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

Brief running title: Allergen immunotherapy impacts sleep.

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Abstract

Background: There are still gaps in the knowledge regarding the effectiveness of house dust mite (HDM) sublingual immunotherapy (SLIT) on allergic rhinitis (AR) and asthma (AA)-associated sleep disorders. A non-interventional study was conducted to assess the effect of the Standardized quality (SQ) HDM SLIT-tablet on safety and symptoms in adults with HDM respiratory allergies. The aim was to describe the status of insomnia and daytime sleepiness in AR and/or AA patients 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 AR, persistent despite the use of symptom-relieving medication; or HDM AA not well controlled by inhaled corticosteroids and associated with mild-to-severe HDM AR. Sleep symptoms were measured using the Insomnia Severity Index (ISI) questionnaire and the Epworth Sleepiness Scale (ESS).

Results: A total of 1,526 adult patients were enrolled and 1,483 were included in the analysis. At baseline, 41.5% of patients reported sleep disorders: 77.0% of them had insomnia and 28.9% suffered from excessive daytime sleepiness. Insomnia was significantly more frequent among patients with uncontrolled AR (83.1%) than those with controlled AR (52.6%) ($p<0.0001$). Over time, 48.3% and 59.7% of patients reported an improvement greater than the minimal clinically important difference on the ISI and ESS scales respectively.

Conclusion: In patients with HDM AR and/or asthma associated sleep disorders, an improvement in subjective insomnia and sleepiness was observed after one 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

Introducción: 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 lago 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

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Summary box:

What do we know about this topic?

Patients suffering from house dust mite (HDM) 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

The findings from recent randomized controlled trials (RCTs) carried out in adults and adolescents with house dust mite (HDM)-induced respiratory allergic disease have led to the approval of SQ HDM Sublingual Immunotherapy (SLIT)-Tablet for a dual indication in allergic rhinitis (AR) and/or allergic asthma (AA) [1-3].

Observational studies have since been set up to measure the effects of this new form of allergy immunotherapy on safety and symptom control. Results from two recent real-life studies in Germany and Denmark/Sweden confirmed the good tolerance which was observed during the 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 quality-of-life deterioration. The SOMNIAAR [7] and DREAM [8] studies showed a strong relationship between AR severity 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 symptoms.

In 2017, the one-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 RCTs 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 the status of insomnia and daytime sleepiness during treatment.

Methods

Study design

This was a non-interventional, French multicenter, non-comparative, longitudinal prospective and descriptive study carried out between May 2018 and September 2020. Participants were adults with a clinical history and positive test of HDM sensitization starting the SQ HDM SLIT-tablet (1 lyophilisate per day of a standardized allergenic extract of Dermatophagoides pteronyssinus and Dermatophagoides farinae) for one of the following two indications: persistent moderate-to-severe HDM AR despite the use of symptom-relieving medication; or HDM AA poorly controlled by inhaled corticosteroids and associated with mild-to-severe HDM AR. Patients who had received any HDM immunotherapy in the 12 months prior to baseline were not included. Patients were expected to attend four visits over a period of 12 months: V1 (start of the study) and V4 (12 months after V1) were in-person and mandatory, but 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 have the primary objective results', which was 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 symptom control of AR and AA at baseline and their status over time in adults treated for HDM respiratory allergies with allergy immunotherapy using the SQ HDM SLIT-tablet. Exploratory objectives were to describe insomnia and daytime sleepiness complaints before and during treatment in the subpopulation of 612 patients with self-reported sleep disorders before initiating the allergy immunotherapy.

The 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) has been established to be 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-rated 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 and early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others and the distress caused by the 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 established to be 6 [17]. The ESS is a self-rated instrument designed to measure the general level of daytime sleepiness. The patient is required to rate their propensity to doze or fall asleep in 8 situations, which correspond 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 and 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 the 2017-A02668-45 identification number 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 on ClinicalTrials.gov (Identifier: NCT03746860).

Statistics

Categorical variables were reported as frequency and percentage, while continuous variables were reported as mean, standard deviation (SD), median and interquartile range (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 Chi² test or Fisher's exact test (qualitative variables), and Student's t-test (quantitative variables).

