Supplement 2: Bayesian Analysis

Bayesian analysis is a highly appropriate analysis strategy when working with small sample sizes. Previous knowledge about the studied item can be taken advantage of by means of the assessment of the plausibility of a given hypothesis after incorporating the new observed data.[1]

The noninferiority hypothesis, formally $\Delta < -10\%$, was tested, taking into account the observed results but also taking into account the results of the trials by Kuzminski et al.[2] and Saraswathy et al.[3]

P1 denotes the percentage of patients who responded to VB12 oral administration, and P0 represents the percentage of those responding to VB12 intramuscular administration. Bayesian analysis allows for calculating the probability of P1 being equal to or smaller than P0 by a specified magnitude, the noninferiority limit ($\Delta < -10\%$). For each of the parameters P1 and P0, both measured at 8, 26 and 52 weeks, we selected *a priori* distributions from the family of beta distributions with parameters **a** and **b**, which are related to the proportions of those responding in each trial arm. The gamma distribution represents the *a priori* hypothesis of the distribution of differences. According to the results of both trials by Kuzminski et al.[2] and Saraswathy et al.,[3] included in the review by Wang et al.,[4] 79.1% and 84.1% of patients normalized their VB12 levels in the oral and IM treatment groups, respectively.[4] The respective CIs associated with these prior data were calculated, and parameters were chosen (**a** and **b** in the beta distribution) such that the maximum density intervals of these distributions approximately coincided with the CI previously obtained (see Figure 1). Beta distributions for the success rate in each arm of the trial were obtained using binomial data. A total of 10000 simulations were made from these *a posteriori* distributions, and the corresponding differences, P1-P0, were calculated yielding an *a posteriori* distribution of differences. This distribution was used to derive simulation-based estimates of the probability of relevant magnitudes concerning Δ: P1-P0>0.10 at weeks 8, 26, and 52. Both PPT and ITT analyses were performed. EPIDAT 4.2 software was used for all computations.

Table 1 shows the *a posteriori* probability of differences in treatment effectiveness between oral and IM routes at different weeks (8, 26 and 52). The probabilities of the differences in treatment effectiveness being >10% between the oral and IM groups were 0.001, 0.201, and 0.036 at weeks 8, 26, and 52, respectively (per protocol analysis). In the intention-to-treat (ITT) analysis, these values were 0.000, 0.015, and 0.060 at weeks 8, 26, and 52, respectively.

References

1. Berger JO, Bayarri MJ. The interplay of bayesian and frequentist analysis. *Stat Sci.* 2004;19(1):58-80.
2. Kuzminskia M, Del Giacco EJ, Allen RH, Stabler SP, Lindenbaum J. Effective treatment of cobalamin deficiency with oral cobalamin. *Blood*. 1998;92(4):1191-1198.
3. Saraswathy AR, Dutta A, Simon EG, Chacko A. Randomized open label trial comparing efficacy of oral versus intramuscular vitamin b12 supplementation for treatment of vitamin b12 deficiency. *Gastroenterology*. 2012:142(1):S-216.
4. Wang H, Li L, Qin LL, Song Y, Vidal-Alaball J, Liu TH. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. *Cochrane Database Syst Rev.* 2018;3:CD004655.

Figure 1. A priori distributions of the differences between oral and intramuscular treatment

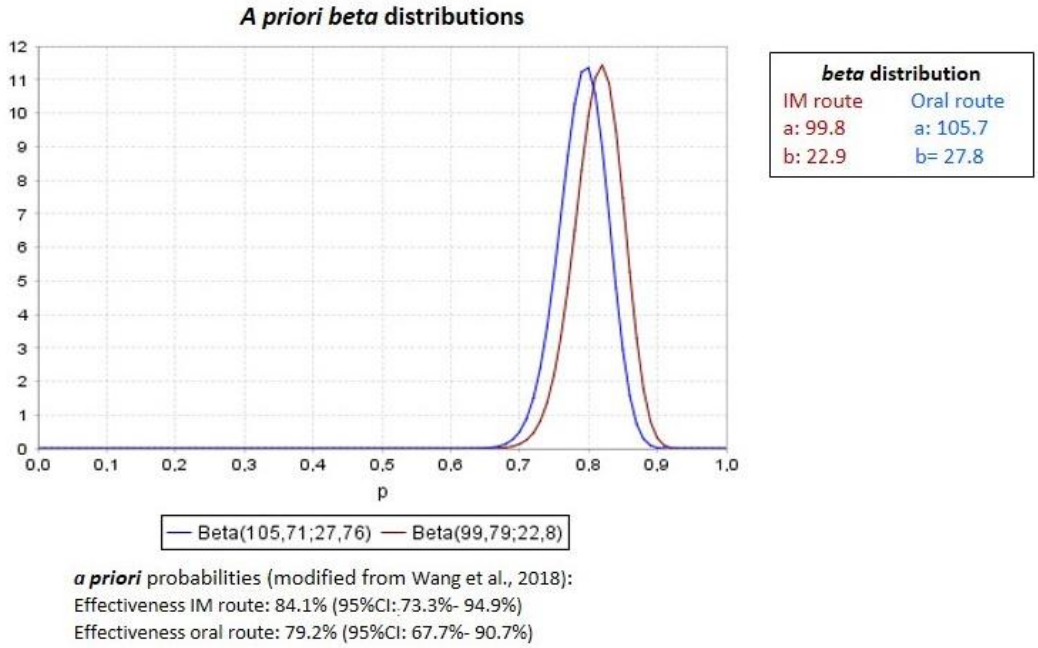

Table 1. *A posteriori* probability of differences in treatment effectiveness between oral and IM routes at 8, 26, and 52 weeks.

A posteriori **probability (Δ < -10%)**	**Week 8**	**Week 26**	**Week 52**
Per-protocol analysis	0.001	0.201	0.036
Intention-to-treat analysis	0.000	0.015	0.060

Δ: threshold of non-inferiority