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Letter to the Editor

Comparable responses of immunological markers in Japanese and European subjects after SQ HDM SLIT-tablet treatment

Dear Editor,

Sublingual allergy immunotherapy (SLIT) tablets constitute an efficacious treatment for patients suffering from House Dust Mite (HDM) allergic rhinitis (AR) and allergic asthma (AA). Large clinical trials have established clinical efficacy of the SQ HDM SLIT-tablet in patient populations in geographically distinct regions such as Japan, Europe and North America.^{1–3} Evaluation of SLIT-tablet efficacy in clinical trials is most often based on changes in clinical symptoms and use of rescue medication.⁴ Although these parameters are clinically relevant and centered around patients' needs, they remain subjective and may be influenced by the individual patient's physical environment, ethnic diversity of the trial populations, and even cultural differences in different geographical regions. Use of objective markers of clinical outcome as well as immunological response to treatment will therefore be valuable for standardization of treatment outcome. Candidate biomarkers related to Allergen Immunotherapy (AIT), including SLIT, were recently evaluated by an EAACI task force.⁵ The task force identified seven domains of markers of AIT, in the form of immunological markers (IgE, different subclasses of IgG, IgE-blocking activity, cellular markers (T-cells, basophils), cytokines and chemokines), and provocation tests as markers of clinical effect.⁵ Importantly, there is currently no consensus on surrogate biomarkers that would be prognostic and/or predictive of clinical response in successful AIT. Given the clear advantage of objective markers of AIT it was recommended to investigate IgG4 as an immunological marker of compliance and IgE-blocking as an immunological marker for clinical outcome.⁵ To investigate the consistency and robustness of immunological markers of SQ HDM SLIT-tablet treatment in successful clinical trials, we report for the first time serological data (HDM IgE, IgG4, IgE-blocking factor [IgE-BF]) from the Japanese HDM AR phase II/III trial TO-203-3-2.¹ Furthermore, we compare HDM IgE-BF data from TO-203-3-2 with corresponding data from two large European SQ HDM SLIT-tablet trials, MITRA (MT-04)² and MERIT (MT-02).⁶ These trials are summarized in Table 1.

The SQ HDM SLIT-tablet contains extract of both *Dermatophagoides pteronyssinus* (*D. pteronyssinus*) and *Dermatophagoides farinae* (*D. farinae*).⁷ Allergen-specific IgE and IgG4 were measured separately for *D. pteronyssinus* and *D. farinae* in serum samples from TO-203-3-2 by ImmunoCap (Thermo-Fisher, Japan). IgE-BF was measured on a modified AdviaCentaur instrument with extract from both *D. pteronyssinus* and *D. farinae*⁸ (ALK-Abelló A/S, Denmark) (see Supplementary Fig. 1 for details of the IgE-BF assay). Human serum samples were collected with full consent from the

donors, and with approval from the local ethical committee. The trial complied with Good Clinical Practice guidelines and the Declaration of Helsinki. All procedures were approved by both the Ethics Committees of Torii and the Institutional Review Board of each clinical site. Written informed consent was obtained from all subjects before the study. The strength of the SQ HDM SLIT-tablet is measured in the proprietary unit SQ-HDM or Japanese Allergen Units (JAU). In Europe and North America, the SQ HDM SLIT-tablet is available as 12 SQ-HDM/20,000 JAU, and in Japan, as 2 SQ-HDM/3300 JAU and 6 SQ-HDM/10,000 JAU.

