ORIGINAL ARTICLE

# SQ HDM Sublingual Immunotherapy Tablet for the Treatment of HDM Allergic Rhinitis and Asthma Improves Subjective Sleepiness and Insomnia: An Exploratory Analysis of the Real-life CARIOCA Study

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## Abstract

*Background:* Knowledge of the effectiveness of house dust mite (HDM) sublingual immunotherapy (SLIT) in allergic rhinitis (AR) and asthma-associated sleep disorders remains incomplete. A noninterventional study was conducted to assess the effect of the standardized quality (SQ) HDM SLIT tablet on safety and symptoms in adults with respiratory allergies caused by HDM. The study also assessed the status of insomnia and daytime sleepiness in patients with AR and/or asthma-associated sleep disorders treated with the SQ HDM SLIT tablet.
*Methods:* This was a 12-month multicenter, longitudinal, and prospective study. Participants started the SQ HDM SLIT tablet for moderate-to-severe HDM-induced AR that was persistent despite the use of symptom-relieving medication or HDM-induced asthma-associated sleep disorders that were not well controlled with inhaled corticosteroids and were associated with mild-to-severe HDM-induced AR. Sleep symptoms were measured using the Insomnia Severity Index (ISI) questionnaire and the Epworth Sleepiness Scale (ESS).
*Results:* A total of 1526 adult patients were enrolled, and 1483 were eventually included in the analysis. At baseline, 41.5% of patients reported sleep disorders; of these, 77.0% had insomnia and 28.9% experienced excessive daytime sleepiness. Insomnia was significantly more frequent among patients with uncontrolled AR (83.1%) than among those with controlled AR (52.6%) ($P<.0001$). Over time, 48.3% and 59.7% of patients, respectively, reported an improvement greater than the minimal clinically important difference in the ISI and ESS scales.
*Conclusion:* In patients with HDM-induced AR and/or asthma-associated sleep disorders, an improvement in subjective insomnia and sleepiness was observed after 1 year of treatment with the SQ HDM SLIT tablet in a real-life setting.

Key words: Allergen immunotherapy. Allergic rhinitis. Allergic asthma. Control. House dust mite. Sleep.

## Resumen

*Antecedentes:* La eficacia de la inmunoterapia sublingual (ITSL) con de ácaros del polvo doméstico (HDM) en los trastornos del sueño asociados a la rinitis alérgica (RA) y el asma (AA) no se encuentra bien documentada. Se realizó un estudio no intervencionista para evaluar el efecto de la tableta bien estandarizada en SQ, HDM SLIT sobre la seguridad y los síntomas relacionados con el sueño en adultos con alergias respiratorias por HDM. El objetivo era describir el estado del insomnio y la somnolencia diurna en pacientes con AR y/o AA tratados con la tableta SQ HDM SLIT.
*Métodos:* Se trata de un estudio multicéntrico, longitudinal y prospectivo de 12 meses de duración. Los participantes comenzaron a tomar la tableta SQ HDM SLIT para tratar la AR por HDM, de moderada a grave, persistente a pesar del uso de medicamentos de control de los síntomas; o el AA por HDM, no bien controlado con corticosteroides inhalados y asociado con AR por HDFM, de leve a grave. Los síntomas del sueño se midieron mediante el cuestionario *Insomnia Severity Index* (ISI) y la *Epworth Sleepiness Scale* (ESS).
*Resultados:* Se reclutaron un total de 1.526 pacientes adultos y 1.483 se incluyeron finalmente en el análisis. Al inicio del estudio, el 41,5% de los pacientes refirieron trastornos del sueño: el 77,0% de ellos tenía insomnio y el 28,9% padecía somnolencia diurna excesiva. El insomnio fue significativamente más frecuente entre los pacientes con RA no controlada (83,1%) que aquellos con RA controlada (52,6%) ($p<0,0001$). A lo largo del estudio, el 48,3% y el 59,7% de los pacientes presentaron una mejoría mayor que la diferencia mínima clínicamente significativa en ambas variables analizadas (ISI y ESS).
*Conclusión:* En un estudio en vida real en pacientes con HDM AR y/o asma asociados a trastornos del sueño, se observó una mejora en el insomnio subjetivo y la somnolencia después de un año de tratamiento con la tableta SQ HDM SLIT.

Palabras clave: Inmunoterapia con alérgenos. Rinitis alérgica. Asma alérgica. Control. Ácaros del polvo doméstico. Sueño.

**Summary box**

- **What do we know about this topic?**
  Patients with house dust mite (HDM)–induced respiratory allergy complain of insomnia and daytime sleepiness.
- **How does this study impact our current understanding and/or clinical management of this topic?**
  In a real-life setting, treatment with an HDM sublingual immunotherapy tablet leads to an improvement in patient-reported insomnia and sleepiness.

