Author’s response to reviews

Title: The efficacy of a cyclin dependent kinase 9 (CDK9) inhibitor, FIT039, on verruca vulgaris: study protocol for a randomized controlled trial

Authors:

Takashi Nomura (tnomura@kuhp.kyoto-u.ac.jp)
Eriko Sumi (sumieri@kuhp.kyoto-u.ac.jp)
Saeko Nakajima (saenakajimakuhp@gmail.com)
Gyohei Egawa (gyohei@kuhp.kyoto-u.ac.jp)
Eiko Toichi (etoichi@kyotolan.hosp.go.jp)
Harue Tada (haru.ta@kuhp.kyoto-u.ac.jp)
Ryuji Uozumi (uozumi@kuhp.kyoto-u.ac.jp)
Takayuki Nakagawa (tknakaga@kuhp.kyoto-u.ac.jp)
Masatoshi Hagiwara (hagiwara.masatoshi.8c@kyoto-u.ac.jp)
Kenji Kabashima (kaba@kuhp.kyoto-u.ac.jp)

Version: 1 Date: 13 Jun 2019

Author’s response to reviews:

Response to comments by the Reviewer and the Associate Editor

We greatly appreciate the valuable comments by the Reviewer and the Associate Editor. Here, we respond to each comment one by one. We accordingly revised the manuscript. Revised parts are indicated with line numbers of the revised version in our responses. Deleted parts are indicated with strike-through in the revised manuscript. And the edited parts are indicated with red as well.

Comment 1: On page 18 in the sample size section, authors declare 80% power allowing for “ineligible patients”. Please define what this means in terms of who is excluded from the analysis.
Response: We have corrected “ineligible patients” to “patients who drop out of this trial and who fail to include the full analysis set” in lines 321 to 322 of the revised manuscript.

Comment 2: The generally accepted method of analyzing a randomized clinical trial is an intent to treat (ITT) analysis, in which all subjects randomized are analyzed. Please discuss whether an ITT analysis is being done and if not, why not.

Response: We will perform statistical analyses for efficacy endpoints according to the intention-to-treat principle. Thus, we have expressed the full analysis set “based on the intention-to-treat principle” in lines 302 to 303 of the revised manuscript, as described in the International Conference on Harmonisation (ICH) E9 guideline.

References:


Comment 3: The power is determined by a one-sided 10% level test. This is equivalent to a 20% two-sided type one error rate. For a trial of 44 subjects this seems unacceptably high. Please justify the need to have such a high type I error rate. It also seems that for this novel therapy a two-sided alpha level is of interest, and so the two-sided alpha is relevant. Even if the one-sided test is of interest, two-sided confidence intervals are also of interest and so some consideration to align the confidence interval with the significance of a one-sided test of level alpha/2 should be considered, otherwise there could be a discordant significance result compared to the 95% confidence interval. The proposed plan needs more clear justification.

Response: We have clarified that the primary efficacy analysis is performed with 80% confidence intervals in lines 307 to 311 of the revised manuscript. Moreover, we have provided the rationale for a one-sided significance level of 10% used in this phase I/II clinical trial in lines 324 and 328 of the revised manuscript.

Minor comments

Comment 2: Can the authors clarify why it had to be a single-blinded trial?

Response: We added the reason why this study is in a single-blinded manner on lines 151 to 152 of the revised manuscript. Since another study to examine the safety and efficacy of FIT039-tablet in patients with cervical intraepithelial neoplasia is ongoing in a single-blinded manner, we need to keep the difference between FIT039 and placebo unpublished.
Comment 3: It might be nice to clarify the power for a key secondary outcome for interpretive purposes.

Response: We did not set any of the “key” secondary endpoints in this phase I/II clinical trial. The efficacy analyses for the secondary endpoints defined in lines 268 to 272 of the original version are considered to be exploratory and not adjusted for multiple testing (corresponding to the lines 269 to 273 in the revised manuscript). Hence, we did not calculate the power for any of the secondary endpoints.

In addition to the above responses, we have edited followings to improve the readability of the manuscript:

(1) Lines 132 to 133 of the revised manuscript: An accepted manuscript by Ajiro et al. is cited as [14] because it has been published as is.

(2) Lines 230 to 231 of the revised manuscript: The part “and is distinguishable from placebo by careful comparison” is removed because of its redundancy with the lines 151 to 152 of the revised manuscript, an added sentence in response to Comment 2.

(3) Line 438 to 439: We add an acknowledge to Dr. Tsuyoshi Mitsuishi who kindly helped us in designing the study protocol.