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In reply: the evaluation of IgG titers' stability from blood samples is necessary

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▸ See the letter "Comments on: a phase 1/2a, dose-escalation, safety and preliminary efficacy study of oral therapeutic vaccine in subjects with cervical intraepithelial neoplasia 3" in volume 31, e43.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
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We appreciate the interest and comments by Dr. Zhang on our study. Please see below our answers to your questions.

Dr. Zhang asked whether the serum samples were tested separately or together at the same time. In fact, blood samples were collected at respective visits over the study, and the isolated sera were immediately frozen and stocked at −80°C until immunological analysis. In previous study evaluating the clinical efficacy of oral vaccine [1], immunologic responses were evaluated using the serum samples stocked in −40°C. For quantification of immunoglobulin G (IgG) antibody levels, Maxisorb™ ELISA plate was incubated at 4°C overnight [2,3]. In our study, the analysis was conducted at the same time after somewhat long storage. Dr. Zhang mentioned that more accurate data could have been acquired if the storage times were short and the analyses had been separately carried out. We agree to the comment in that some of human papillomavirus 16 (HPV16) E7-specific IgG in the serum might be degraded following the storage up to 2 years or so. In order to address Dr. Zhang' question, we are willing to do further research in the upcoming clinical phase 2b study.

The baseline titers of HPV16 E7-specific IgG were assessed for the blood samples collected from the patients before the initial treatment. In addition, colposcopic biopsy and Reid Colposcopic index score were also assessed before and after initial treatment. The IgG titers were extremely low except for one patient (D0401), however, there was no further evaluation. Nevertheless, the mean titer of enrolled patients increased after treatment, which indicated that systemic humoral immune responses were induced by our oral therapeutic vaccine.

Like Dr. Zhang's comment, the HPV16 E7-specific IgG titers may be influenced by storage conditions. Unfortunately, the correlation between storage conditions and IgG titers could not be examined due to unavailability of the long-term samples.

In conclusion, we investigated the clinical potential of oral therapeutic vaccine (*Lactobacillus casei* expressing HPV 16 E7) for the treatment of cervical intraepithelial neoplasia (CIN), which may replace conventional surgical treatment such as conization or loop electrosurgical excision procedure. Meanwhile, additional clinical research should be done for clinical

use and further studies related to the stability of the long-term stored samples should be considered in the clinical trial phase 2b study.

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