Predictive factors of ARCT, ACT, ESS and ISS improvement were analyzed with univariate analysis. Explanatory variables (listed in full in Tables S2, S3, S4, and S6 of the supplemental material) with a p-value <0.25 at the univariate level were fed into multivariable analyses using a stepwise selection. Backward elimination was then applied and only explanatory variables with a p-value <0.05 at the multivariable level remained in the definitive models.

The statistical analyses were performed using SAS® Version 9.4.

Results

Patients

Between 09 May 2018 and 29 May 2019, 1,526 patients were enrolled in 185 French sites. The analysis population comprised all patients who had taken the SQ HDM SLIT-tablet at least once (n=1,483). Of the 1,483 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 supplemental material, Table S1. At V1, 41.5% (612/1,474) 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) suffered from excessive daytime sleepiness (ESS score 11-24). Both AR alone and AA+AR populations presented with similar sleep symptom patterns. Insomnia was significantly more frequent among patients with uncontrolled AR (83.1%) than those with controlled AR (52.6%) ($p<0.0001$).

A total of 852 (57%) patients completed the study (see supplemental material, Figure S1). The mean (SD) duration of SQ HDM-Tablet treatment was 380 (57) days. Baseline characteristics (BMI, smoking habits, history of allergy, concomitant respiratory allergy, lung function, number of patients with sleep disorders related to the allergy, therapy taken during the 12 months prior to study inclusion, including symptomatic medication for rhinitis, the severity of rhinitis, severity and level of control of asthma, and the rate of exacerbations) was similar among patients who completed V2 (n=1,210), V3 (n=793) and V4 (n=852), see Table S1.

Sleep disorders

Among the 612 patients with sleep disorders at baseline, there were 180 participants with scores for both V1 and V4 ISI, and 171 with ratings for both V1 and V4 ESS. These subgroups of patients with available ESS and/or ISI questionnaires were not different from the 612 patients with sleep disorders at baseline nor with the included 1483 patients having completed V1 (data not shown). The change of insomnia and daytime sleepiness symptoms between V1 and V4 is 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. A total of 59.7% (n=102/171) of patients reported an ESS improvement $\geq$ $MCID_{ESS}$ 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 ARCT improvement $\geq$ $MCID_{ARCT}$ (71/84; 84.5%,

Figure 1). Similarly, the majority of patients reporting an improvement in ESS ≥ $MCID_{ESS}$ (78/99; 78.8%) also reported better AR control ≥ $MCID_{ARCT}$ (Figure 2).

Univariate analysis (Table S2) indicates that age, antihistamine and/or nasal corticosteroid prescription at the end of V1 and the ISI score at baseline were associated with change of the ISI score over time. Multivariable logistic regression analysis (Table 3) indicates that age (33 to 41 years old), antihistamine/nasal corticosteroid prescriptions at the end of V1 and the ISI score at baseline were significantly associated with change of the ISI score over time. For the ESS score, multivariable logistic regression analysis (Table 4) indicates that the absence of respiratory allergy (other than HDM), and the ESS score at baseline were significantly associated with change of 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=418/1,384) 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 improvement or stability trend 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 ($p=0.0039$) and lower ARCT score ($p<0.0001$) 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 $\geq$ $MCID_{ACT}$ 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, 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. By multivariate analysis, the only factor significant for improved asthma control was the ACT score at baseline ($p<0.0001$) (Table S7). There were 272 participants with ICS data at both V1 and V4, and 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 a third (30.5%) reduced the dose between baseline and V4.

Discussion

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

In our study, 41.5% of the patients reported having experienced sleep symptoms related to their HDM respiratory allergies in the month prior to inclusion. Leger *et al* conducted the MORPHEE prospective, cross-sectional, observational study to characterize the sleep disorders associated with respiratory allergy to HDM upon initiation of sublingual immunotherapy in routine clinical practice [9]. It involved 189 French trial sites and included 1,750 participants suffering from HDM respiratory allergies who initiated sublingual immunotherapy. In the MORPHEE study, sleep disorders were a reason for consultation in over 73% of the adult patients, which is twice the percentage usually observed in the overall French population (37%). While the percentage of patients reporting insomnia and daytime sleepiness in the CARIOCA study was lower, the quality of sleep was worse. In the MORPHEE study, the mean (SD) ISI score was 10.1 (5.9) for adults and the mean (SD) ESS score was 6.7 (4.3) at baseline. In the CARIOCA study, the mean ISI score was 12.1 (5.5) and the mean ESS score 7.9 (4.7). This is probably due to a greater percentage of participants in the CARIOCA study having 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 degree of sleep symptoms and the severity 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 was similar between groups. Improvement in insomnia and daytime sleepiness was mostly reported in patients with significant ARCT improvement,