## Introduction

Findings from recent randomized controlled trials carried out in adults and adolescents with house dust mite (HDM)–induced respiratory allergy have led to the approval of the standardized quality (SQ) HDM sublingual immunotherapy (SLIT) tablet for the dual indication of allergic rhinitis (AR) and/or allergic asthma (AA) [1-3].

Observational studies have since been undertaken to measure the effects of this new form of allergy immunotherapy on safety and symptom control. Results from 2 recent real-life studies in Germany and Denmark/Sweden confirmed the good tolerance observed during clinical development [4,5].

In several epidemiological studies [6], respiratory allergies have been shown to impact sleep and daytime functioning, accounting for most of the impairment in quality of life. The studies SOMNIAAR [7] and DREAM [8] showed a strong relationship between severity of AR and sleep impairment. The recent French multicenter MORPHEE study highlighted the high frequency of sleep disorders and their significant impact on patients with AR induced by HDM, particularly in those with severe and persistent AR [9]. However, a knowledge gap exists concerning the impact of allergy immunotherapy on insomnia and daytime sleepiness.

In 2017, the 1-year French observational CARIOCA study involving a large cohort of adult patients with HDM respiratory allergies and starting treatment with the SQ HDM SLIT tablet was launched. The safety results were consistent with those reported in previous randomized controlled trials and real-life studies for the treatment of patients with HDM-induced AR and/or AA [3-5,9-11]. Here, we report the beneficial effects of the SQ HDM SLIT tablet on insomnia and daytime sleepiness during treatment.

## Methods

### *Study Design*

This was a noninterventional, multicenter, noncomparative, longitudinal prospective and descriptive study carried out in France between May 2018 and September 2020. Participants were adults with a clinical history of and positive test results for sensitization to HDM starting SQ HDM SLIT (1 lyophilized tablet per day of a standardized allergenic extract of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) for 1 of the following 2 indications: persistent moderate-to-severe HDM-induced AR despite the use of symptom-relieving medication; or HDM-induced AA poorly controlled by inhaled corticosteroids (ICS) and associated with mild-to-severe HDM-induced AR. Patients who had received any HDM immunotherapy in the 12 months prior to baseline were not included. Patients were expected to attend 4 visits over a period of 12 months: V1 (start of the study) and V4 (12 months after V1) were in-person and mandatory; the conduct and modality (in-person or telephone) of V2 and V3 and the examinations were at the physician's discretion. The study design has been described in detail elsewhere, as has the primary objective outcome measure, safety [11].

### *Objectives and Group Definition*

The analyses reported here are the secondary and exploratory analyses of the CARIOCA study. The secondary objectives of the study were to describe control of symptoms of AR and AA at baseline and their status over time in adults treated for HDM-induced respiratory allergies with allergy immunotherapy using the SQ HDM SLIT tablet. The exploratory objectives were to describe insomnia and daytime sleepiness before and during treatment in the subpopulation of 612 patients with self-reported sleep disorders before initiating allergy immunotherapy.

AR was medically assessed according to the ARIA classification and included the frequency (intermittent or persistent) and severity (mild or moderate-severe) of symptoms. The control level of AR symptoms was assessed using the 5-item Allergic Rhinitis Control Test (ARCT) patient questionnaire [12]. Its minimal clinically important difference (MCID) is set at 3 [13]. Asthma symptom control was assessed according to the Global Initiative for Asthma (GINA) control score and the 5-item Asthma Control Test (ACT) patient questionnaire, with an MCID of 3 [14].

The severity of sleep symptoms at baseline and over time was measured using the Insomnia Severity Index (ISI) questionnaire [15] and the Epworth Sleepiness Scale (ESS) [16]. The ISI is a brief self-administered instrument designed to assess the patient's perception of both nocturnal and diurnal symptoms of insomnia. It comprises 7 items to evaluate the severity of sleep onset, sleep maintenance, early morning awakening problems, sleep dissatisfaction, interference of sleeping difficulties with daytime functioning, noticeability of sleep problems by others, and the distress caused by sleep difficulties. Items are scored using a 5-point Likert scale ranging from 0 (no problem) to 4 (very severe problem), and its MCID has been set at 6 [17]. The ESS is a self-administered

**Table 1.** Baseline Demographic and Disease-Associated Characteristics of Patients in the Analysis Population (N=1483).

