



Efficacy and safety of house dust mite sublingual immunotherapy tablets in allergic rhinitis: A systematic review and meta-analysis

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ABSTRACT

Background: House dust mite (HDM) sublingual immunotherapy (SLIT) tablets have been approved for the treatment of patients with allergic rhinitis (AR). However, the meta-analysis on the efficacy of HDM-SLIT tablets for HDM-induced AR patients remained limited.

Methods: Five databases were searched including: PubMed/MEDLINE, EMBASE, Web of Science, the Cochrane Central Register of Controlled Trials, and CINAHL for randomized controlled trials (RCTs) that addressed the efficacy and safety of HDM-SLIT tablets compared with placebo until January 2022. The primary outcome was a combined symptom and medication score (CSMS) after treatment.

Results: Eight eligible RCTs were identified with a total of 3601 patients treated with HDM-SLIT tablets and 2783 patients who received a placebo. The CSMS was significantly lower in the HDM-SLIT tablet group compared with the placebo (standardized mean difference (SMD) -0.28 [95% CI: -0.32 to -0.23]). There was a significant reduction in rhinitis symptom scores, rhinitis medication scores, total combined conjunctivitis scores, and rhinoconjunctivitis quality of life questionnaire scores. The consistent efficacy compared to the placebo has been exhibited over the different kinds and doses of HDM tablets (6 SQ, 12 SQ, 300 IR, and 500 IR) and age groups (>5 years old, adolescents and adults) with low degrees of variability across the studies. There was no significant difference in proportions of participants who were injected with epinephrine between the treatment- and placebo groups.

Conclusions: HDM-SLIT tablet is an effective treatment in reducing rhinitis symptoms and medication use in AR patients with favorable safety. They also improve quality of life and conjunctivitis symptoms.

Keywords: Allergic rhinitis, Efficacy, House dust mite, Safety, Sublingual immunotherapy

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<http://doi.org/10.1016/j.waojou.2022.100691>

Received 15 June 2022; Received in revised form 5 August 2022; Accepted 5 August 2022

Online publication date xxx

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INTRODUCTION

Allergic rhinitis (AR) is a common condition affecting up to 40% of the population worldwide.^{1,2} AR is characterized by repeated symptoms of sneezing, itchy nose, rhinorrhea, and nasal obstruction. It also has a significant economic burden with both direct and indirect costs, loss of work productivity, and quality of life.³ The standard treatment of AR has been with allergen avoidance strategies and pharmacotherapy. However, for patients who fail to respond to pharmacotherapy, allergen immunotherapy (AIT) has become apparent as a treatment option.⁴⁻⁶

AIT modulates the immune system and is currently considered to be the only treatment with a potentially long-lasting disease modification.⁴⁻⁶ The traditional routes of AIT are administered as subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT). Both have been proven efficacious in several randomized controlled trials (RCTs) and meta-analyses.⁷⁻¹⁰ The use of SLIT has become a more favored approach due to the convenience of application and high safety profile.^{11,12} The formulations of SLIT include drops and tablets. The use of SLIT tablets has spread gradually and replaced the SLIT drops because of their easier-to-use more reliable allergen dose, and scientific evidence on clinical efficacy.

The house dust mite (HDM) is one of the most common allergens worldwide, and the major strains are *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*. HDM has a well-established causal role in AR and asthma patients.¹³ The efficacy of HDM-specific AIT in patients with allergic respiratory conditions has been demonstrated in several meta-analyses of double-blind, placebo-controlled (DBPC) trials of SCIT and SLIT in adults and children with AR and allergic asthma.^{10,14,15} They have shown that HDM-AIT is effective in relieving symptoms, decreasing rescue medication use, and improving quality of life scores. However, there is a high degree of heterogeneity in the study designs, study populations, AIT formulations, and outcome criteria used in clinical trials.¹⁶ The most recent network meta-analysis indirect comparison of HDM-SCIT and HDM-SLIT has suggested that SCIT may be more effective than SLIT drops and tablets in controlling AR symptoms. However, the numbers of participants in SCIT- and

SLIT drops-RCTs were very small in comparison to the large well-design DBPC trials of SLIT tablets. Additionally, the RCTs on SCIT and SLIT drops are highly variable in allergen formulations, dosing, and clinical outcome measurements.¹⁰ Recently, the European Academy of Allergy and Clinical Immunology (EAACI) proposed a harmonized, standardized definition of the combined symptom and medication score (CSMS) for use as a primary endpoint in AIT trials.¹⁷

To our knowledge, there are only two HDM-SLIT tablets that have been approved in various parts of the world; standardized quality (SQ)-HDM, and index of reactivity (IR)-HDM. No meta-analysis to date has analyzed the efficacy SLIT tablets exclusively in HDM-induced AR patients using the CSMS as a primary outcome. The current study aimed to evaluate the efficacy of SLIT tablets on HDM-induced AR patients on rhinitis symptom and medication scores, conjunctivitis scores, quality of life, and safety.

METHODS

Protocol and registration

This systematic review and meta-analysis were conducted following the Cochrane Handbook for Systematic Reviews of Interventions version 6.0¹⁸ and reported in compliance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA).¹⁹ We registered the study protocol in PROSPERO (Registration Number CRD42021268890). Due to the nature of the study, it was considered exempt from ethics approval.

Data source and search strategy

Five electronic databases were searched including PubMed, EMBASE, Web of sciences, the Cochrane Central Register of Controlled Trials, and CINAHL for relevant literature from their inception through to January 1, 2022, restricted to the English language. A literature search was carried out by 2 independent authors (PK, and ML) using a structured search strategy (the search strategies are provided in [Table E1](#)). Controlled vocabulary terms were utilized specifically for each database as applicable such as the Medical Subject Heading (MeSH) for PubMed grey literature was obtained to identify additional

studies that were not published or controlled by commercial publishers through Google Scholar advanced search. All the reference lists of identified publications were checked for additional eligible publications.

Study selection

Two authors (PK, and ML) independently screened titles and abstracts of all retrieved research articles from databases and identified articles that met the inclusion criteria. The reasons for the exclusion of any study were compared and discussed. Any disagreement was resolved by a consensus meeting with the third author (PP).