confirming the positive association between AR severity 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 from the pivotal MT-06 study showing a statistically significant difference from placebo for 4 of the 7 domains of the RQLQ, including the sleep impairment one [19]. Our current open-label study brings further support.

The results of this study also showed that treatment with the SQ HDM SLIT-tablet improved AA and AR control 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 II randomized, double-blind, placebo-controlled MT-02 trial reported by Mosbech *et al* investigated the efficacy of the SQ HDM SLIT-tablet in adults and adolescents with HDM-induced respiratory allergic disease [3]. After one year of treatment with 6 SQ-HDM, 34% of the patients were able to discontinue ICS use completely. Moreover, in 6 SQ-HDM group patients, 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). The efficacy of the SQ HDM SLIT-tablet in real life has thus been demonstrated and further confirms previous findings on the benefits of an HDM tablet on improved control of AR and AA [4,5].

Limits of the study

Due to the observational design of the study, it is important to 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 fully complete the study in accordance to the protocol, with 14% 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 questionnaires were not different from the 612 patients with sleep disorders at baseline nor with the included 1483 patients having completed V1.

As there is no control arm in our observational study, it is impossible to assess the relative effect of pharmacotherapeutic treatments and allergen immunotherapy. Due to the study design, and in particular the absence of sleep night testing like a 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 symptoms, not on a specific disorder such as OSA for example. Furthermore, we do not have an objective assessment of insomnia and sleepiness symptoms: we use self-questionnaires (ISI and Epworth scale) and not objective tests such as the wakefulness maintenance test.

Conclusion

In patients suffering from sleep disorders associated with HDM respiratory allergies, an improvement in insomnia and daytime sleepiness was observed after one 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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Conflict of interest

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

ES reports personal fees for teaching and research from: ALK, GlaxoSmithKline, Menarini, Viatris, Zambon and Sanofi Regeneron.

CL reports personnel fees for lectures and travel grants from ALK, AZ, Boerhinger, Ménarini, Mundipharma, MSD, Pfizer, Sanofi.

AC is employee of ALK.

PD reports non personal honorarias for teaching, research from: ALK, AstraZeneca, GlaxoSmithKline, Menarini, Puressentiel, Stallergenes Greer, ThermoFisher Scientific, Viatris, Zambon.

