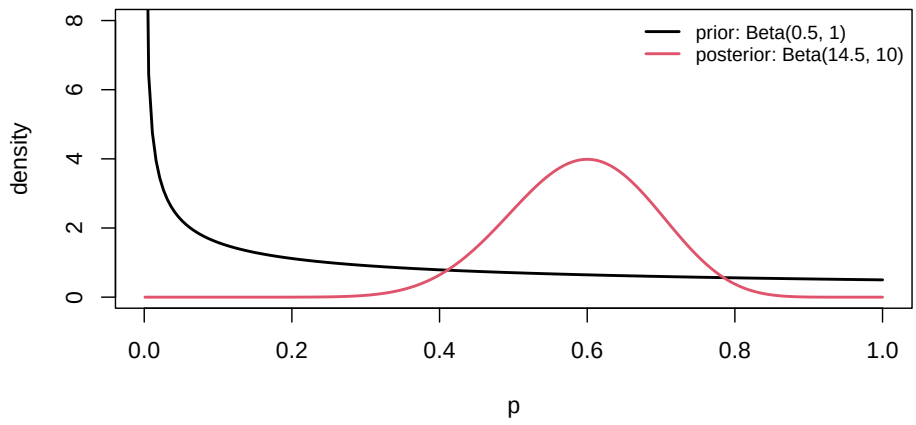


Figure 2.9: Secukinumab group: prior and the posterior distribution of the response rate

Secukinumab	Distribution	mean($\frac{\alpha}{\alpha+\beta}$)	median	equi-tailed 95% interval/ credible interval
Prior	Beta(0.5, 1)	0.333	0.25	[0.001, 0.951]
Posterior	Beta(14.5, 10)	0.592	0.594	[0.396, 0.774]

Table 2.6: Summarisation of prior and posterior distribution of the response rate for Secukinumab group

For the Secukinumab group, the plot of the Beta(0.5, 1) prior and the posterior distribution of the response rate is shown in figure 2.9. Furthermore, a summarization of its posterior distribution with posterior mean, median, and the equi-tailed 95% credible interval (95%CrI) is in table 2.6.

The posterior response rate of Secukinumab group p lies between 0.396 and 0.774 with probability 95%, when a Beta(0.5, 1) prior is assumed.

Posterior distribution of the response rate for placebo group:

$$\begin{aligned} p \mid y_1, \ldots, y_n &\sim Beta(11+1, 32+6-1) \\ &\sim Beta(12, 37) \end{aligned}$$

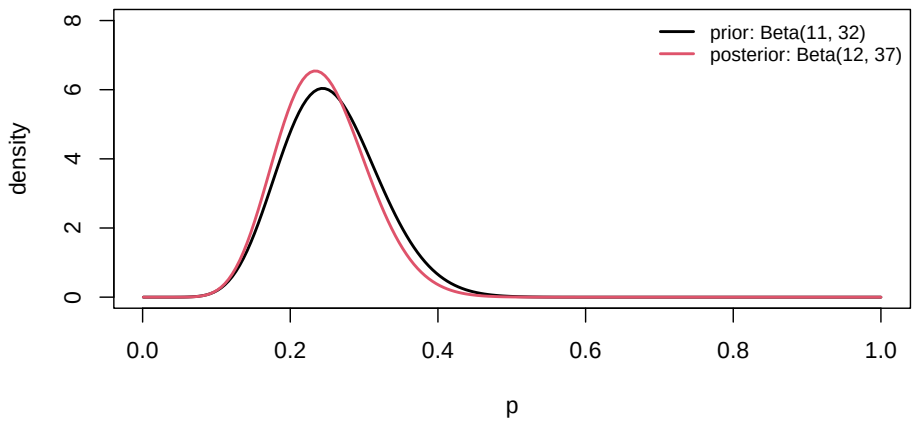


Figure 2.10: Placebo group: prior and the posterior distribution of the response rate

