House dust mite sublingual allergen immunotherapy tablet is safe and well-tolerated in Dutch clinical practice

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Abstract

Background 49% of clinically diagnosed allergic rhinitis (AR) patients are sensitized to house dust mite (HDM). If allergen avoidance and symptomatic medication fail, allergen immunotherapy may be indicated. We investigated safety and tolerability of HDM-sublingual immunotherapy HDM SLIT-tablets in adults in daily clinical practice in the Netherlands. **Methods** Daily intake of 12 SQ-HDM SLIT-tablet was investigated in the prospective, multi-center, observational study. It comprised 4 consultations in 1 year. Data on safety, tolerability, treatment satisfaction, symptomatic medication, compliance, and clinical effectiveness (Control of Allergic Rhinitis and Asthma Test; CARAT) were collected. Descriptive and longitudinal regression data analysis was performed. **Results** 415 adult patients, mean age 36.6 years, 61.4% female, 36% asthmatic were included. 65.3% of patients experienced possibly-related adverse events (AEs). These mostly mild (67%) AEs comprised: oral allergic reactions (58.6%), respiratory (12.4%) and gastrointestinal symptoms (9.4%). 60 (14.5%) patients stopped due to AEs and 76 (18.3%) for non-AE reasons. Mean CARAT scores improved clinically significant by 6 points and symptomatic medication use decreased from 96.1% to 77.4%. 74.5% of patients tolerated the treatment well. Most patients were compliant (>86.5%) and patients (62.4 %) and investigators (69.4%) were satisfied with treatment. **Conclusions** HDM-SLIT-tablet is a safe and well-tolerated AR treatment. AEs occur often but are mostly mild and decreasing during the first year. CARAT scores improved and symptomatic medication use decreased suggesting better control of AR with HDMSLIT-tablet treatment. Compliance, tolerability, and treatment satisfaction are good. However, patient follow-up and compliance remain important points of attention when starting HDM SLIT-tablet.

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SHORT Title: HDM SLIT-tablet safety in Dutch clinical practice

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ABSTRACT

Background

49% of clinically diagnosed allergic rhinitis (AR) patients are sensitized to house dust mite (HDM). If allergen avoidance and symptomatic medication fail, allergen immunotherapy may be indicated. We investigated safety and tolerability of HDM-sublingual immunotherapy HDM SLIT-tablets in adults in daily clinical practice in the Netherlands.

Methods

Daily intake of 12 SQ-HDM SLIT-tablet was investigated in the prospective, multi-center, observational study. It comprised 4 consultations in 1 year. Data on safety, tolerability, treatment satisfaction, symptomatic

medication, compliance, and clinical effectiveness (Control of Allergic Rhinitis and Asthma Test; CARAT) were collected. Descriptive and longitudinal regression data analysis was performed.

Results

415 adult patients, mean age 36.6 years, 61.4% female, 36% asthmatic were included. 65.3% of patients experienced possibly-related adverse events (AEs). These mostly mild (67%) AEs comprised: oral allergic reactions (58.6%), respiratory (12.4%) and gastrointestinal symptoms (9.4%).

60 (14.5%) patients stopped due to AEs and 76 (18.3%) for non-AE reasons. Mean CARAT scores improved clinically significant by 6 points and symptomatic medication use decreased from 96.1% to 77.4%. 74.5% of patients tolerated the treatment well. Most patients were compliant (>86.5%) and patients (62.4 %) and investigators (69.4%) were satisfied with treatment.

Conclusions

HDM-SLIT-tablet is a safe and well-tolerated AR treatment. AEs occur often but are mostly mild and decreasing during the first year. CARAT scores improved and symptomatic medication use decreased suggesting better control of AR with HDMSLIT-tablet treatment. Compliance, tolerability, and treatment satisfaction are good. However, patient follow-up and compliance remain important points of attention when starting HDM SLIT-tablet.

Keywords: Allergic Rhinitis, Control of Allergic Rhinitis and Asthma Test (CARAT), House dust mite (HDM), Safety, Sublingual immunotherapy tablet

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INTRODUCTION

Allergic rhinitis (AR) affects 17% to 29% of the adult population in Europe, thereby constituting a serious public health problem. An incidence rate of AR of approximately 9 per 1000 patient-years has been reported for children as well as for adults in Dutch general practices. In addition, allergy to house dust mites (HDM), generally induced by*Dermatophagoides (D) pteronyssinus* or *D. farinae* , is the most common inhalant allergy with sensitization in 49% of subjects with a clinical diagnosis of AR in Western Europe.