In groups of patients receiving AIT the expression of allergen-specific antibodies is known to follow typical patterns in terms of concentrations and kinetics. The group mean concentration of allergen-specific IgE increases at the early stages of treatment followed by a decrease, while mean allergen-specific IgG4 levels increase sharply during the first weeks to months of treatment and may continue to rise at a reduced rate throughout the treatment period.⁹ Correlations between increased expression allergen-specific antibodies of different isotypes (IgE, IgG, IgG1, IgG4) as a result of AIT has been demonstrated.¹⁰ As seen in Figure 1A, B, these patterns are reproduced in the Japanese TO-203-3-2 trial. Here, the IgG4 levels reached a plateau between week 12 and 20 with no further increase. No differences between *D. pteronyssinus* and *D. farinae* responses were seen (data not shown). Similar antibody responses have previously been reported from the European MITRA trial² and a North American SQ HDM SLIT-tablet Phase III trial.³ In TO-203-3-2, mean IgE and IgG4 change from baseline responses are all statistically significantly different from placebo but in contrast to the allergen-specific IgE response where there was no difference between the two active doses, a small but statistically significant difference between 6 SQ-HDM/10,000 JAU and 12 SQ-HDM/20,000 JAU was seen for IgG4 (Fig. 1B). A similar difference between the IgG4 responses to 6 SQ-HDM/10,000 JAU and 12 SQ-HDM/20,000 JAU has been reported for the European MITRA trial.²

While IgG4 represents an antibody titer, the functional IgE-BF assay⁸ is a measure of the inhibition of IgE-allergen binding by allergen-specific non-IgE antibodies and possibly other serological factors and may therefore be more closely related to the immunological mechanism underlying the immune-modulatory effects of AIT. The two European trials MT-02 and MITRA IgE-BF showed a dose-response relationship similar to IgG4 (Fig. 1 C, D), but in the Japanese TO-203-3-2 trial no statistically significant difference was seen between the IgE-BF responses to 6 SQ-HDM/10,000 JAU

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Table 1
SQ HDM SLIT-tablet trials.

Trial	Phase	Primary endpoint	Target population	Region	Age/years	Doses	Serum samples (N/treatment group)	Reference
TO-203-3-2	II/III	Total combined rhinitis score (TCRS)	HDM AR	Japan	12–64	6 SQ-HDM/10,000 JAU 12 SQ-HDM/20,000 JAU	313–319 (sIgE, sIgG4) 120 (IgE-BF)	¹
MERIT (MT-02)	II	ICS dose reduction	HDM AA + AR	Europe	≥14	1 SQ-HDM 3 SQ-HDM 6 SQ-HDM/10,000 JAU	34–39 (IgE-BF)	⁶
MITRA (MT-04)	III	Time to first moderate or severe asthma exacerbation during ICS reduction	HDM AA + AR	Europe	≥18	6 SQ-HDM/10,000 JAU 12 SQ-HDM/20,000 JAU	227–237 (IgE-BF)	²

Serum samples from three SQ HDM SLIT-tablet trials, one conducted in Japan (TO-203-3-2) and two in Europe (MT-02 and MITRA) were used for determination and comparison of allergen-specific immune responses during treatment. AA, allergic asthma; AR, allergic rhinitis; IgE-BF, IgE blocking-factor; sIgE, allergen-specific IgE; sIgG4, allergen-specific IgG4. N/treatment group specifies the number of sera included from each trial in the indicated analyses.