Placebo	Distribution	mean($\frac{\alpha}{\alpha+\beta}$)	median	equi-tailed 95% interval/ credible interval
Prior	Beta(11, 32)	0.256	0.252	[0.139, 0.395]
Posterior	Beta(12, 37)	0.245	0.241	[0.136, 0.373]

Table 2.7: Summarisation of prior and posterior distribution of the response rate for placebo group

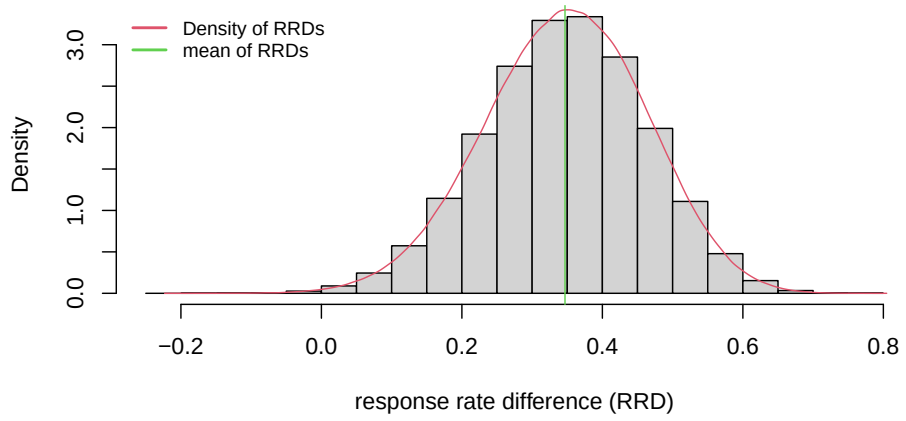
The same for the placebo group, the plot of its Beta(11, 32)) prior and the posterior distribution of the response rate is shown in figure 2.10. Moreover, a summarization of its posterior distribution with posterior mean, median, and the equi-tailed 95% credible interval (95%CrI) is in table 2.7.

The posterior response rate of placebo group p lies between 0.136 and 0.373 with probability 95%, when a Beta(11, 32) prior is assumed.

2.4.3 Posterior probability of superiority

The predefined criterion for declaring the superiority of secukinumab over placebo requires a posterior probability of at least 95% that the ASAS20 response rate for secukinumab patients is higher than that for placebo patients. Using Monte Carlo samples from the posterior distribution in the Secukinumab and placebo group, the estimate of the posterior probability of superiority (PPS) can be computed.

Response rate difference (RRD)



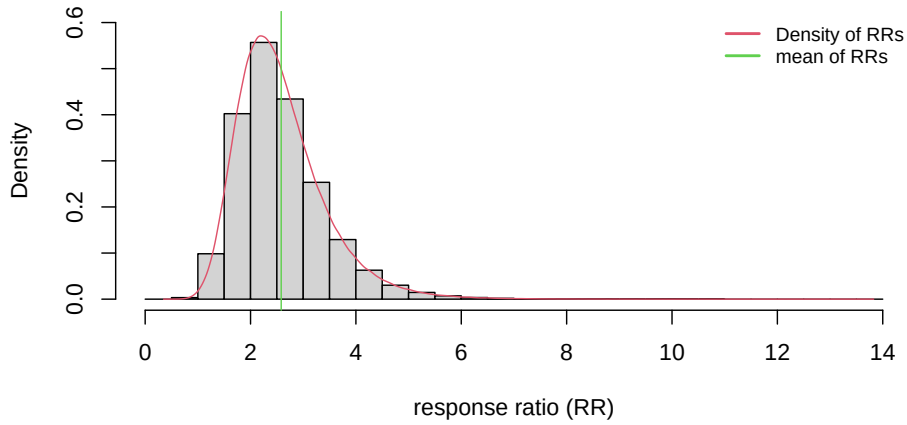

```
##   2.5%    50%  97.5%
## 0.1157 0.3494 0.5627
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
## -0.2037  0.2697  0.3494  0.3468  0.4268  0.7852
## [1] 0.998323
## [1] 4e-05
```