We included randomized controlled trials (RCT), regardless of sample size, which fulfilled the following criteria: 1) reported on patients with HDM-induced allergic rhinitis with or without other atopic diseases eg, atopic asthma, allergic conjunctivitis, in any age group; 2) reported the effects of HDM-SLIT tablets in any dose for at least one-year duration compared with placebo as a control group, and 3) reported the outcomes of interest. The exclusion criteria of articles were 1) no full text available, 2) non-English studies, 3) studies that use allergoid HDM-SLIT tablets, 4) studies that recruited patients mainly suffering from allergic asthma, 5) studies with inconsistent outcome indicators, or 6) studies with primary outcome evaluated by allergen provocation test such as allergen exposure chamber.

Outcome measures

The primary outcomes were efficacy, mean difference of CSMS (which may be used in other terms; total combined rhinitis score [TCRS], or a combined score) between patients who received HDM-SLIT tablets compared with the placebo group during the end of the treatment period.

The secondary outcomes were the mean difference of rhinitis symptom scores (RSS), rhinitis medication scores (RMS), total combined conjunctivitis scores (TCCS), Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), and global evaluation of treatment efficacy (defined as the patient's self-reported improvement) compared between patients received HDM-SLIT tablet and placebo group. All these outcomes were also assessed during the end of the treatment period.

The acceptability of treatment is defined by the study of patient dropout for any reason, encompassing efficacy and tolerability.

The safety outcomes were assessed by the number of patients who had any treatment-related adverse events (TRAE) and adverse events (AE) leading to discontinuing the treatment compared between 2 groups.

Data extraction

Two authors (PK, and ML) independently extracted data on study authorship, year of publication, country, study design, inclusion and exclusion criteria, patient characteristics, details of the intervention and control, sample size, outcome measures, and main results. Data extraction was cross-checked, and any discrepancies were reconciled through discussion with the third author (PP). For studies with incomplete outcome data, we contacted the corresponding authors of those studies via e-mail. If there was no response within 2 weeks, the data were imputed (if feasible) or reported as missing.

For continuous outcomes (eg, CSMS, RSS, etc.), we extracted the exact mean value and their standard deviation (SD) on the full analysis set (FAS) in each group and the number of participants was extracted. If studies presented the means and SD only in figures, we extracted the data from the figures using the Digitizeit program (<http://www.digitzeit.de/>). For studies reporting medians and interquartile range, means and SD were calculated using methods proposed by Wan et al.²⁰ If the SD of the score were not available, the imputation of SD was calculated based on the 95% the difference in the score between the HDM-SLIT and placebo groups according to the recommendations by the Cochrane Handbook for Systematic Reviews of Interventions.¹⁸

For binary outcomes eg, global evaluation, or safety: We extracted the number of patients who reported being better and much better at the end of the treatment. The safety outcome was extracted as the number of patients who developed TRAE included mild, moderate, and severe in each treatment arm.

Risk of bias assessment

Two authors (PK, and PP) independently assessed the methodological quality of included trials, and consensus was reached by discussion with a third party (ML) in case of discrepancy. The quality of each study was rated using Risk-of-Bias 2 (RoB2) tool for RCTs by the Cochrane collaboration.²¹ The methodological quality was assessed in 5 domains, as follows: 1) bias arising from the randomization process; 2) bias due to deviations from intended interventions; 3) bias due to missing outcome data; 4) bias in the measurement of the outcome; and 5) bias in the selection of reporting the result. Each study was rated according to the RoB2 algorithm.

Data synthesis and analysis

All statistical analyses were performed using Stata statistical package version 17 (StataCorp, College Station, Texas, USA). A two-tailed, P-value less than 0.05 was used for statistical significance. A meta-analysis was performed by using DerSimonian and Laird random-effects model to estimate the pooled estimates with their 95% confidence intervals (95% CI).²² For continuous outcomes eg, CSMS that is, continuous data with varying scales of measurements, standardized mean difference (SMD) was used for data pooling. For SMD, the definition of treatment effects by Cohen for meaningful interpretation was followed; a pooled difference of 0.2, 0.5, and 0.8 was considered to be a small effect, medium effect, and large effect, respectively.²³ For dichotomous outcomes eg, the acceptability of treatment and safety outcomes were summarized by pooled relative risk (RR) with 95% CI.

Heterogeneity was assessed using the I^2 statistic, which ranges between 0% and 100%, with higher values indicating greater degrees of variability across the study results. I^2 values of 25%, 50%, and 75% have been suggested to indicate low, moderate, and high heterogeneity, respectively.¹⁸

In addition, subgroup analysis was analyzed according to age (children 5-11 years and ≥ 12 years old), and dose of treatment which were divided into four groups: defined as patients who received 6 SQ-HDM or equivalent (10,000

Japanese Allergy Unit (JAU)); 12 SQ-HDM or equivalent (20,000 JAU); 300 IR-HDM; and 500 IR-HDM sublingual tablet formulation.

All results of the meta-analyses were visualized by forest plots. Funnel plots were generated to detect publication bias.

Grading the strength of evidence

We graded the strength of evidence for the primary outcome (CSMS) by considering the ROB of each study, inconsistency of the results, indirectness of evidence, imprecision, and reporting bias following the Grading of Recommended Assessment, Development, and Evaluation approach (GRADE).²⁴

RESULTS

The systematic literature search details are provided in Fig. 1. A total of 1132 studies were identified from five electronic databases. Of these studies, 524 studies were duplicates and removed. By screening titles and abstracts, 56 full texts of potentially relevant studies were retrieved. After exclusion for study type, population, investigation treatment, outcome measures, and full text available, 8 studies were included in the systematic review and meta-analysis.²⁵⁻³² Characteristics and main findings of the selected studies are presented in Table 1 and Table E2.