| Parameters | | AR alone (n=984) | AA+AR (n=499) | Total (N=1483) |
|---|---|---|---|---|
| Mean (SD) age, y | | 34.2 (11.6) | 34.3 (11.2) | 34.2 (11.5) |
| Sex, No. (%) | | | | |
| Male | | 403 (41.0) | 213 (42.7) | 616 (41.5) |
| Female | | 581 (59.0) | 286 (57.3) | 867 (58.5) |
| Smoking habits, No. (%) | | | | |
| Nonsmoker | | 789 (80.2) | 396 (79.4) | 1,185 (79.9) |
| Previous smoker | | 76 (7.7) | 50 (10.0) | 126 (8.5) |
| Active smoker (+ occasional) | | 96 (9.8) | 46 (9.2) | 142 (9.6) |
| Passive smoker | | 14 (1.4) | 6 (1.2) | 20 (1.3) |
| Unknown | | 9 (0.9) | 1 (0.2) | 10 (0.7) |
| Body mass index, kg/m$^2$, No. | 1438 | 1182 | 781 | 835 |
| Mean (SD) | 24.1 (4.2) | 24.1 (4.2) | 24.2 (4.2) | 24.1 (4.0) |
| Allergy history, No. (%) | | 984 | 499 | 1483 |
| At least 1 respiratory allergy or sensitization (other than HDM) | | 573 (58.2)[a] | 370 (74.1)[a] | 943 (63.6) |
| Rhinitis according to the ARCT score, No. (%) | | 923 | 461 | 1384 |
| Uncontrolled (<20) | | 683 (74.0) | 283 (61.4) | 966 (69.8) |
| Controlled (≥20) | | 240 (26.0) | 178 (38.6) | 418 (30.2) |
| Level of asthma control according to the ACT score, No. (%) | | NA | 440 | 440 |
| Well controlled (≥20) | | NA | 232 (52.7) | 232 (52.7) |
| Partly controlled (15-19) | | NA | 125 (28.4) | 125 (28.4) |
| Uncontrolled (<15) | | NA | 83 (18.9) | 83 (18.9) |
| Sleep disorders related to HDM respiratory allergies in the previous month, No. (%) | | 977 | 497 | 1474 |
| Yes | | 402 (41.1) | 210 (42.3) | 612 (41.5) |
| No | | 575 (58.9) | 287 (57.7) | 862 (58.5) |
| Total ISI score for patient-reported sleep disorders | | 371 | 194 | 565 |
| Median (IQR) | | 13.0 (9.0-16.0) | 11.5 (7.0-16.0) | 12.0 (8.0-16.0) |
| Total ISI score by class for patient-reported sleep disorders, No. (%) | | 371 | 194 | 565 |
| No clinically significant insomnia (0-7) | | 75 (20.2) | 55 (28.4) | 130 (23.0) |
| Subthreshold insomnia (8-14) | | 167 (45.0) | 73 (37.6) | 240 (42.5) |
| Clinical insomnia (moderate severity) (15-21) | | 117 (31.5) | 57 (29.4) | 174 (30.8) |
| Clinical insomnia (severe) (22-28) | | 12 (3.2) | 9 (4.6) | 21 (3.7) |
| Total ESS score for patient-reported sleep disorders | | 357 | 182 | 539 |
| Median (IQR) | | 8.0 (4.0-11.0) | 8.0 (4.0-12.0) | 8.00 (4.0-11.0) |
| Total ESS score by class for patient-reported sleep disorders, No. (%) | | 357 | 182 | 539 |
| Lower normal daytime sleepiness (0-5) | | 128 (35.9) | 54 (29.7) | 182 (33.8) |
| Higher normal daytime sleepiness (6-10) | | 132 (37.0) | 69 (37.9) | 201 (37.3) |
| Mild excessive daytime sleepiness (11-12) | | 40 (11.2) | 21 (11.5) | 61 (11.3) |
| Moderate excessive daytime sleepiness (13-15) | | 40 (11.2) | 24 (13.2) | 64 (11.9) |
| Severe excessive daytime sleepiness (16-24) | | 17 (4.8) | 14 (7.7) | 31 (5.8) |

Abbreviations: AA, allergic asthma; ACT, Asthma Control Test; AR, allergic rhinitis; ARCT, Allergic Rhinitis Control Test; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index.
[a] $P<.0001$

instrument designed to measure the general level of daytime sleepiness. Patients are required to rate their propensity to doze or fall asleep in 8 situations corresponding to 8 common daily activities. Each situation can be scored on a 4-point scale, from 0 (would never doze) to 3 (high chance of dozing), and the total score can range from 0 to 24. Its MCID is 2 [18].

### *Ethical Considerations*

The study was carried out in compliance with Good Pharmacovigilance Practice guidelines, the Declaration of Helsinki (1964, and its amendments and subsequent clarifications), and the reference methodology MR 003 published by the French Data Protection Agency (CNIL). It was registered with identification number 2017-A02668-45 and was approved by the Ethics Committee in October 2017. The patients gave their written informed consent to participate in the study. The CARIOCA study is registered at ClinicalTrials.gov (Identifier: NCT03746860).

