Author’s response to reviews

Title: A Phase 1, Randomized, Open-Label, Single-Dose Study to Assess the Relative Bioavailability of a Subcutaneous Dose of FKB327 When Administered Using a Prefilled Syringe, a Prefilled Auto-Injector, or a Vial with Disposable Syringe in Healthy Subjects

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Summary of requested changes and suggested responses

Yesim Tuncok (Reviewer 1): No changes requested

Alfred Balch (Reviewer 2):

1. Standard BE determination, with one wrinkle being that a crossover was not done, I can guess why, but maybe ought to be laid out for those less familiar with this kind of trial.

Response:

The following explanation was added starting on page 7, line 129: “A parallel-group study design was chosen, because adalimumab has a long elimination half-life and a crossover design would substantially increase the duration of the study. Furthermore, a crossover design was not considered appropriate to confirm PK characteristics in the present study, because in a previous phase 1 study comparing the PK characteristics of FKB327, EU-Humira, and US-Humira, ADAs were detected in approximately 70% of subjects across all treatment groups.”

2. Manuscript is well-written and clear, and methods seem appropriate. As a clarification, even though results relate to geometric mean parameters, data analysis is done on log-transformed data, with the assumptions that go with that (line 154, clarified later). For data like this with large CV, the CV and standard deviation of log are very different should be clarified when sigma for design of trial and summary statistics are reported.

Response:

Clarification has been provided under the “Sample size and statistical methods” section on page 9, second paragraph starting on line 197 of the manuscript, which states, “For these parameters,
LS means were calculated for the test product and RP. Mean differences between the test product and RP were calculated. The residual variance from the model was used to calculate 90% CI for the difference between the test product and RP. These values were back-transformed to give geometric LS means, a point estimate, and 90% CI for the ratio of the test product relative to the RP. This procedure is equivalent to Schuirmann’s two one-sided tests at the 0.05 level of significance.

3. Reference group should be identified for the BE.

Response:

The following sentence was added on page 9, line 184. “In the assessment of relative bioavailability, 3 comparisons were made (test product: reference product)—FKB327 PFS: FKB327 vial, FKB327 AI: FKB327 vial, and FKB327 AI: FKB327 PFS.”

4. Second analysis labeled as secondary.

Response:

The first sentence of the paragraph on page 11, line 251 was modified to read “The secondary analysis of PK parameters by body weight showed…”

The first sentence of the paragraph on page 12, line 259 was modified to read “The secondary analysis of PK parameters by injection site showed…”

Primary and secondary PK parameters in Table 2 were labeled to parallel how this was done in Table 3.