All 8 studies were RCTs, of which 4 studies had a three-arm parallel design,^{25,26,28,29} and 4 studies^{27,30-32} had a two-arm design included a total of 3601 patients were treated with HDM-SLIT tablets and 2783 patients who received placebo. Four studies were performed in Japan, 2 in Europe, 1 in North America, and 1 in multiple continents (Europe, North America, Russia, and Israel). Seven hundred and ninety-one patients were treated with 6 SQ-HDM or equivalent, 1131 patients received 12 SQ-HDM or equivalent, 1247 received a 300 IR sublingual tablet formulation, and 432 patients received 500 IR. The treatment duration of all studies was approximately one year (52 weeks).²⁶⁻³² Only 1 study reported the response during the subsequent treatment-free year.²⁵

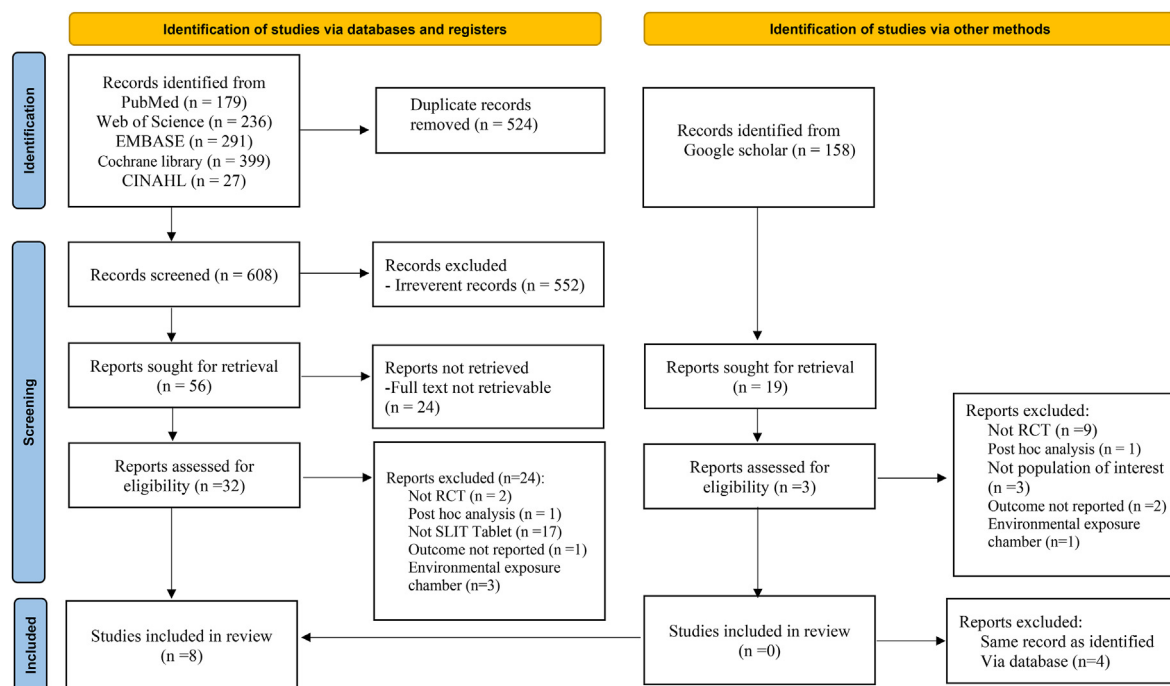


Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of included and excluded studies.

Risk of bias for included studies

Fig. 2 shows the risk of bias within all included RCTs. In terms of study quality, seven studies were found to have a low risk of bias. Only one study had some concerns regarding missing outcome data.³² Details on the risk-of-bias evaluation for each included study are shown in Table E3.

The combined symptom and medication score (CSMS)

The primary outcome was the average CSMS at 44-52 weeks after the treatment. Results are shown in Fig. 3A. The CSMS was significantly lower in all HDM-SLIT tablet groups compared with placebo (SMD -0.28 [95% CI: -0.32 to -0.23]; $p < 0.01$). For subgroup analysis according to the dose of treatment, the reduction in the CSMS compared with the placebo group was SMD -0.35 [95% CI: -0.45 to -0.25] for the 6 SQ-HDM groups, SMD -0.28 [95% CI, -0.36 to -0.20] for 12 SQ-HDM group, SMD -0.25 [95% CI: -0.33 to -0.18] for 300 IR group, and SMD -0.23 [95% CI: -0.36 to -0.10] for 500 IR group, respectively. The pooled SMD of CSMS was not significantly different across treatment groups ($p = 0.43$).

The rhinitis symptom scores (RSS) and rhinitis medication scores (RMS)

Our meta-analysis revealed a significant reduction of RSS in the HDM-SLIT tablet group relative to the placebo group with pooled SMD of -0.27 [95% CI: -0.32 to -0.23]; $p < 0.01$, Fig. 3B. In comparison with placebo, 6 SQ-HDM (SMD -0.33 [95% CI: -0.50 to -0.17]), 12 SQ-HDM (SMD -0.27 [95% CI: -0.34 to -0.19]), 300 IR (SMD -0.26 [95% CI: -0.33 to -0.18]), and 500 IR (SMD -0.24 [95% CI: -0.37 to -0.11]) were shown to have low treatment effects with statistical significance in each subgroup. However, the pooled SMD of RSS had no significant differences between groups ($p = 0.82$).

In addition, subgroup analysis was analyzed according to age (children 5-11 years and ≥ 12 years old). The pooled SMD was significant decrease -0.36 [95% CI: -0.54 to -0.19] for patients 5-11 years old, and -0.26 [95% CI: -0.31 to -0.22] for patients with ≥ 12 years old. The pooled SMD of RSS showed no differences between age groups ($p = 0.29$) (Figure E1).

Fig. 4A showed a significant reduction of RMS in the HDM-SLIT group relative to the placebo group with SMD -0.11 [95% CI: -0.16 to -0.07]; $p < 0.01$.