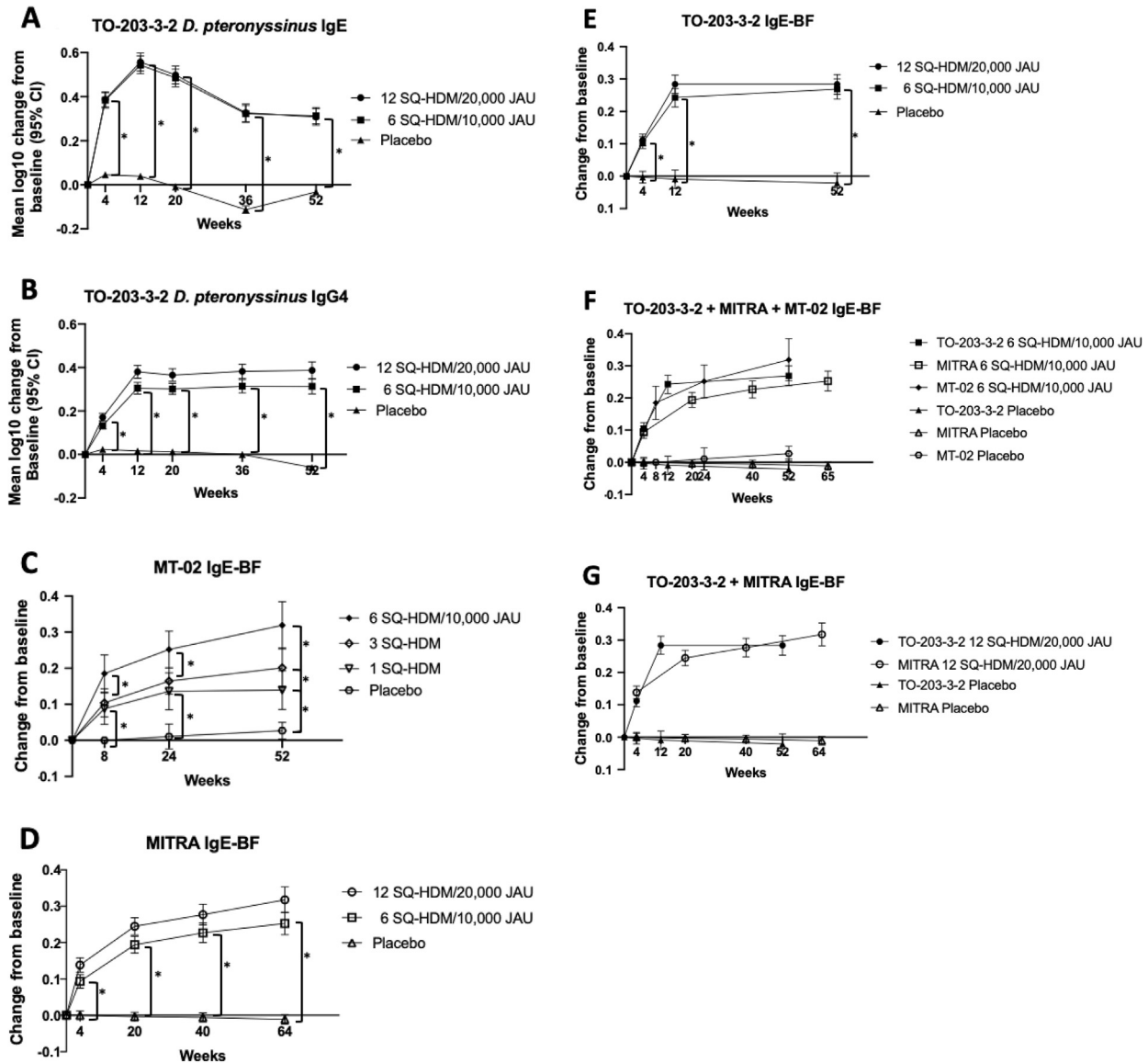


Fig. 1. Serum samples from the Japanese TO-203-3-2 AR trial were examined for IgE (**A**) and IgG4 (**B**) against *Dermatophagoides pteronyssinus*, and IgE blocking-factor (IgE-BF, combined *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) (**C–G**). The European trials MT-02 and MITRA were examined for IgE-BF (**C, D**). The IgE-BF responses of the two active doses in TO-203-3-2 were compared (**E**). The IgE-BF responses in the TO-203-3-2 and MITRA trials were compared for 6 SQ-HDM/10,000 JAU (**F**) and 12 SQ-HDM/20,000 JAU (**G**). All active groups were statistically significantly different from placebo at all time-points. Statistical analyses were done using GraphPad Prism version 7.02 (GraphPad Software, San Diego, California). All data points are illustrated as mean (95% CI). **p* < 0.05. **All panels:** Solid circles: TO-203-3-2 12 SQ-HDM/20,000 JAU, solid squares: TO-203-3-2 6 SQ-HDM/10,000 JAU, solid upward triangle: TO-203-3-2 placebo, open circles: MITRA 12 SQ-HDM/20,000 JAU, open squares: MITRA 6 SQ-HDM/10,000 JAU, open upward triangle: MITRA placebo, solid diamond: MT-02 6 SQ-HDM/10,000 JAU, open diamond: MT-02 3 SQ-HDM, open downward triangle MT-02 1 SQ-HDM, open hexagon: MT-02 placebo. JAU: Japanese allergen unit. **Panels A, B:** V0 = baseline visit, Vi = visit at the week indicated on the x-axis. Mean log10 change from baseline (95% CI): Log10 value of the change in antibody concentration (IgE: kU/L, IgG4: mg/L) between Vi and V0. *D. pteronyssinus*: *Dermatophagoides pteronyssinus*. **Panels C–G:** IgE-BF: IgE blocking factor. "Change from baseline" (the unit of IgE-BF): between 0 (= no presence of IgE-blocking components) and 1 (= all IgE blocked from binding to allergen).