Figure 2.11: Response rate difference (RRD) distribution

The response rate difference (RRD) distribution based on both MC samples is shown in figure 2.11. The median of the RRD distribution is 0.3500, which means that the midpoint of the response rate difference is around 0.3500. The corresponding equi-tailed 95%CrI is from 0.1164 to 0.5584, which means that the response rate difference of responding to Secukinumab and Placebo lies between 0.1164 and 0.5584 with a probability of 95% when a Beta(14.5,10) posterior is used for Secukinumab and a Beta(12,37) posterior is used for the Placebo group. Then the estimate of PPS is computed, 99.8% with a Monte Carlo standard error of 0.00045, and is greater than the threshold of 95%.

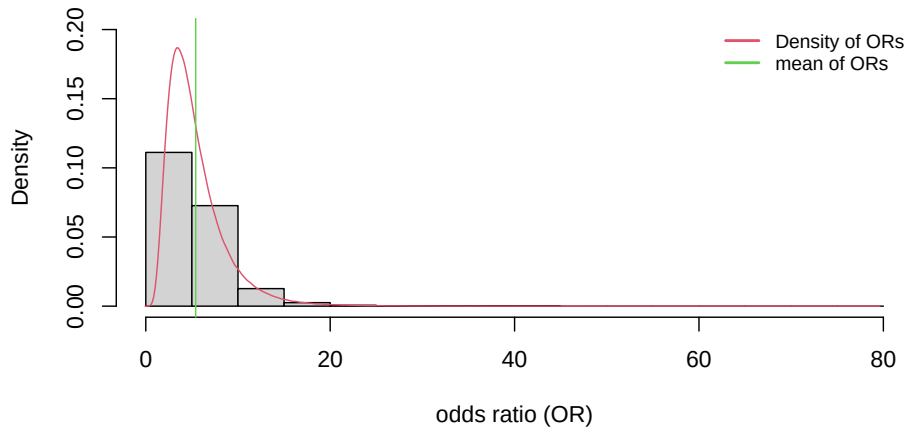
Response ratio (RR) and odds ratio (OR)

The response ratio (RR) 2.12 and odds ratio (OR)2.13 can also estimate PPS. The summarization of PPS and corresponding MC standard error based on RRD, RR, and OR is in table 2.8.




```
##   2.5%    50%  97.5%
## 1.3606 2.4426 4.6194
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##  0.4777  1.9962  2.4426  2.5819  3.0073 13.6993
## [1] 0.998323
## [1] 4e-05
```

Figure 2.12: Response ratio (RR) distribution




```
##    2.5%     50%   97.5%
##  1.6561  4.6367 13.7185
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##  0.3641  3.2398  4.6367  5.4150  6.6824 79.1778
## [1] 0.998323
## [1] 4e-05
```

Figure 2.13: Odds ratio (OR) distribution

	Mean	Median	95%CrI	PPS	MCse(PPS)
Response rate difference (RRD)	0.3467	0.3500	0.1164 - 0.5584	0.998	0.00045
Response ratio (RR)	2.5761	2.4442	1.3749 - 4.5813	0.998	0.00045
Odds ratio (OR)	5.3896	4.6485	1.6621 - 13.2891	0.998	0.00045

Table 2.8: Comparison of response rate difference (RRD), response ratio (RR) and odds ratio (OR)

2.5 Data collection

All interested results are collected in the following table 2.9.

Group	n	Responders x (%) with 95%CI	Prior distribution Response rate (mean)	Posterior distribution Response rate (mean)	Difference (S-P) 95%CrI	PPS (MCse)
Secukinumab	23	14 (60.9%, 40.8-77.8%)	Beta(0.5, 1) 33%	Beta(14.5, 10) 59.2%	34.7% 11.6-55.8%	99.8% (0.00045)
Placebo	6	1 (16.7%, 3-56.4%)	Beta(11.32) 25.6%	Beta(12, 37) 24.5%		

Table 2.9: Data collection based on the study of Baeten et al. (2013).