### *Statistical Analysis*

Categorical variables were reported as frequency and percentage, while continuous variables were reported as mean (SD) and median (IQR).

The population for these secondary and exploratory analyses was the same as for the main analysis and included all patients who had taken the SQ HDM SLIT tablet at least once. The groups were compared using the $\chi^2$ test or Fisher exact test (qualitative variables) and *t* test (quantitative variables).

Factors predicting an improvement in ARCT, ACT, ESS, and ISS values were assessed using univariate analysis. Explanatory variables (listed in full in Tables S2, S3, S4, and S6 of the supplemental material) with a *P* value <.25 at the univariate level were included in the multivariate analyses using a stepwise selection approach. Backward elimination was then applied, and only explanatory variables with *P*<.05 at the multivariate level remained in the definitive models.

The statistical analyses were performed using SAS Version 9.4.

## Results

### *Patients*

Between May 9, 2018 and May 29, 2019, a total of 1526 patients were enrolled at 185 French sites. The analysis population comprised all patients who had taken the SQ HDM SLIT tablet at least once (n=1483). Of the 1483 patients in the analysis population, 499 (33.6%) reported clinical manifestations of AA. According to ARIA, 82.9% of the patients had persistent moderate-severe rhinitis. Other baseline demographic and disease characteristics are presented in Table 1 and the supplemental material, Table S1. At V1, 41.5% (612/1474) of the patients reported sleep symptoms in the month prior to inclusion: 41.1% (402/977) of patients with AR alone and 42.3% (210/497) with AA+AR. Overall, 77.0% (435/565) of these patients had insomnia (ISI score, 8-28) and 28.9% (156/539) experienced excessive daytime sleepiness (ESS score, 11-24). Both the AR alone and the AA+AR populations presented with similar sleep symptom patterns. Insomnia was significantly more frequent among patients with uncontrolled AR (83.1%) than among those with controlled AR (52.6%) (*P*<.0001).

A total of 852 (57%) patients completed the study (see supplemental material, Figure S1). The mean (SD) duration of treatment with the SQ HDM SLIT tablet was 380 (57) days.

**Table 2.** Changes in Insomnia and Daytime Sleepiness Between V1 and V4 (Population With Sleep Disorders at Baseline and Having Completed V4).

| Parameters | AR alone (n=218) | AA+AR (n=104) | Total (N=322) |
|---|---|---|---|
| Difference in the ISI total score | | | |
| Median (IQR) | –5.5 (–10.0 to –2.0) | –5.0 (–8.0 to –2.0) | –5.00 (–10.0 to –2.0) |
| Status of the ISI total score according to $MCID_{ISI}$, No. (%) | | | |
| Improved between V1 and V4 (≤–6) | 60 (50.0) | 27 (45.0) | 87 (48.3) |
| Unchanged between V1 and V4 (–6 to 6) | 56 (46.7) | 31 (51.7) | 87 (48.3) |
| Deteriorated between V1 and V4 (≥6) | 4 (3.3) | 2 (3.3) | 6 (3.3) |
| Missing | 98 | 44 | 142 |
| Difference in the ESS total score | | | |
| Median (IQR) | –3.0 (–6.0 to 0.0) | –2.0 (–4.0 to 0.0) | –2.0 (–5.0 to 0.0) |
| Status of the ESS total score according to $MCID_{ESS}$, No. (%) | | | |
| Improved between V1 and V4 (≤–2) | 68 (61.8) | 34 (55.7) | 102 (59.7) |
| Unchanged between V1 and V4 (–2 to 2) | 25 (22.7) | 21 (34.4) | 46 (26.9) |
| Deteriorated between V1 and V4 (≥2) | 17 (15.5) | 6 (9.9) | 23 (13.4) |
| Missing | 108 | 43 | 151 |

Abbreviations: AA, allergic asthma; ACT, Asthma Control Test; AR, allergic rhinitis; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index. MCID, minimal clinically important difference; V, visit.

Baseline characteristics (body mass index, smoking habits, history of allergy, concomitant respiratory allergy, lung function, sleep disorders related to allergy, therapy taken during the 12 months prior to study inclusion [including symptomatic medication for rhinitis], severity of rhinitis, severity and level of control of asthma, and the rate of exacerbations) were similar for patients who completed V2 (n=1210), V3 (n=793), and V4 (n=852) (Table S1).