Study	Country	Type/duration	Inclusion criteria	Study size (n)	Intervention (n)	Age (y)	Female (%)	Polysensitized (%)	Asthma (%)	Outcome assessment
Bergmann 2014	7 European countries	RDBPC, 2 years (treatment for 1st year, observed in 2nd year)	18-50 YO HDM-induced AR ±controlled asthma HDM SPT ≥3 mm and HDM slgE ≥0.7 kU/mL without other allergens induced AR ARTSS ≥5	509	500 IR-HDM tablets, n = 169	30.1 ± 8.4	51	55	29	Primary end point: AASS during the year 1 primary period Secondary end points: ARTSS, ARSS, ARMS, and the patient's global evaluation of treatment efficacy
					300 IR-HDM tablets, n = 170	29.0 ± 8.5	56	48	32	
					Placebo, n = 170	30.0 ± 8.9	49	54	29	
Nolte 2016	USA, Canada	RDBPC, 52 weeks	≥12 YO with HDM induced AR/C ±controlled asthma HDM SPT ≥5 mm and slgE ≥0.7 kU/mL DSS ≥6/≥5 with 1 severe symptom	1482	12 SQ-HDM tablets, n = 741	35 ± 14	60	75	31	Primary end point: TCRS during last 8 treatment weeks Secondary end points: the average rhinitis DSS, DMS TCS, VAS, RQLQ asthma DSS Serum HDM specific IgE, IgG4 level at run-in week 4, week 20, end of trials
					Placebo, n = 741	35 ± 14	58	77	31	
Demoly 2016	12 European countries	RDBPC, 52 weeks	18-65 YO HDM-induced AR/C ±controlled asthma (GINA step 1-2) HDM SPT ≥3 mm and slgE ≥0.7 kU/mL DSS ≥6/≥5 with 1 severe symptom No seasonal AR/C	992	12 SQ-HDM tablet, n = 318	32.1 ± 10.6	49	66	48	Primary end point: TCRS during last 8 treatment weeks Secondary end points: the average RCSS, RCMS, CCS, CSS, CMS, TCS, RQLQ, symptom-free days, global evaluations
					6 SQ-HDM tablet, n = 336	32.5 ± 11.2	51	71	45	
					Placebo, n = 338	32.2 ± 10.9	51	69	45	
Okubo 2017	Japan	RDBPC, 52 weeks	12-64 YO HDM-induced AR without asthma DSS ≥7 Positive HDM NPCT HDM slgE ≥0.35 kU/mL without ≥5 kU/mL of other allergens	946	12 SQ-HDM (20,000 JAU) tablet, n = 314	26.8 ± 12.1	54	82	-	Primary end point: TCRS during last 8 treatment weeks Secondary end points: RSS, RMS, CCS, CSS, CMS, JRQLQ
					6 SQ-HDM (10,000 JAU) tablet, n = 313	27.2 ± 12.0	50	76	-	
					Placebo, n = 319	26.8 ± 11.7	59	80	-	

Okamoto 2017	Japan	RDBPC, 52 weeks	12-64 YO HDM-induced AR/ C ±controlled asthma Positive HDM NPCT HDM sIgE ≥0.7 kU/mL without other allergens induced AR ARTSS ≥6	968	500 IR-HDM tablets, n = 296	30.5 ± 11.7	57	70	NA	Primary end point: AASS during last 8 treatment weeks Secondary end points: ARTSS, AMS, ACS, ATRCS, JRQLQ Serum HDM specific IgE, IgG4 level at baseline and week 52
					300 IR-HDM tablets, n = 315	30.0 ± 11.8	54	69	NA	
					Placebo, n = 316	30.2 ± 11.6	57	69	NA	
Masuyama 2018	Japan	RDBPC, 52 weeks	5-17 YO HDM-induced AR ±controlled asthma DSS ≥7 Positive HDM NPCT HDM sIgE >0.35 kU/mL without >5 kU/mL of other allergens	458	6 SQ-HDM (10,000 JAU) tablet, n = 227	10.8 ± 2.9 (56%, age 5-11 YO)	34	78	4	Primary end point: TCRS during last 8 treatment weeks Secondary end points: RSS, RMS, CCS, CSS, CMS, JRQLQ Serum HDM specific IgE, IgG4 level at baseline and week 52
					Placebo, n = 231	10.7 ± 3.1 (58%, age 5-11 YO)	33	68	3	
Okamoto 2019	Japan	RDBPC, 52 weeks	5-16 YO HDM-induced AR without persistent asthma (required inhaled steroids) Positive HDM NPCT HDM sIgE ≥0.7 kU/mL without other allergens induced AR ARTSS ≥6	438	300 IR-HDM tablets, n = 219	10.3 ± 2.7	40	81	13	Primary end point: AASS during last 8 treatment weeks Secondary end points: ARTSS, AMS, ACS, ATRCS, JRQLQ Serum HDM specific IgE, IgG4 level at baseline and week 52
					Placebo, n = 219	10.4 ± 2.7	37	80	15	
Demoly 2021	9 European countries, USA Israel, Canada, Russia	RDBPC, 52 weeks	12-65 YO HDM-induced AR/ C with self-reported troublesome symptoms ±controlled asthma (GINA step 1-2) HDM SPT ≥5 mm and sIgE ≥0.35 kU/mL without other significant allergens induced AR	1607	300 IR-HDM tablets, n = 802	29.5 ± 13.1	51	44	38	Primary end point: average TCS during last 4 treatment weeks Secondary end points: the average CSMS, RMS, RCTSS, PSCD, RQLQ
					Placebo, n = 805	29.6 ± 12.6	52	46	37	

Table 1. Characteristics of included studies. RDBPC, randomized, double-blind, placebo-controlled trial; HDM, house dust mite; AR/C, allergic rhinitis/conjunctivitis; SPT, skin prick test; sIgE, specific IgE; DSS, daily symptom score; NPCT, nasal provocation test; ARTSS, average rhinitis total symptom score; GINA, Global Initiative for Asthma; SQ, standardized quality unit; IR, index of reactivity; JAU, Japanese allergen unit; TCRS, total combined rhinitis score; DMS, daily medication score; TCS, total combined score; VAS, visual analog scale; RQLQ, rhinoconjunctivitis quality of life questionnaire; RCSS, rhinoconjunctivitis symptom score; RCMS, rhinoconjunctivitis medication score; CCS, conjunctivitis combined score; CSS, conjunctivitis symptom score; CMS, conjunctivitis medication score; RSS, rhinitis symptom score; RMS, rhinitis medication score; JRQLQ, Japanese rhinoconjunctivitis quality of life questionnaire; AASS, average adjusted symptom score; ARTSS, average rhinitis total symptom score; AMS, average medication score; ACS, average combined score; ATRCS, average total rhinoconjunctivitis score; RCTSS, rhinoconjunctivitis total symptom score; PSCD, proportion of symptom-controlled days

Study	Risk of bias domains					Overall	Domains
	D1	D2	D3	D4	D5		
Bergman 2014	+	+	+	+	+	+	D1 Bias arising from the randomization process
Demoly 2016	+	+	+	+	+	+	D2 Bias due to deviations from the intended interventions
Nolte 2016	+	+	+	+	+	+	D3 Bias due to missing outcome data
Okamoto 2017	+	+	+	+	+	+	D4 Bias in measurement of the outcome
Okubo 2017	+	+	+	+	+	+	D5 Bias in selection of the reported result
Masuyama 2019	+	+	+	+	+	+	Judgement
Okamoto 2018	+	+	+	+	+	+	Low risk
Demoly 2021	+	+	!	+	+	!	Some concerns

Fig. 2 Risk-of-bias assessment of included studies.