Chapter 3

Discussion

3.1 Study design and sample size computation

For the true response rate of 60% on secukinumab and 25% on placebo, the optimal sample size for a 1:1 design with 80% power and a significance level of 5% is 31, whereas using Monte Carlo simulation, the minimum sample size for a 4:1 design is 20 patents from secukinumab group and 5 patients from placebo group with a POC more significant than 90%.

3.2 Prior elicitation

The logit transformed model implemented by JAGS proves that the elicitation of the prior response rate of the placebo group is in a reasonable range.

In the case of the treatment group, the MC simulation justifies that a beta distribution with shape parameters of 0.5 and 1 is correctly chosen as the prior distribution.

3.3 Data analysis

Conventional statistical tests for an association between two variables agree that the treatment variables (secukinumab or placebo) and the outcome variables (response or not) are independent. The 95% CI of relative risk does not cover value 1, indicating a statistically significant treatment effect. The 95% CI of the odds ratio includes value 1, indicating no statistically significant to show the association between secukinumab exposure and the outcome of the responder.

Bayesian analyses give a different answer. The odds ratio computed using the MC sample is 5.3896 with 95% CrI from 1.6621 to 13.2891 excluding value 1, indicating that the secukinumab exposure is associated with an increased response rate.

Furthermore, the posterior probability of superiority based on RRD, RR, or OR agrees with the value of 99.8% with an MC standard error of 0.00045, which is greater than the criterion of 95%.

Appendix A

Appendix

A.1 Study design and sample size computation

A.1.1 Sample size computation

```
# optimal sample size for a 1:1 design
power.prop.test(p1 = .6, p2 = .25, sig.level = .05, power = .8)

# proof of concept (POC)
set.seed(2022)
mPOC <- 10000  # 10000 samples
# Secukinumab group: 20 patients, response rates of 60%
pS_POC <- rbinom(mPOC, 20, 0.6)/20 # estimated response rate
# Placebo group: 5 patients, response rates of 25%
pP_POC <- rbinom(mPOC, 5, 0.25)/5 # estimated response rate
# Difference of two estimated response rate
dPOC <- pS_POC-pP_POC
meanD_POC <- mean(dPOC)

hist(dPOC, freq = F, breaks = 20,
     xlab = expression(p_s - p_p),
     main = "")
lines(density(dPOC), col = 2)
abline(v = meanD_POC, col = 3, cex = 2)
abline(v = 0, col = 4, cex = 2)
legend("topleft", legend=c("Density of difference", "mean of difference",
                           "p_s - p_p = 0"),
       col=2:4, lty=1, cex=.8, lwd=2, box.lty=0)
# Compute the estimate of POC
P_POC <- ecdf(dPOC)
plot(P_POC,
     main = "",
```

```
     xlab = "Difference of two estimated response rate")
1-P_POC(0)
# or
sum(dPOC>0)/length(dPOC)
# Estimate of the Monte Carlo SE(POC)
MCsePOC <- sqrt(var(dPOC>0)/length(dPOC>0)) # Monte Carlo standard errors
round(MCsePOC, digits = 4)
```

A.1.2 Study design

```
# for-loop of 4:1 study design with 1 to 10 folds sample sizes
poc <- numeric()
mcse <- numeric()
for (n in 1:10) {
  pS <- rbinom(mPOC, 4*n, 0.6)/(4*n)
  pP <- rbinom(mPOC, n, 0.25)/n
  d <- pS-pP

  P <- ecdf(d)
  poc <- c(poc,  1-P(0))
  mcse <- c(mcse, round(sqrt(var(d>0)/length(d>0)), digits = 5))
}
list(poc, mcse)

plot(1:10, poc, type="b",
     xlab = "n mutiple", ylab = "POC")
abline(h=0.9, col=2)
abline(v=5, col=3)
legend("topleft", legend=c("POC = 90%", "n = 5"),
       col=2:3, lty=1, cex=.8, lwd=2, box.lty=0)
poc <- numeric()
mcse <- numeric()
for (n in 1:10) {
  pS <- rbinom(mPOC, 4*n, 0.6)/(4*n)
  pP <- rbinom(mPOC, n, 0.25)/n
  d <- pS-pP

  P <- ecdf(d)
  poc <- c(poc,  1-P(0))
  mcse <- c(mcse, round(sqrt(var(d>0)/length(d>0)), digits = 5))
}
```

```r
plot(1:10, mcse, type = "b",
     xlab = "n mutiple", ylab = "Monte Carlo standard errors")
```