Next to symptomatic treatment (antihistamines, decongestants, and nasal corticosteroids), treatment with sublingual immunotherapy (SLIT) has increased in recent years. Several clinical trials have shown that treatment with HDM SLIT-tablet immunotherapy effectively reduced symptoms associated with HDM AR with or without asthma. Hence, treatment with HDM SLIT-tablet has become common practice. However, most data concerning tolerability, side effects and compliance have been obtained in clinical trials and not in a daily clinical practice setting. While RCTs have high internal validity and are needed to demonstrate a favorable risk/benefit profile, the controlled clinical trial setting with patient selection based on in- and exclusion criteria may impact the generalizability of the results to daily practice.

To assess the general applicability of the efficacy and safety data collected in randomized controlled trials (RCT's), we set out to conduct a complementary multi-center, observational study in outpatient clinics. The study objectives were to assess the safety, tolerability, treatment satisfaction, compliance, and clinical effectiveness of HDM SLIT-tablet treatment, when prescribed as part of regular clinical practice.

METHODS

2.1 Study participants

415 patients (age 18-65 years) with HDM-induced AR with or without asthma were recruited from 71 general practices or outpatient clinics of allergologists, dermatologists, Ear-Nose-Throat (ENT) specialists or pulmonologists in the Netherlands between September 2017 and March 2019. A patient was diagnosed with HDM allergy, when having a positive skin prick test to HDM extract or allergen specific HDM IgE level of ^{3} 0.35 IU/mL next to an appropriate clinical history. The decision to initiate treatment with HDM

SLIT-tablet was made at the discretion of the physician. Key discontinuation criteria were patient-based decision or treatment-related adverse event (AE). The study was approved by the Dutch Clinical Research Federation/nWMO Advisory Committee Twente (no. NWMO17.04.017) and the applicable ethics committees and institutional review boards. All patients gave written informed consent. The study complies with the Declaration of Helsinki.

2.2 Study design

This is a non-interventional, prospective, multi-center, observational study. Data were collected and recorded during three patient visits and one phone consultation. The first visit included on-site administration of HDM SLIT-tablet and collection of baseline characteristics. An interview by phone followed a week later. The second visit followed three months and the final visit 1 year after the initial visit, respectively. During each visit the allergic symptoms, Control of Allergic Rhinitis and Asthma Test (CARAT) questionnaire, (change in) concomitant medication, lung function measurements (only if indicated according to the treating physician) and safety evaluations (AEs/SAEs) were recorded.

2.3 Collection, recording and reporting of adverse events

All safety data were assessed by the treating physician. Standard definitions were used for adverse event, seriousness, and outcome. Relatedness was defined as either ''Possible": a causal relationship is conceivable and at least reasonably possible; or ''Unlikely": the event is most likely related to a different etiology than the medicinal product. AEs with unclear causality were categorized as possibly related. Safety data solicited were all serious adverse events (SAE), all causal AEs, and AEs of special interest. Any unsolicited safety data reported by physicians were also included. All AEs reported were categorized by preferred term and system organ class (Medical Dictionary for Regulatory Activities versions 23.0).

2.4 Study treatment

In this study, patients were treated with HDM SLIT-tablet (ACARIZAX®; 12-SQ-HDM sublingual lyophilizate immunotherapy ALK-Abelló A/S, Hørsholm, Denmark). HDM SLIT-tablet is approved for the treatment of HDM induced AR by the Dutch authorities since July 2016 and reimbursed as of October 2017. HDM SLIT-tablet is a lyophilisate containing standardized allergen extract from two house-dust-mite species, *D. pteronyssinus* and *D. farinae.* The first dose was self-administered under medical supervision, and subjects were monitored for 30 minutes after first intake. Subsequent doses were self-administered at home. The tablet was to be placed under the tongue and allowed to remain there until dissolved. Subjects were advised not to swallow during the first minute after administration, food and beverage was not allowed for 5 minutes thereafter. The study duration was one year.

2.5 Statistical analysis

Regarding safety, the frequencies, and proportions of possibly treatment-related adverse events (AEs) were calculated. All AEs having at least a possible relation with the study drug were described (details see supporting information). Of all AEs reported the frequency and proportion per severity category, course, outcome, and drug adjustment in response to the AE were calculated.

To test whether the occurrence of any AE changed over time, the occurrence of any AE at 1 week, 3 months and 1 year was compared to the occurrence shortly after the first administration using multilevel modelling to account for the repeated observations within patients.

Treatment compliance was estimated and categorized by treating physician: 100-80% (compliant), between 50% and 80%, or less than 50% and described per visit (n (%)).

Treatment satisfaction experienced by patients and observed by physicians (very satisfied, satisfied, unsatisfied, very unsatisfied) and treatment tolerability (very good, good, moderate, poor) were described as proportions.