Rhinoconjunctivitis quality of life questionnaire (RQLQ)

A total of three studies assessed RQLQ with 1836 patients in the HDM-SLIT group and 1659 patients in the placebo group.^{26,27,32} There was a significant reduction of RQLQ score in the HDM-SLIT group relative to the placebo group with pooled SMD of -0.23 [95% CI: -0.29 to -0.16]; $p < 0.01$ (Fig. 4B).

Global evaluation of treatment efficacy

A summary of 5 studies^{25,26,28,30,31} with 1903 patients in the HDM-SLIT group and 1210 patients in the placebo group assessed for the number of patients' self-reported improvement at the end of treatment is shown in Fig. 4C. The proportion of patient in HDM-SLIT group (1471/1903, 77.3%) reported improvement to be significantly higher than the placebo (759/1210, 62.7%), $RR = 1.23$ [95% CI: 1.16 to 1.30]; $p < 0.01$.

Total combined conjunctivitis scores (TCCS)

Three studies^{26,28,30} reported TCCS, and we demonstrated a significant reduction in the HDM-SLIT group relative to the placebo group with pooled SMD of -0.23 [95% CI: -0.33 to -0.12]; $p < 0.01$ (Fig. 4D).

The acceptability of treatment

The number of patients in the HDM-SLIT group (635/3609, 17.6%) showed significantly higher dropout for any reason than placebo (371/2823, 13.2%), $RR 1.32$ [95% CI: 1.06 to 1.63]; $p = 0.01$ (Figure E2(A)).

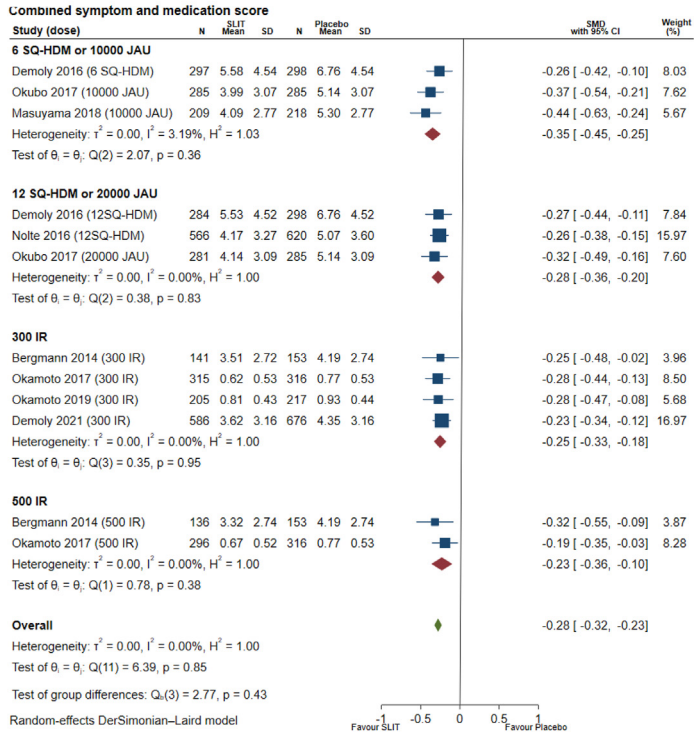
Safety outcomes

A total of 8 studies reported TRAE, 4255 patients received HDM-SLIT Tablet and 3138 patients received placebo. The adverse events of the included trials' participants were summarized in Table E4. Of the 2839 (66.7%) of treatment groups and 809 (25.8%) of the placebo group reported TRAE. Eight participants from the treatment group (0.20%) and 7 participants from the placebo group (0.24%) were injected with epinephrine due to systemic reactions during the trials. No fatal reaction was reported. HDM-SLIT group showed a significantly higher probability to develop TRAE than the placebo group, $RR 2.80$ [95% CI: 2.02 to 3.89]; $p < 0.01$ (Fig. 5). Most patients reported mild to moderate severity of TRAE. Only 11 (0.3%) patients in the HDM-SLIT group reported severe TRAE from three studies.^{26,31,32} There was no severe TRAE in the placebo group that showed no significant risk of patient-developed TRAE by subgroup dose ($p = 0.70$). In addition, our study showed a statistically significant higher probability occurred adverse events leading to discontinuation in the patients who received HDM-SLIT tablet, $RR 2.08$ [95% CI: 1.40 to 3.07; $p < 0.01$], Figure E2(B).

Assessment of heterogeneity, publication bias, and strength of evidence

From the results of the meta-analysis, most of the outcomes showed no heterogeneity ($I^2 < 25\%$), including CSMS, RSS, RMS, and RQLQ. There was some evidence of low to moderate statistical heterogeneity, TCCS ($I^2 = 41.41\%$) and global evaluation ($I^2 = 43.89\%$). Only one outcome carried high heterogeneity, which was treatment-

A.



B.