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FIGURES

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

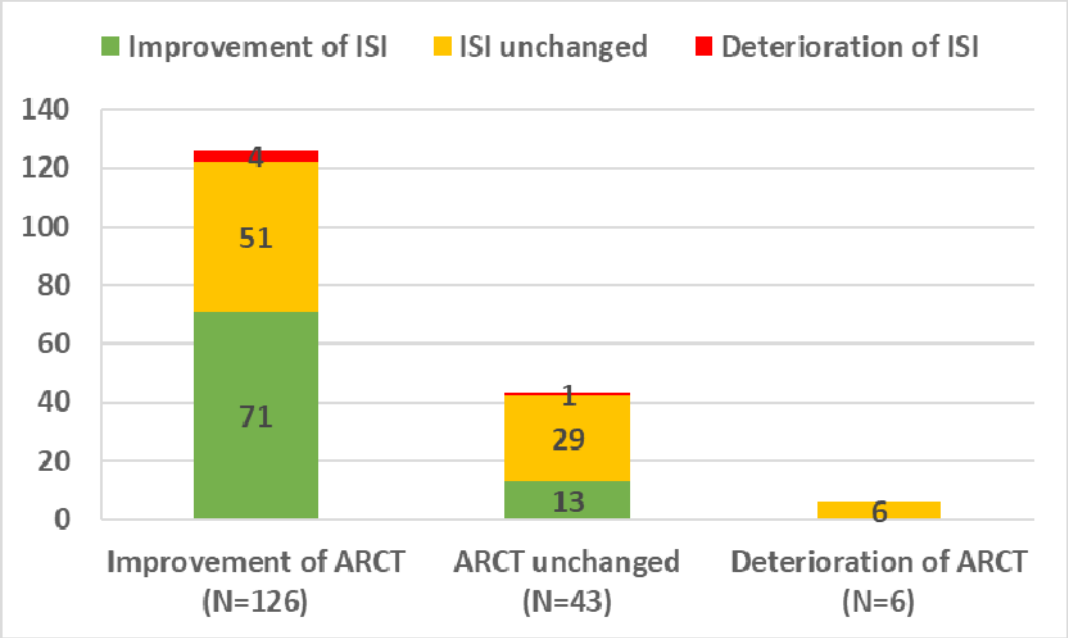
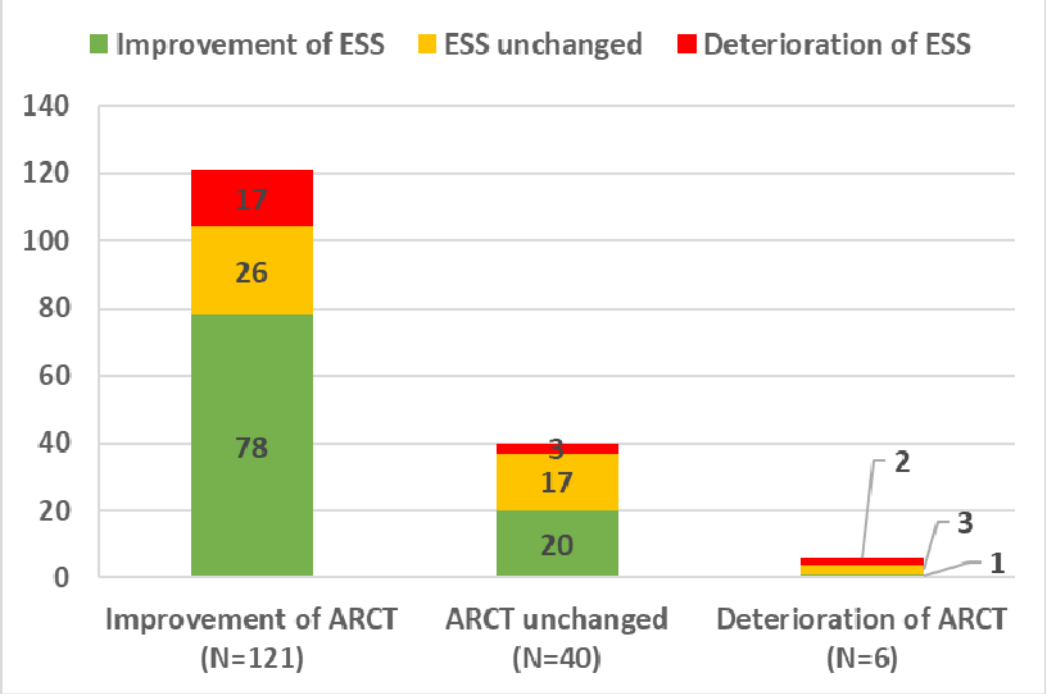


Figure 2. Change between V1 and V4 for the ARCT and ESS scores (N=175).



TABLES

Table 1. Baseline demographic and disease characteristics of patients in the analysis population (N=1,483)