### *Sleep Disorders*

Among the 612 patients with sleep disorders at baseline, there were 180 participants with scores for both the V1 and the V4 ISI, and 171 with ratings for both the V1 and the V4 ESS. These subgroups of patients with available ESS and/or ISI questionnaire results did not differ from the 612 patients with sleep disorders at baseline or from the 1483 patients included after V1 (data not shown). Changes in insomnia and daytime sleepiness symptoms between V1 and V4 are presented in Table 2. Overall, 48.3% (n=87/180) of patients reported an improved ISI $\geq MCID_{ISI}$ between V1 and V4, and in the subgroups, improvements were reported by 50.0% (n=60/120) of patients with AR alone and by 45.0% (n=27/60) of patients with asthma. In addition, 59.7% (n=102/171) of patients reported an improvement in ESS $\geq MCID_{ESS}$ between V1 and V4, and in the subgroups, improvements were reported by 61.8% (n=68/110) of patients with AR alone and by 55.7% (n=34/61) of patients with asthma. Improvement in insomnia $\geq MCID_{ISI}$ was mostly reported in patients with an improvement in ARCT $\geq MCID_{ARCT}$ (71/84; 84.5%, Figure 1). Similarly, most patients reporting an improvement in ESS $\geq MCID_{ESS}$ (78/99; 78.8%) also reported better control of AR $\geq MCID_{ARCT}$ (Figure 2).

Univariate analysis (Table S2) showed that age and antihistamine and/or nasal corticosteroid prescription at the end of V1 and the ISI score at baseline were associated with changes in the ISI score over time. Multivariate logistic regression analysis (Table 3) indicates that age (33 to 41 years), antihistamine/nasal corticosteroid prescriptions at the end of

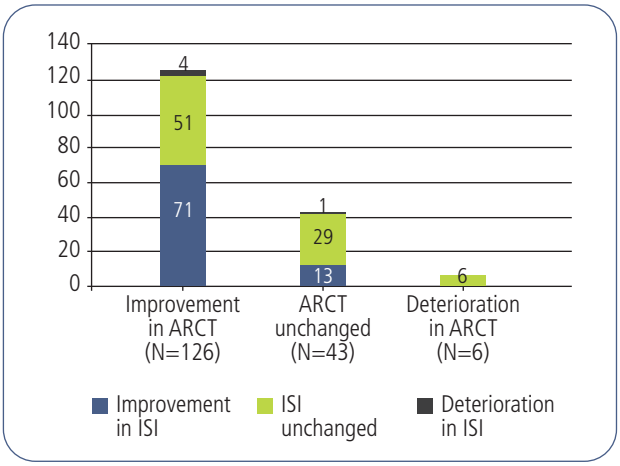


**Figure 1.** Change between V1 and V4 for the ARCT and ISI scores (N=175).

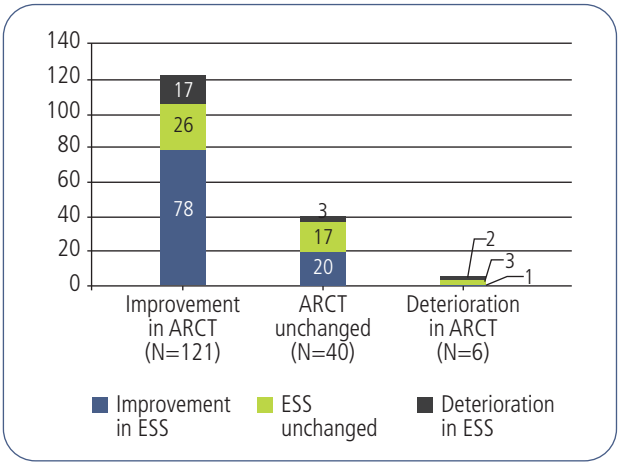


**Figure 2.** Change between V1 and V4 for the ARCT and ESS scores (N=175).

**Table 3.** Multivariate Logistic Regression Analysis.[a]

| Variable | OR (95%CI) | *P* Value |
|---|---|---|
| Age (at inclusion) (quartiles) | | |
| ≤Q1, 26 | 1.00 | |
| (Q1, 26; Median, 33) | 1.99 (0.69-5.72) | .2024 |
| (Median, 33; Q3, 41) | 3.33 (1.07-10.41) | .0385 |
| > Q3, 41 | 0.47 (0.15-1.45) | .1891 |
| Prescription of antihistamines at the end of V1 | | |
| No | 3.63 (1.21-10.87) | .0211 |
| Yes | 1.00 | |
| Prescription of nasal corticosteroids at the end of V1 | | |
| No | 1.00 | |
| Yes | 3.22 (1.41-7.34) | .0055 |
| ISI score (at inclusion) (quartiles) | | |
| ≤Q1, 8 | 1.00 | |
| (Q1, 8; Median, 12) | 17.46 (4.96-61.41) | <.0001 |
| (Median, 12; Q3, 16) | 34.69 (9.35-126.77) | <.0001 |
| >Q3: 16 | 51.08 (12.65-206.27) | <.0001 |

Abbreviation: ISI, Insomnia Severity Index.
[a]Variable of Interest: ISI score, improvement (change ≥ $MCID_{ISI}$) vs no improvement (change < $MCID_{ISI}$), V1 vs V4.