and 12 SQ-HDM/20,000 JAU (Fig. 1E). Although a direct link between treatment-induced changes of allergen-specific antibody levels and clinical effect in individual patients remains to be established, it is interesting to note that on the group level the lowest IgE-BF responses were seen with the two doses (1 and 3 SQ-HDM, Fig. 1C) that did not reach clinical effect in the MT-02 trial.⁶ Whether the finding of no statistically significant difference between the IgE-BF response to the two doses in TO-203-3-2 indicates actual differences between the Japanese and European populations or simply reflects that both 6 SQ-HDM/10,000JAU and 12 SQ-HDM/20,000 JAU are near the optimal dose cannot be determined from the current data. However, the latter is supported by the fact that both doses have demonstrated clinical efficacy in a European as well as a Japanese population.^{1,2} Additionally, overlay plots of the IgE-BF data from the Japanese and European SQ HDM SLIT-tablet trials are almost superimposable (Fig. 1 F, G) which further emphasizes the striking similarities of the SQ HDM SLIT-tablet induced serological immune responses in the two geographically distinct populations.

In conclusion, immunological data from clinical trials in Japan and Europe indicates that at the group level, the immunomodulatory effects of 6 SQ-HDM/10,000 JAU and 12 SQ-HDM/20,000 JAU are comparable, which is in alignment with the finding that both SQ HDM SLIT-tablet doses are clinically efficacious.^{1,2,6} Furthermore, the reproducibility of the IgE-BF responses in the European and Japanese populations that comprise both HDM AA and AR patients supports the robustness and reproducibility of the SQ HDM SLIT-tablet as a treatment option for HDM-induced allergic disease in different geographical regions and populations.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2019.10.006>.

Conflict of interest

KOD and MK are employees of Torii Pharmaceuticals. KL, HI, PSA and TS are shareholders of ALK-Abelló. PSA and TS are employees of ALK-Abelló. KL, HI and JCV are advisors to ALK-Abelló. TM is advisor to Torii Pharmaceuticals. HM has no conflict of interest.

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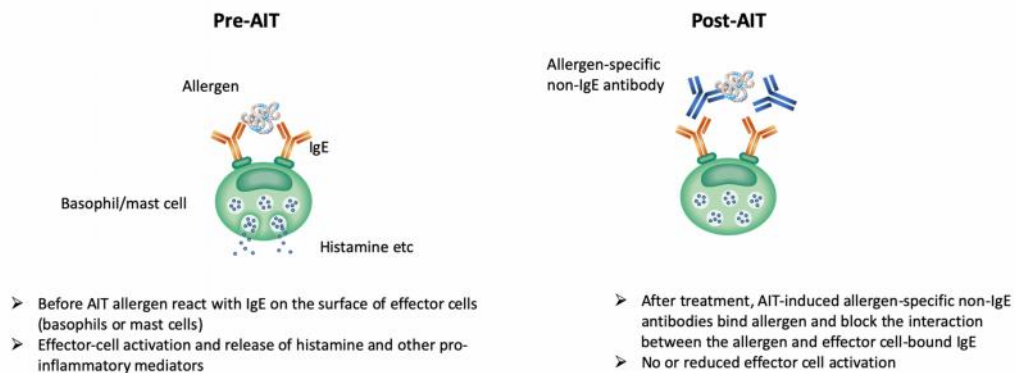
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Supplementary Figure 1

IgE-blocking antibodies in-vivo



IgE blocking antibodies in-vitro