Post hoc clinical effectiveness analyses

The CARAT questionnaire is a validated useful tool for facilitating optimal control of both asthma and allergic rhinitis simultaneouslyand is described in a recent EAACI position paper and included in Dutch guidelines. CARAT scores vary from 0 points (worst) to 30 points (best) outcome. The minimal clinical important difference (MCID) for CARAT scores was established at a 4 points difference in 2015. Changes equal or more than MCID, with a P <0.05 for difference in means, were considered indicative for clinical effectiveness.

RESULTS

Patient Population

Patient's demographics and baseline characteristics are shown in**Table 1** . The mean age of the predominantly female population (61.4%) was 36.6 years. Average time between onset of AR symptoms and initiation of SLIT treatment was 8 years. 36.1% had concomitant allergic asthma. The proportion of polysensitized patients was 79%. Main co-sensitizations were grass pollen (76.5%), tree pollen (54%), and animal dander (48.5%).

The majority of patients completed the study (**Figure 1**). Younger patients and patients treated by general practitioners (GP) were more likely to discontinue treatment. Other categories did not differ significantly.

3.2 Safety

AEs were frequent, but mostly local and mild (**Tables 2 and 3**). In total 970 AEs were reported in 271 (65.3%) patients. 836 AEs were possibly related to the study drug (86.2%) and described in Tables 2 and 3. Data on relatedness were missing for 3.3% of AEs. Overall, 65.3% of patients experienced at least one AE over the study period, most frequently oral allergy reactions (oral paresthesia (11.0%), throat irritation (10.2%) and oral pruritus (8.1%), see also Table E1).

Of all AEs reported 563 (67.3%) were mild, 196 (23.4%) moderate and 64 (7.7%) severe. 81 (9.7%) AEs resulted in treatment discontinuation, 29 (3.5%) in temporary discontinuation and the majority of AEs 724 (86.6%) had no effect on treatment. The most prevalent severe AEs leading to discontinuation were swollen tongue (0.7%), mouth swelling (0.6%), nausea (0.5%). Most patients fully recovered (81.1%), in 10 (1.2%) cases the patient recovered with some symptoms remaining at end of study, in 36 (4.3%) cases the patient did not recover during the study and in 112 (13.4%) cases this was unknown (**Table 3**)

24 SAEs were reported. Only 1 SAE (angioedema) was related to the study drug. It occurred at the 3-month visit. The patient recovered fully after discontinuation of treatment.

The percentage of patients reporting AEs decreased from 51.8% at day 1 to 5.8% after 1 year in those remaining on treatment. The odds that a patient had any AE compared to having any AE(s) directly after first intake, decreased after 1 week (Odds Ratio (OR) = 0.33, P<0.0001), 3 months (OR = 0.13, P <0.0001), and 1 year (OR = 0.04, p<0.0001). These results did not change after correction for potential confounders.

3.3 Treatment adherence: persistence and compliance

In total 138 patients discontinued the treatment (60 because of AEs, 76 due to motivation/other reasons). Treatment persistence was, therefore, 66.7% overall (**Figure 1**). Subsequently, 248 (59.8%) patients intended to continue treatment for another 2 years in line with the guidelines. A high treatment compliance, i.e., at least 80% of medication taken daily, was observed for those that persisted with treatment. High compliance was reported for 96.7%, 91.5% and 86.6% of patients at week 1, 3 months and 1 year, respectively.

3.4 Perceived treatment tolerability and treatment satisfaction

Of patients that answered, the majority (72.8%) was satisfied/very satisfied with the treatment, and 27.2% unsatisfied/very unsatisfied. The majority of physicians agrees (80.0% and 20.0%, respectively) (**Table 4**). Treatment tolerability was reported to be well to very well according to 74.5% of patients and 80.1% according to their physicians (**Table 4**).

3.5 Effectiveness of the treatment

CARAT

When CARAT scores at 1 week, 3 months and 1 year of treatment were compared to pre-treatment values using linear multilevel modelling, scores increased with 2.14 (95% CI 1.59 – 2.69,P <0.0001), 4.69 (4.11 – 5.26, P<0.0001), and 5.92 (5.30 – 6.55, P <0.0001), respectively. The accepted MCID is 4 points. Therefore, these results indicate that most patients improved after 3 months and 1 year of treatment (**Figure 2, Table E2**).

When separately analyzing the AR only and AR+AA subgroups, the AR+AA group had a numerical larger improvement (6.90 vs 5.38 points; P=0.06) after 1 year of treatment (see **Table E2**).

3.6 Symptomatic medication

The use of any symptomatic medication decreased significantly from 96.1% at day 1 of HDM SLIT-tablet treatment to 85.9% at 1 week, 83.0% at 3 months and 75.5% at 1 year of treatment, respectively.