**Table 4.** Multivariate Logistic Regression Analysis.[a]

| Variable | OR (95%CI) | *P* Value |
|---|---|---|
| At least 1 respiratory allergy (other than HDM respiratory allergies) | | .0038 |
| No | 2.20 (1.04-4.65) | |
| Yes | 1.00 | |
| ESS score (at inclusion) | 1.21 (1.12-1.31) | <.0001 |

Abbreviation: ESS, Epworth Sleepiness Scale.
[a]Variable of interest: ESS score, improvement (change ≥ $MCID_{ESS}$) vs no improvement (change < $MCID_{ESS}$), V1 vs V4.

V1, and the ISI score at baseline were significantly associated with changes in the ISI score over time. For the ESS score, multivariate logistic regression analysis (Table 4) indicated that the absence of respiratory allergy (other than HDM) and the ESS score at baseline were significantly associated with changes in the ESS score over time (see Table S3 for univariate analysis).

### *Rhinitis Control*

The percentage of patients in the total population reporting controlled AR (ARCT score ≥20) increased from 30.2% (n=418/1384) at V1 to 71.9% (n=669/930) at V2, 80.4% (n=530/659) at V3, and 88.0% (n=570/648) at V4. Among patients with ARCT data at both V1 and V4 (n=641), 71.3% reported an improved ARCT ≥$MCID_{ARCT}$, and in the subgroups, improvements were reported by 73.8% (n=321/435) of patients with AR alone and by 66.0% (n=136/206) of patients with asthma (Table 5).

The trend toward improvement or stability in rhinitis control was similar in the AR alone and AA+AR subgroups (Figure S2). The results from the univariate analysis are presented in Table S4. Multivariate analysis revealed that no respiratory allergy other than HDM respiratory allergies (*P*=.0039) and lower ARCT score (*P*<.0001) at baseline were significantly associated with an improved ARCT ≥$MCID_{ARCT}$ score at V4 (Table S5).

### *Asthma Control*

Among patients with ACT data at both V1 and V4 (n=174), 46.6% reported an improved ACT ≥$MCID_{ACT}$ between V1 and V4 (Table 6). Seven patients (n=7/174; 4.0%) reported exacerbation of symptoms over time. Among patients with uncontrolled asthma at baseline (n=28), almost all reported an improvement, with 85.7% (n=24/28) of them rating their asthma as uncontrolled at baseline and well controlled at V4 (Figure S3). Factors significantly associated with asthma control by univariate analysis are presented in Table S6. In the multivariate analysis, the only factor that remained significant for improved asthma control was the ACT score at baseline (*P*<.0001) (Table S7). There were 272 participants with ICS data at both V1 and V4, and the dose was unknown for 9 and 14 patients, respectively (Table 7). For almost two thirds of patients (61.0%), the ICS dose remained unchanged over time, and in almost a third (30.5%), the dose was reduced between baseline and V4.

**Table 6.** Change in the ACT Score Between V1 and V4 (Population With Allergic Asthma at Baseline Having Completed V4, N=272).

| Parameters | Total (N=272) |
|---|---|
| Difference in the ACT score | |
| Median (IQR) | 2.0 (0.0-5.0) |
| Status of the ACT score according to $MCID_{ACT}$, No. (%) | |
| Improved between V1 and V4 (≥3) | 81 (46.6) |
| Unchanged between V1 and V4 (–3 to 3) | 85 (48.8) |
| Deteriorated between V1 and V4 (≤–3) | 8 (4.6) |
| Missing | 98 |

Abbreviations: ACT, Asthma Control Test; MCID, minimal clinically important difference; V, visit.

**Table 7.** Change in Inhaled Corticosteroid (ICS) Prescription Between V1 and V4 (N=272).[a]

| Parameters | Total (N=272) |
|---|---|
| Reduced ICS dose, No. (%) | 76 (30.5) |
| ICS dose unchanged, No. (%) | 152 (61.0) |
| Increased ICS dose, No. (%) | 23 (9.2) |
| Missing | 21 |

[a]Percentages are based on patients with inhaled corticosteroid dose data at V1 and V4.

## Discussion

To our knowledge, this is the first prospective study to show the promising effects of allergy immunotherapy on the status of subjective insomnia and daytime sleepiness in patients with HDM-induced AR with and without AA.