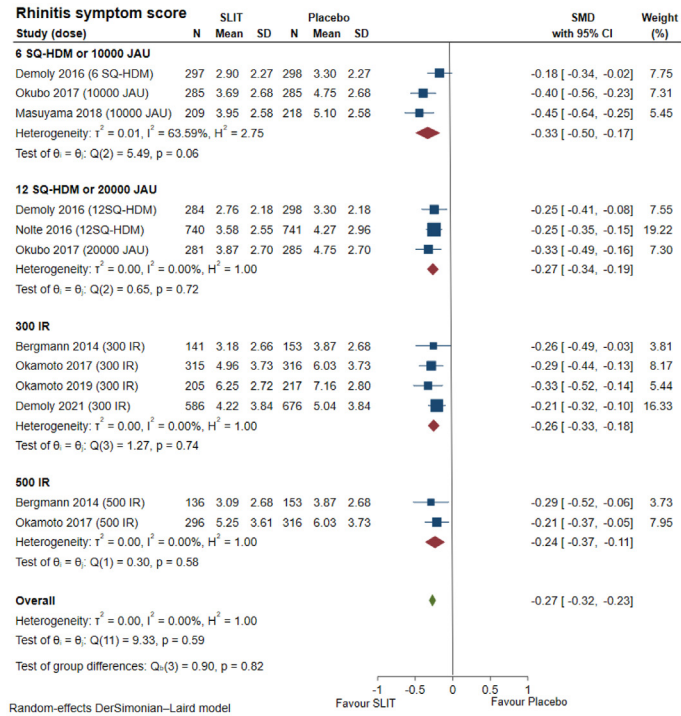


Fig. 3 Forest plot showing results of pairwise meta-analysis of randomized controlled trials examining; (A) the comparative combined symptom and medication score, (B) the comparative rhinitis symptoms score of HDM-SLIT tablet group compared with placebo at 44-52 weeks after the treatment.

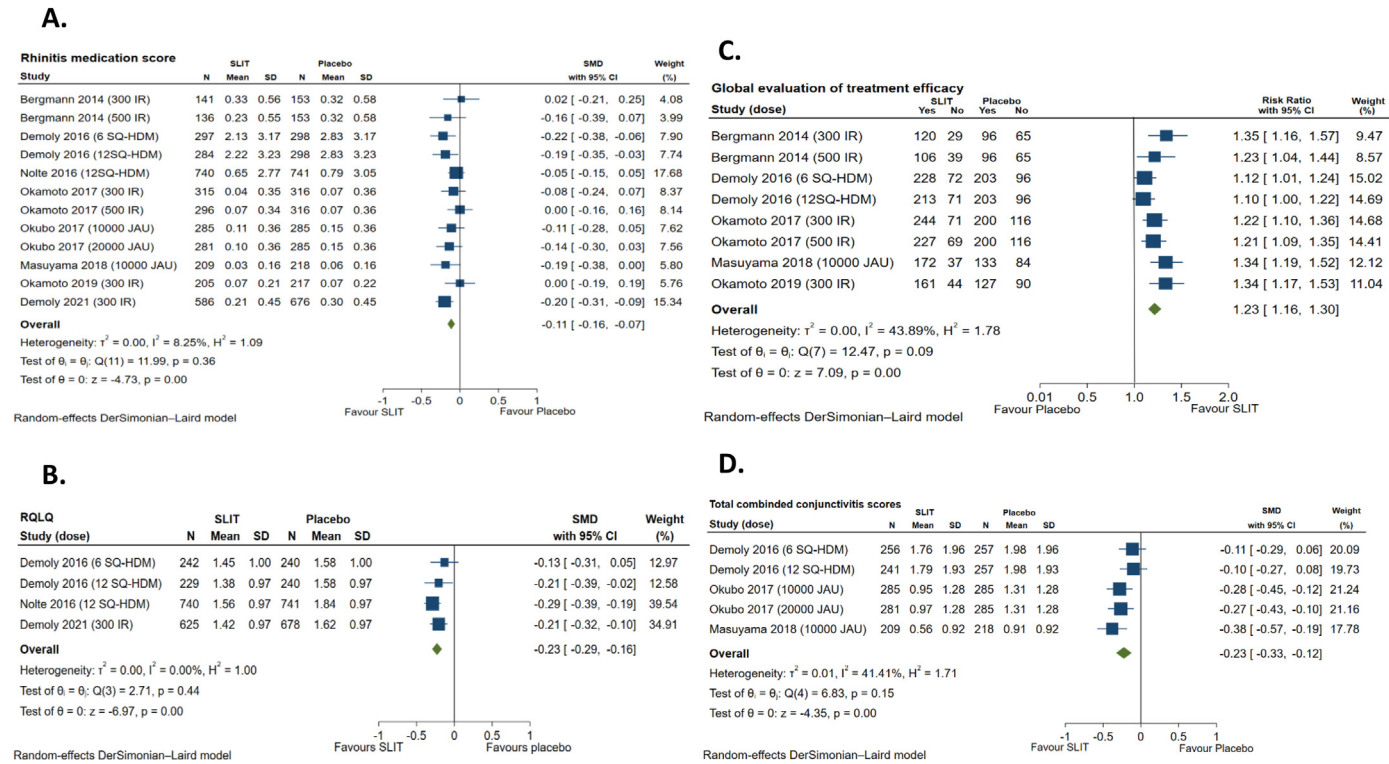


Fig. 4 Forest plot showing results of pairwise meta-analysis of randomized controlled trials examining the efficacy of HDM-SLIT tablet group compared with placebo (44–52 weeks after the treatment): (A) Rhinitis medication score, (B) RQLQ, (C) Global evaluation, and (D) Total combined conjunctivitis score.