A.2 Prior elicitation

A.2.1 Placebo group

```r
# logit transformation
plCase <- c(23,12,19,9,39,6,9,10)
plTotal <- c(107,44,51,39,139,20,78,35)
plRate <- plCase/plTotal
logitRate <- log(plRate/(1 - plRate)) #logit transformed placebo response rate
                                      #corresponds to y in pl1Model
seLogitR <- sqrt(1/plCase + 1/(plTotal - plCase)) #standard error of logitRate
varLogitR <- seLogitR^2 #variance of logitRate
precLogitR <- 1/varLogitR #precision of logitRate

hist(logitRate, freq = F, breaks = 8,
     xlab = "logit transformed placebo response rates",
     main = "")
lines(density(logitRate), col = 2)
legend("topleft", legend = "Density of logit-transformed rate", col =2,
       lty=1, cex=.8, lwd=2, box.lty=0)

# model implementation using JAGS
#Input data for pl1Model
pl1Data <- list(y = logitRate, prec_s = precLogitR)
#define parameters
pl1Pars <- c("theta_new", "p_new")
#initiate
initsJags <- list(list(.RNG.name = "base::Wichmann-Hill", .RNG.seed = 314159),
                  list(.RNG.name = "base::Marsaglia-Multicarry",
                       .RNG.seed = 159314),
                  list(.RNG.name = "base::Super-Duper", .RNG.seed = 413159),
                  list(.RNG.name = "base::Mersenne-Twister", .RNG.seed = 143915))

#model formulation
pl1_modelString = "
model{
for(i in 1:length(y)){
y[i] ~ dnorm(theta[i], prec_s[i]);
theta[i] ~ dnorm(mu, prec_tau);
```

```
}

#predictive distribution for theta
theta_new ~ dnorm(mu, prec_tau)

# predictive distribution at the probability scale
p_new <- exp(theta_new)/(1+exp(theta_new));

#prior
mu ~ dnorm(0.0, 1.0E-4);
prec_tau ~ dgamma(1.0E-3, 1.0E-3);
}
"
writeLines(pl1_modelString, con="pl1Model.txt") # write to a file
#JAGS 4 chains
pl1Jags <- jags.model(
  file = "pl1Model.txt",
  data = pl1Data,
  inits = initsJags,
  n.chains = 4,
  n.adapt = 10000
)
#burn-in
update(pl1Jags, n.iter = 10000)
#sampling/monitoring
fitJagsCodaPl1 <- coda.samples(
  model = pl1Jags,
  variable.names = pl1Pars,
  n.iter = 100000,
  thin = 10
)
summary(fitJagsCodaPl1)
plot(fitJagsCodaPl1)

# moments matching
betaPar <- function(mean, variance) {
  alpha <- ((1 - mean) / variance - 1 / mean) * mean ^ 2
  beta <- (mean*(1-mean)^2 - variance + mean * variance)/variance
  return(pars = list(alpha = alpha, beta = beta))
}
#apply on p_new
betaPar(mean = 0.2588, variance = 0.06374^2)
```