Parameters		AR alone (N=984)	AA+AR (N=499)	Total (N=1,483)
Age (years), Mean (SD)		34.2 (11.6)	34.3 (11.2)	34.2 (11.5)
Gender, n (%)				
Male		403 (41.0)	213 (42.7)	616 (41.5)
Female		581 (59.0)	286 (57.3)	867 (58.5)
Smoking habits, n (%)				
Non-smoker		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)
BMI (kg/m²), N	**1438**	**1182**	**781**	**835**
Mean (SD)	24.1 (4.2)	24.1 (4.2)	24.2 (4.2)	24.1 (4.0)
Allergy history, n (%)		**984**	**499**	**1,483**
At least one respiratory allergy or sensitization (other than HDM)		573 (58.2)[a]	370 (74.1)[a]	943 (63.6)
Rhinitis according to the ARCT score, n (%)		**923**	**461**	**1,384**
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, n (%)		**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 past month, n (%)		**977**	**497**	**1,474**
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, n (%)		**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, n (%)	**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: AR= Allergic Rhinitis; AA+AR= Allergic Asthma and Allergic Rhinitis, ARCT= Allergic Rhinitis Control Test; ACT= Asthma Control Test; ESS= Epworth Sleepiness Scale; ISI= Insomnia Severity Index; [a] = $p<0.0001$

Table 2. Change of 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;-2.0)	-5.0 (-8.0;-2.0)	-5.00 (-10.0;-2.0)
Status of the ISI total score according to MCID$_{ISI}$, N (%)			
Improved between V1 and V4 (≤ -6)	60 (50.0)	27 (45.0)	87 (48.3)
Unchanged between V1 and V4 (]-6 ; 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;0.0)	-2.0 (-4.0;0.0)	-2.0 (-5.0;0.0)
Status of the ESS total score according to MCID$_{ESS}$, N (%)			
Improved between V1 and V4 (≤ -2)	68 (61.8)	34 (55.7)	102 (59.7)
Unchanged between V1 and V4 (]-2 ; 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

MCID= minimal clinically important difference

Table 3. Multivariate logistic analysis. Variable of interest: ISI score, improvement [change ≥ $MCID_{ISI}$] vs. no improvement [change < $MCID_{ISI}$], V1 versus V4.

Variable	OR [95% CI]	p-value
Age (at inclusion) (quartiles)		
≤ Q1: 26	1.00	
]Q1: 26; Median: 33]	1.99 [0.69 ; 5.72]	0.2024
]Median: 33; Q3: 41]	3.33 [1.07 ; 10.41]	0.0385
> Q3: 41	0.47 [0.15 ; 1.45]	0.1891
Prescription of antihistamines at the end of V1		
No	3.63 [1.21 ; 10.87]	0.0211
Yes	1.00	
Prescription of nasal corticosteroids at the end of V1		
No	1.00	
Yes	3.22 [1.41 ; 7.34]	0.0055
ISI score (at inclusion) (quartiles)		
≤ Q1: 8	1.00	
]Q1: 8; Median: 12]	17.46 [4.96 ; 61.41]	<0.0001
]Median: 12; Q3: 16]	34.69 [9.35 ; 126.77]	<0.0001
> Q3: 16	51.08 [12.65 ; 206.27]	<0.0001

Table 4. Multivariate logistic analysis. Variable of interest: ESS score, improvement [change ≥ $MCID_{ESS}$] vs. no improvement [change < $MCID_{ESS}$], V1 versus V4.

Variable	OR [95% CI]	p-value
At least one respiratory allergy (other than HDM respiratory allergies)		**0.0038**
No	2.20 [1.04 ; 4.65]	
Yes	1.00	
ESS score (at inclusion)	**1.21 [1.12 ; 1.31]**	**<0.0001**

Table 5. Change of 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 $MCID_{ARCT}$ N (%)			
Improved between V1 and V4 (≥ 3)	321 (73.8)	136 (66.0)	457 (71.3)
Unchanged between V1 and V4 (]-3 ; 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

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Table 6. Change of 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 $MCID_{ACT}$, N (%)	
Improved between V1 and V4 (≥ 3)	81 (46.6)
Unchanged between V1 and V4 (]-3 ; 3[)	85 (48.8)
Deteriorated between V1 and V4 (≤ -3)	8 (4.6)
Missing	98

Table 7. Change of inhaled corticosteroid prescription between V1 and V4 (N=272).

	Total (N=272)
Reduced ICS dose, n (%)	76 (30.5)
ICS dose unchanged, n (%)	152 (61.0)
Increased ICS dose, n (%)	23 (9.2)
Missing	21

Percentages are based on patients with ICS dose data at V1 and V4