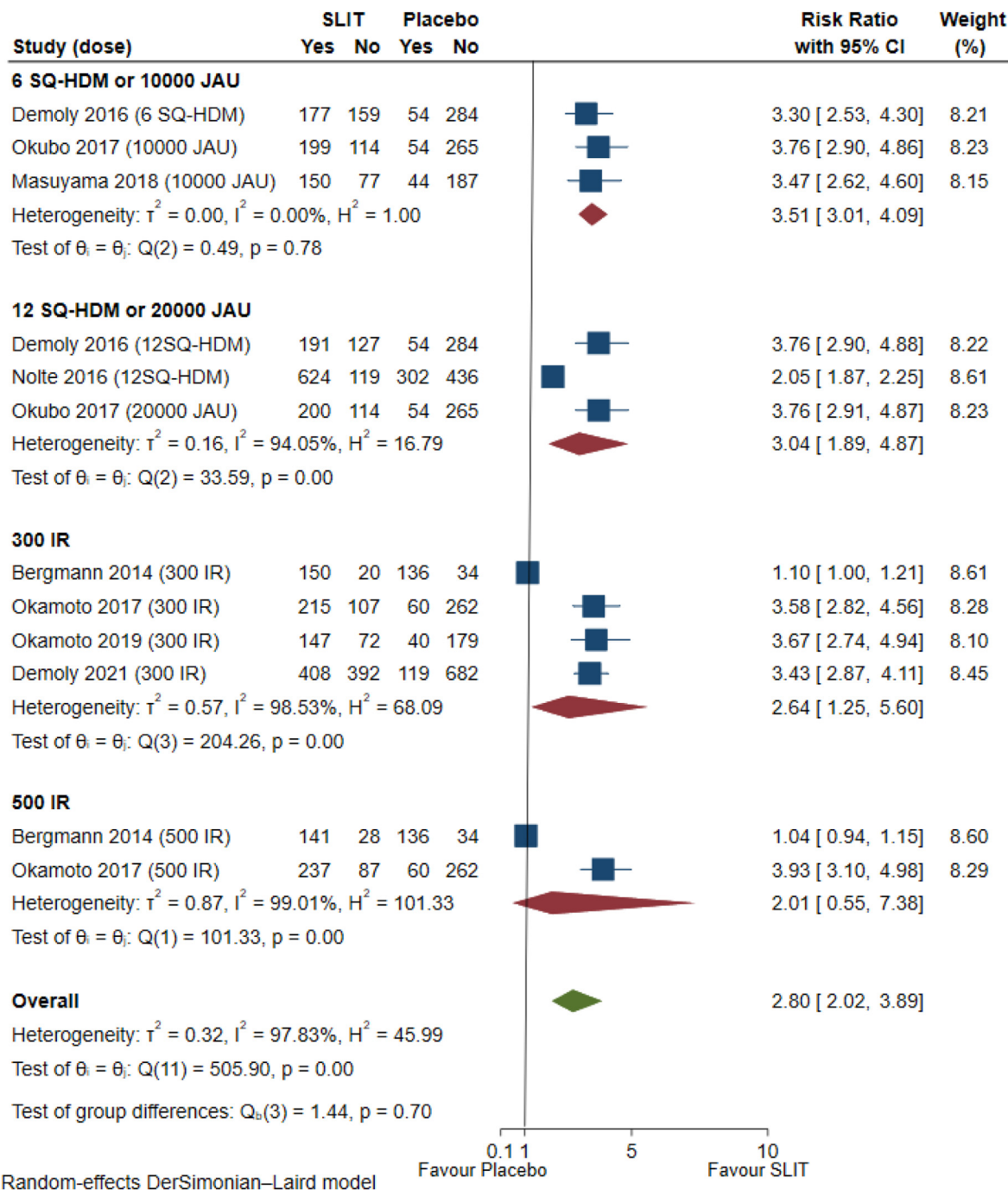


Fig. 5 Forest plot showing results of pairwise meta-analysis of randomized controlled trials examining comparative number of patients with any treatment-related adverse events (TRAE) in the HDM-SLIT tablet group compared with placebo.

related adverse events with an $I^2 = 97.83\%$. The funnel plot for the primary outcome of our study (CRMS) showed no evidence of publication bias (Figure E3). We graded the strength of evidence for TCRS, it showed high. The summary of grading is provided in Table E5.

DISCUSSION

This systematic review of HDM-SLIT tablets has identified 8 double-blinded, placebo-controlled RCTs with sufficient data for inclusion in the meta-analysis. It included a total of 3601 patients who

were treated with HDM-SLIT tablets and 2783 patients who received a placebo. HDM-SLIT tablet effectively improved the clinical rhinitis symptom and medication use which was evaluated by CSMS, RSS, and RMS in children, adolescents, and adults. Moreover, it improved conjunctivitis symptoms and quality of life with favorable safety profiles.

To our knowledge, this is the first meta-analysis that analyzed the CSMS, according to the recommendation of EAACI¹⁷ as a primary outcome. The SMD of the primary outcome of the pooled HDM-SLIT tablet was -0.28 [95% CI: 0.33 to -0.23]. The consistent efficacy compared to the placebo has been exhibited in both SQ- and IR- HDM SLIT tablets in different doses (6 SQ, 12 SQ, 300 IR, and 500 IR) with low degrees of variability across the studies. We did not find a difference in clinical response of CSMS and RSS between each group in the subgroup analysis. The World Allergy Organization (WAO) proposed the definition of a minimum clinically relevant effect for AIT is more than a 20% difference in clinical improvement from placebo.³³ Unfortunately, we could not calculate the pooled difference in clinical improvement due to insufficient data.

Although there was statistically significant improvement across the different doses of HDM-SLIT tablet compared to the placebo, a 3-arm RCT of 6 SQ-, 12SQ-HDM tablets, and placebo in 992 adults with AR demonstrated that the results were more robust for 12 SQ-HDM tablets (relative difference in TCRS VS placebo: 22% ($p = 0.001$) in 12 SQ-HDM; 18% ($p = 0.002$) in 6 SQ-HDM).²⁶ The efficacy of 12 SQ-HDM tablets met statistically significant reduction in all secondary endpoints eg, RSS, RMS, combined rhinoconjunctivitis score, and improved quality of life.²⁶ This may be one of the reasons for the approval of 12 SQ-HDM tablets for the treatment of AR in adults and adolescents. There were 2 studies including the children aged under 12 years (5-18 years old) which were performed in Japan.^{30,31} These RCTs showed that the 6 SQ- and 300 IR-HDM tablets were well-tolerated and effective in the young children. The effective dosing of HDM-SLIT in children may be lower than in adolescents and adults.

The results of reduction in RMS of HDM-SLIT tablet were less prominent than the RSS in all

included studies. This may imply that the use of as-needed relief medication may not be well-correlate with the clinical improvement. The interpretation of AIT's clinical efficacy with medication scores alone might potentially underestimate the true effect of AIT.¹⁷ Regarding the regulatory authorities such as the European Medicines Agency (EMA) guideline 2008 recommends that the phase-3 AIT clinical trial should be evaluated by natural exposure (field trial), the allergen exposure chamber can be used not only for phases-1 and -2 or for confirmatory of phase-3 field trial results.^{17,34} Hence, we excluded the studies that evaluated the primary outcome by allergen provocation test such as allergen exposure chamber.