**Table 5.** Change in the ARCT Score Between V1 and V4 (Population Having Completed V4, N=852).

| Parameters | AR alone (n=580) | AA+AR (n=272) | Total (N=852) |
|---|---|---|---|
| Difference in the ARCT score | | | |
| Median (IQR) | 5.0 (2.0-9.0) | 4.0 (1.0-8.0) | 5.0 (2.0-9.0) |
| Status of the ARCT score, according to $MCID_{ARCT}$, No. (%) | | | |
| Improved between V1 and V4 (≥3) | 321 (73.8) | 136 (66.0) | 457 (71.3) |
| Unchanged between V1 and V4 (–3 to 3) | 101 (23.2) | 61 (29.6) | 162 (25.3) |
| Deteriorated between V1 and V4 (≤–3) | 13 (3.0) | 9 (4.4) | 22 (3.4) |
| Missing | 145 | 66 | 211 |

Abbreviations. AA, allergic asthma; AR, allergic rhinitis; ARCT, Allergic Rhinitis Control Test; ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; MCID, minimal clinically important difference; V, visit.

In our study, 41.5% of patients reported sleep symptoms related to their HDM-induced respiratory allergies in the month prior to inclusion. Leger et al [9] conducted the prospective, cross-sectional, observational MORPHEE study to characterize the sleep disorders associated with respiratory allergy to HDM upon initiation of SLIT in routine clinical practice. The study involved 189 French trial sites and included 1750 participants with HDM-induced respiratory allergies who initiated sublingual immunotherapy. In the MORPHEE study, sleep disorders were a reason for consultation in over 73% of the adult patients, that is, twice the percentage usually observed in the French population (37%). While the percentage of patients reporting insomnia and daytime sleepiness in the CARIOCA study was lower, sleep quality was worse. In the MORPHEE study, the mean (SD) baseline ISI score was 10.1 (5.9) for adults and the mean (SD) ESS score was 6.7 (4.3). In the CARIOCA study, the mean ISI score was 12.1 (5.5) and the mean ESS score 7.9 (4.7), probably because a greater percentage of participants in the CARIOCA study had persistent moderate-severe rhinitis according to ARIA (82.9% vs 67.3% in the MORPHEE study). For 69.8% of the patients, the symptoms were not controlled. The relationship between the severity of sleep symptoms and of AR symptoms was demonstrated in another study [8]. At V4, 48.3% of patients reported an improved $\geq MCID_{ISI}$ score. According to the ESS, a meaningful improvement in daytime sleepiness was observed between V1 and V4 for 59.7% of the patients. The change patterns were similar between the groups. An improvement in insomnia and daytime sleepiness was mostly reported in patients with a significant improvement in their ARCT value, confirming the positive association between severity of AR and deterioration in sleep quality shown in the SOMNIAAR and DREAM studies [7,8]. The impact of the SQ HDM SLIT tablet on sleep was suggested in the pivotal MT-06 study, which showed a statistically significant difference with placebo for 4 of the 7 domains of the Rhinoconjunctivitis Quality of Life Questionnaire, including sleep impairment [19]. Our current open-label study brings further support to these findings.

The results of this study also showed that treatment with the SQ HDM SLIT tablet improved control of AA and AR while reducing the use of ICS. Overall, a third (30.5%) of patients reduced their dose between baseline and V4, and for 61.0% of patients, the ICS dose remained unchanged. The large phase 2 randomized, double-blind, placebo-controlled MT-02 trial by Mosbech et al [3] investigated the efficacy of the SQ HDM SLIT tablet in adults and adolescents with HDM-induced respiratory allergic disease [3]. After 1 year of treatment with 6 SQ-HDM, 34% of the patients were able to discontinue ICS completely. Moreover, in the 6 SQ-HDM group, a statistically significant lower daily dose of ICS was required to maintain asthma control. The greatest reduction was observed among patients needing a higher dose (400-800 μg). Consequently, the real-life efficacy of the SQ HDM SLIT tablet has been demonstrated, thus further confirming previous findings on the benefits of an HDM tablet in improving control of AR and AA [4,5].

Our study is subject to a series of limitations. Owing to its observational design, we must remember that uncontrolled biases may interfere with the results. This observational design resulted in 40% of patients (for details see Demoly et al [11]) failing to complete the study in accordance with the protocol (14% of participants were lost to follow-up). However, analysis revealed similar baseline characteristics in the population of patients who completed V2, V3, and V4. Subgroups of patients with available ESS and/or ISI data did not differ from the 612 patients with sleep disorders at baseline or with the 1483 patients who completed V1.

The lack of a control arm means that it is impossible to assess the relative effect of pharmacotherapeutic treatments and allergen immunotherapy. Given the study design, and in particular the absence of nighttime sleep testing (eg, polysomnography), it is important to keep in mind that our results suggest a favorable impact of the SQ HDM SLIT tablet on insomnia and sleepiness and not on a specific disorder such as obstructive sleep apnea. Furthermore, we did not make an objective assessment of insomnia and sleepiness: we used self-administered questionnaires (ISI and ESS) and not objective tests such as the wakefulness maintenance test.