A.2.2 Treatment group

```
N <- 1000000
pp <- rbeta(N, 11, 32)
pt <- rbeta(N, 0.5, 1)

diffP <- pt-pp
hist(diffP,
     xlab = "Response rate difference", freq = F,
     main = "",
     ylim = c(0, 2.2))
lines(density(diffP), col = 2)
abline(v=mean(diffP), col = 4, cex = 2)
legend("topleft",
       legend = c("density of rrd", "mean of rrd"),
       col = c(2, 4),
       lty=1, cex=.8, lwd=2, box.lty=0)

above <- diffP>0 #logic variable, true or false
mean(above) #the mean of above gives the proportion how many pt is larger than pp
sqrt(var(above)/length(above)) # MC standard error of above
```

A.3 Data analysis

A.3.1 Classical analyses

```
dfDACA <- data.frame(matrix(c(23-14, 14, 6-1, 1), nrow = 2, byrow = TRUE))
colnames(dfDACA) <- c("non-Responders", "Responders")
rownames(dfDACA) <- c("Secukinumab", "Placebo")
chisq.test(dfDACA)
fisher.test(dfDACA)
Epi::twoby2(
  exposure = rep(rownames(dfDACA), times = rowSums(dfDACA)),
  outcome = rep(c("Non_resp", "Resp", "Non_resp", "Resp"), times = c(dfDACA[1,], dfDACA[2,]
    )
```

A.3.2 Bayesian analyses

```
# 95%CI for the true probability of response
#in the Secukinumab and placebo groups
CIsecu <- DescTools::BinomCI(14, 23, conf.level = .95, method = "wilson")
```

```r
CIplacebo <- DescTools::BinomCI(1, 6, conf.level = .95, method = "wilson")

# plot of both Beta(0.5, 1) and Beta(11, 32) priors and summarization
pDABA <- seq(1e-3,1, length=200)
# plot
plot(pDABA, dbeta(pDABA, 0.5, 1), type="l",
     xlab ="p",
     ylab="prior density", col=1,
     ylim=c(0, 8), lwd=2)
lines(pDABA, dbeta(pDABA, 11, 32), ylab="density", col=2, lwd=2)
legend("topright",
       legend = c("Beta (0.5, 1)",
                  "Beta (11, 32)"),
       col = 1:2, box.lty=0, lty=1, cex=.8, lwd=2)
# prior mean of Beta(0.5, 1)
pmSecu <- 0.5/(0.5+1)
# 2.5%, 50%(i.e. median), 97.5% quantiles of Beta(0.5, 1)
pm_eISecu <- qbeta(c(0.025, 0.5, 0.975), 0.5, 1)
# prior mean of Beta(11, 32)
pmPlacebo <- 11/(11+32)
# 2.5%, 50%(i.e. median), 97.5% quantiles of Beta(11, 32)
pm_eIPlacebo <- qbeta(c(0.025, 0.5, 0.975), 11, 32)

#Secukinumab group: prior and the posterior distribution of the response rate
plot(pDABA, dbeta(pDABA, 0.5, 1), type="l",
     xlab ="p",
     ylab="density", col=1,
     ylim=c(0, 8), lwd=2)
lines(pDABA, dbeta(pDABA, 14.5, 10), col=2, lwd=2)
legend("topright", legend=c("prior: Beta(0.5, 1)", "posterior: Beta(14.5, 10)"),
       col=1:2, lty=1, cex=.8, lwd=2, box.lty=0)

# posterior mean of Beta(14.5, 10)
pomSecu <- 14.5/(14.5+10)
# 2.5%, 50%(i.e. median), 97.5% quantiles of Beta(14.5, 10)
pom_eISecu <- qbeta(c(0.025, 0.5, 0.975), 14.5, 10)

#Placebo group: prior and the posterior distribution of the response rate
plot(pDABA, dbeta(pDABA, 11, 32), type="l",
     xlab ="p",
     ylab="density", col=1,
     ylim=c(0, 8), lwd=2)
```

```r
lines(pDABA, dbeta(pDABA, 12, 37), col=2, lwd=2)
legend("topright", legend=c("prior: Beta(11, 32)", "posterior: Beta(12, 37)"),
       col=1:2, lty=1, cex=.8, lwd=2, box.lty=0)

# posterior mean of Beta(12, 37)
pomPlacebo <- 12/(12+37)
# 2.5%, 50%(i.e. median), 97.5% quantiles of Beta(12, 37)
pom_eIPlacebo <- qbeta(c(0.025, 0.5, 0.975), 12, 37)
```