Only 3 included studies evaluated the results of HDM-SLIT tablet on ocular symptoms by TCCS.^{26,28,30} This meta-analysis confirmed the result of a previous systematic review which showed that SLIT is moderately effective in reducing total and individual ocular symptom scores in participants with allergic rhinoconjunctivitis.^{9,35} For other participants' self-evaluation of treatment success, the global evaluation of improvement was significantly higher than the placebo group (RR = 1.21 [95% CI: 1.14 to 1.29]). The improvement in quality of life was demonstrated in the reduction of RQLQ score relative to placebo with SMD of -0.23 [95% CI: 0.29 to -0.16]. All these pooled results confirmed the HDM-SLIT tablet efficacy with low to moderate heterogeneity.

In contrast to SCIT, there is no longitudinal surveillance of safety data on SLIT tablets.³⁶⁻³⁹ SLIT has proven to be potentially safer than SCIT. Although the reported local side effects of SLIT are very common, severe systemic side effects rarely occur.¹² In data of SLIT tablet clinical trials in the United States, no fatalities were reported. Epinephrine was administered to 35 subjects (0.2% of 8152 SLIT-related adverse events). None were considered serious or life-threatening.⁴⁰ In line with this systemic review, there was a significantly higher rate of TRAE in the treatment group compared to the placebo (65.1% vs 22.7%). Only 0.3% of the events were severe. Eight participants from the treatment group (0.20%) were treated with epinephrine during the trials which the rate is comparable to the participants in the placebo group ($n = 7$, 0.24%) (Table E4). Even though the systemic reactions

due to SLIT are uncommon, the bothersome local adverse side effects might lead to the common reason for discontinuation of treatment.¹² The current meta-analysis showed a significantly higher probability of TRAE leading to discontinuation in the patients who received HDM-SLIT tablets, RR 2.09 [95% CI: 1.27 to 3.44].

Although the current guidelines recommend treatment with SLIT for at least 3 years,^{5,41} the clinical trials of HDM-SLIT tablets were documented for only a one-year treatment period. A two-year double-blinded RCT on HDM-SLIT tablets with treatment for the first year and treatment-free observed in the second year showed the persistence benefit of symptom improvement during the second year.²⁵ This may lead to the question of the necessity of a three-year treatment duration. On the other hand, in a large well-design double-blind placebo RCT in AR children were treated with grass pollen-SLIT tablet for 3 years. It demonstrated the sustained improvement of AR symptoms, a significantly fewer number of asthma symptoms, and medication usage in SLIT treated children at two years after SLIT cessation.⁴² Whether the long-term treatment efficacy and disease modification effect apply to other allergen-SLIT tablets remains unknown. The longer duration RCT of treatment and follow-up with HDM-SLIT tablets is required.

Even if the current meta-analysis included several large well-designed RCTs, there were some limitations; because we aimed to use the CSMS as a primary outcome, there were two scoring systems (TCRS and AASS) across the studies which had to be adjusted before analysis. Likewise, the inconsistent scoring systems for the secondary outcomes and different characteristics of individual studies might have led to significant heterogeneity. Additionally, most studies were conducted in Japan, European countries, and North America, limiting the generalizability to other populations.

In conclusion, the current systematic review and meta-analysis demonstrate that HDM-SLIT tablets are an effective treatment in reducing rhinitis symptoms and relieving medication use in AR patients. They also improve quality of life and conjunctivitis symptoms. Efficacy of treatment has been shown across AR patients aged over 5 years. The adverse events related to treatment are common, but the majority are mild and transient. The

use of epinephrine due to serious reactions rarely occurred. Although HDM-SLIT tablet has been considered as an effective and safe treatment modality, the use of HDM-SLIT in the real-world practice in some countries is still very limited. The potential barriers are the duration of treatment, inaccessible of treatment products, high expense, the limited awareness of patients and unfamiliarity with SLIT among practitioners.

Abbreviations

AR, allergic rhinitis; AIT, allergen immunotherapy; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; RCT, randomized clinical trial; HDM, house dust mite; DBPC, double-blind, placebo-controlled; CSMS, combined symptom and medication score; SQ, standardized quality; IR, index of reactivity; EAACI, the European Academy of Allergy and Clinical Immunology; PRISMA, Systematic Review and Meta-analysis; MeSH, the Medical Subject Heading; TCRS, total combined rhinitis score; RSS, rhinitis symptom scores; RMS, rhinitis medication scores; TCCS, total combined conjunctivitis scores; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; TRAE, treatment-related adverse events; AE, adverse events; SD, standard deviation; FAS, the full analysis set; RoB2, Risk-of-Bias 2; SMD, standardized mean difference; 95% CI, 95% confidence intervals; RR, relative risk; JAU, Japanese Allergy Unit; GRADE, the Grading of Recommended Assessment, Development, and Evaluation; WAO, the World Allergy Organization.

Funding

No external funding received.

Ethics statement

We registered the study protocol in PROSPERO (Registration Number CRD42021268890). Due to the nature of the study, it was considered exempt from ethics approval.

Availability of data and materials

The datasets generated during the current study are available from the corresponding author upon reasonable request.

Author contributions

(i) Concept and Design: Prapasri Kulalert and Mongkol Lao-Araya; Analysis and Interpretation of Data: Prapasri Kulalert, Phichayut Phinyo and Mongkol Lao-Araya (ii) Drafting the Article: Prapasri Kulalert (iii) Final Approval of the Version to be Published: Prapasri Kulalert, Phichayut Phinyo and Mongkol Lao-Araya.

Authors' consent for publication

Yes (from all authors).

Potential conflicts of interest statement

No funding has been received for this manuscript. ML has received honoraria for scientific lectures from Abbott, Thailand; AstraZeneca, Thailand; GSK, Thailand; Viatrix, Thailand; Menarini, Thailand; Takeda, Thailand; and Organon, Thailand. All other authors have no conflict of interest within the scope of the submitted work.

Acknowledgments

We would like to thank Miss Korawan Deewaja (Head of Nongyao Chaiseri Library: Health Sciences Library, Thammasat University Library) for her assistance in database searching.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.waojou.2022.100691>.

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