## Conclusion

In patients with sleep disorders associated with HDM-induced respiratory allergies, an improvement in insomnia and daytime sleepiness was observed after 1 year of treatment with the SQ HDM SLIT tablet. In addition, our study reports clinically relevant improvements in rhinitis and asthma control, with significant reductions in ICS use and asthma symptoms.

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### *Conflicts of Interest*

DJ reports personal fees from ALK, AstraZeneca, GlaxoSmithKline, and Sanofi Regeneron.

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## References


1. Virchow JC, Backer V, Kuna P, Prieto L, Nolte H, Villesen HH, et al. Efficacy of a House Dust Mite Sublingual Allergen Immunotherapy Tablet in Adults With Allergic Asthma: A Randomized Clinical Trial. JAMA. 2016;315:1715-25.
2. Demoly P, Matucci A, Rossi O, Vidal C. A year-long, fortnightly, observational survey in three European countries of patients with respiratory allergies induced by house dust mites: Methodology, demographics and clinical characteristics. BMC Pulm Med. 2016;16:85.
3. Mosbech H, Deckelmann R, de Blay F, Pastorello EA, Trebas-Pietras E, Andres LP, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol. 2016;134:568-75.e7.
4. Sidenius K, Arvidsson P, Indbryn R, Emanuelsson CA. A Real-Life One-Year Non-Interventional Study Assessing Safety, Tolerability, and Treatment Outcome of the SQ HDM SLIT-Tablet (Acarizax®) in House Dust Mite Allergic Rhinitis With or Without Asthma. Pulm Ther. 2021;7:221-36.
5. Reiber R, Wolf H, Futschik T, Schwab JA, Hölscher U, Schnitker J, et al. Safety and tolerability of the standardized quality house dust mite sublingual immunotherapy tablet in real life: A noninterventional, open-label study. J Allergy Clin Immunol Pract. 2021;9:3221-3.e5.
6. Muliol J, Maurer M, Bousquet J. Sleep and allergic rhinitis. J Investig Allergol Clin Immunol. 2008;18:415-9.
7. Colás C, Galera H, Añibarro B, Soler R, Navarro A, Jáuregui I, et al. Disease severity impairs sleep quality in allergic rhinitis (The SOMNIAAR study). Clin Exp Allergy. 2012;42:1080-7.
8. Léger D, Annesi-Maesano I, Carat F, Rugina M, Chanal I, Pribil C, et al. Allergic rhinitis and its consequences on quality of sleep: An unexplored area. Arch Intern Med. 2006;166:1744-8.
9. Leger D, Bonnefoy B, Pigearias B, de La Giclais B, Chartier A. Poor sleep is highly associated with house dust mite allergic rhinitis in adults and children. Allergy Asthma Clin Immunol. 2017;13:36.
10. Corzo JL, Carrillo T, Pedemonte C, Plaza Martin AM, Martín Hurtado S, Dige E, et al. Tolerability during double-blind randomized phase I trials with the house dust mite allergy immunotherapy tablet in adults and children. J Investig Allergol Clin Immunol. 2014;24:154-61.
11. Demoly P, Leroyer C, Serrano E, Le Maux A, Magnier G, Chartier A. The SQ HDM SLIT-Tablet is safe and well tolerated in patients with House Dust Mite allergic rhinitis with or without asthma: A «real-life» French study. Clin Transl Allergy. 2022;12:e12129.
12. Demoly P, Jankowski R, Chassany O, Bessah Y, Allaert FA. Validation of a self-questionnaire for assessing the control of allergic rhinitis. Clin Exp Allergy. 2011;41:860-8.
13. Chiriac AM, Zhu R, Izquierdo L, Molinari N, Demoly P. The minimal important difference of the allergic rhinitis control test. J Allergy Clin Immunol Pract. 2022;10:1924-6.e2.
14. Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. J Allergy Clin Immunol. 2009;124:719-23.e1.
15. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med. 2001;2:297-307.
16. Kaminska M, Jobin V, Mayer P, Amyot R, Perraton-Brillon M, Bellemare F. The Epworth Sleepiness Scale: self-administration versus administration by the physician, and validation of a French version. Can Respir J. 2010;17:e27-34.
17. Yang M, Morin CM, Schaefer K, Wallenstein GV. Interpreting score differences in the Insomnia Severity Index: using health-related outcomes to define the minimally important difference. Curr Med Res Opin. 2009;25:2487-94.
18. Crook S, Sievi NA, Bloch KE, Stradling JR, Frei A, Puhan MA, et al. Minimum important difference of the Epworth Sleepiness Scale in obstructive sleep apnoea: estimation from three randomised controlled trials. Thorax. 2019;74:390-6.
19. Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized, double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol. 2016;137:444-51.e8.


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