A.3.3 Posterior probability of superiority

```r
# Monte Carlo samples
set.seed(2022)
# secukinumab group: posterior Beta(14.5, 10)
samplesS1 <- rbeta(N, 14.5, 10)
ESS1 <- mean(samplesS1)
seESS1 <- sqrt(var(samplesS1)/N) # Monte Carlo standard errors
# placebo group: posterior Beta(12, 37)
samplesP1 <- rbeta(N, 12, 37)
ESP1 <- mean(samplesP1)
seESP1 <- sqrt(var(samplesP1)/N) # Monte Carlo standard errors

# Response rate difference (RRD)
RRDs <- samplesS1 - samplesP1
meanRRDs <- mean(RRDs)
hist(RRDs, freq = F, breaks = 20,
     xlab = "response rate difference (RRD)",
     main = "")
lines(density(RRDs), col = 2)
abline(v = meanRRDs, col = 3, cex = 2)
legend("topleft", legend=c("Density of RRDs", "mean of RRDs"),
       col=2:3, lty=1, cex=.8, lwd=2, box.lty=0)

# median and equi-tailed 95%CrI of the distribution of RRD
round(quantile(RRDs, c(0.025, 0.5, 0.975)), digits = 4)
summary(RRDs)

P_RRD <- ecdf(RRDs)
1-P_RRD(0)
# or
# sum(RRDs>0)/length(RRDs)
# mean(RRDs>0)
```

```r
sePPSrrd <- sqrt(var(RRDs>0)/length(RRDs>0)) # Monte Carlo standard errors
round(sePPSrrd, digits = 5)

# Response ratio (RR) and odds ratio (OR)
RRs <- samplesS1/samplesP1 # response ratio (RR)
meanRRs <- mean(RRs) # mean of RRs
hist(RRs, freq = F, breaks = 20,
     xlab = "response ratio (RR)",
     ylim = c(0, .6), main = "")
lines(density(RRs), col = 2)
abline(v = meanRRs, col = 3, cex = 2)
legend("topright", legend=c("Density of RRs", "mean of RRs"),
       col=2:3, lty=1, cex=.8, lwd=2, box.lty=0)
# median and the equi-tailed 95%CrI of the distribution of RRD
round(quantile(RRs, c(0.025, 0.5, 0.975)), digits = 4)
summary(RRs)
# the estimate of PPS based on RR
P_RR <- ecdf(RRs)
1-P_RR(1)
# or
# sum(RRs>1)/length(RRs)
# mean(RRs>1)
# the MC standard error (MCse) of PPS based on RR
sePPSrr <- sqrt(var(RRs>1)/length(RRs>1))
round(sePPSrr, digits = 5)
ORs <- (samplesS1/(1-samplesS1))/(samplesP1/(1-samplesP1)) # odds ratio (OR)
meanORs <- mean(ORs) # mean of ORs
hist(ORs, freq = F, breaks = 20,
     xlab = "odds ratio (OR)",
     ylim = c(0, .2), main = "")
lines(density(ORs), col = 2)
abline(v = meanORs, col = 3, cex = 2)
legend("topright", legend=c("Density of ORs", "mean of ORs"),
       col=2:3, lty=1, cex=.8, lwd=2, box.lty=0)
# median and the equi-tailed 95%CrI of the distribution of OR
round(quantile(ORs, c(0.025, 0.5, 0.975)), digits = 4)
summary(ORs)
# the estimate of PPS based on OR
P_OR <- ecdf(ORs)
1-P_OR(1)
# or
# sum(ORs>1)/length(ORs)
```

```r
# mean(ORs>1)
# the MC standard error (MCse) of PPS based on OR
sePPSor <- sqrt(var(ORs>1)/length(ORs>1))
round(sePPSor, digits = 5)
```

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