DISCUSSION

In this observational study, safety, tolerability, satisfaction, compliance, and clinical effectiveness were assessed for HDM SLIT treatment in Dutch daily practice. AEs observed are mostly mild to moderate and decrease in frequency with treatment duration, confirming HDM SLIT-tablet safety. Moreover, symptomatic medication uses decrease, and CARAT scores improve with treatment, indicating clinical effectiveness. Thus confirming safety and clinical efficacy previously established in trials. In addition, compliance is high in treatment-persistent patients and both patients and physicians assess treatment to be tolerable and satisfactory.

In this study, 271 (65.3%) patients experienced AEs. Oral allergy reactions (58.6%) were most frequently observed, followed by airway complaints (12.4%), and GI reactions (9.4%). In the phase III trial by Demoly et al. 67% of patients on 12 SQ-HDM experienced AEs comprising: oral pruritis (20%), throat irritation (14%) and mouth oedema (8%); indicating similarity in frequency and location of AEs in clinical trial and in daily-practice setting. The proportion of AEs experienced by patients in real-life is higher than in France (32%) but lower than in Scandinavia (80%). Possible explanations for the observed differences may include differences in study design and environmental factors such as climate and time spend indoors.

CARAT questionnaires were used to monitor treatment as recommended by Dutch guidelines. As the MCID for CARAT is established, significant increases in CARAT scores that are more than the MCID may indicate clinical effectiveness. Therefore, post hoc analyses on changes in mean CARAT scores were conducted. CARAT scores increased significantly and clinically meaningful after 3 months (> 4 points) and 1 year (6 point) treatment compared to baseline. This shows clinical effectiveness and confirms the previously established clinical efficacy.

In real life, patients often do not fill out their prescriptions as advised, while AIT treatment needs to be persisted for 3 years. In the past, major issues were reported with SLIT drops compliance in the Netherlands. Only 7% of patients was found to consistently and timely pick up refills. In the present study, compliance (defined as 80-100% of SLIT-tablets taken daily) was excellent: 96.7% at 1 week, 91.5% at 3 months and 86.6% at 1 year, respectively. This is in line with recent studies. In a Swedish-Danish study SLIT-tablet compliance was 93.2% at 1-year. Moreover, data from the Danish prescription register showed a compliance rate of 53% and 57% for SLIT-tablet and SCIT, respectively, after 3-years treatment. Furthermore, compliance in a recent Dutch grass pollen SLIT-tablet study was 76%. Possible explanations for the observed differences include: increased attention on compliance, the definition of compliance, different study populations, and differences in SLIT type (drops vs tablets).

Ways to improve compliance include more patient visits and selecting patients dedicated to persisting treatment. For example compliance in clinical trials is generally higher than in real-life studies. In addition, solid patient education on SLIT-tablet treatment may help. Part of patient education may be reassuring patients,

that AEs will decrease over time as validated by this study. Moreover, if AEs occur, adding symptomatic medication may be considered.

Discontinuation was higher in this real-life study compared to the phase III trial by Demoly et al. 14.5% of patients stopped treatment due to AEs and 18.3% patients stopped because of motivational/other reasons versus 4.1% and 6.6% in the trial, respectively. However, discontinuation was in line with a recent Dutch real-life grass pollen SLIT-tablet study, which reported discontinuation in 9.8% of patients due to AEs and 15.3% because of other reasons. Possible explanations may be the more intensive follow up of patients in trials and variations in patient populations.

Patients and their physicians were asked about satisfaction and tolerability of treatment when they discontinued or completed the study. Responding patients (74.5%) and physicians (80.1%) reported treatment to be well to very-well tolerable. Moreover, most patients (72.8% of responders; 62.4% of all patients) and their physicians (80.0% responders; 69.4% for all patients) were satisfied with treatment. This is in line with previously reported satisfaction for SLIT-tablet therapy.

Strengths and limitations

The study was limited to 1 year. Therefore, AEs that developed, subsequently, may be missed. Since previous studies have shown that most (serious) AEs occur at the beginning of treatment and AEs decrease over time from 51.8% at day 1 to 5.8% after 1 year in this study, we consider this risk to be low.

138 out of 415 patients did not complete the study. Discontinuation of treatment is a common problem when administering SLIT. This might have had impact on our outcomes i.e. there could be an underestimation of the safety and tolerability effects and an overestimation of effectiveness. Nonetheless, no major differences were observed in baseline characteristics of patients that continued versus those that discontinued treatment, indicating that outcomes are representative for all patients.

Implications for clinical practice

HDM SLIT-tablet should only be prescribed to motivated patients. It is also important to emphasize the high likelihood of developing one or more AEs (>65%). At the same time, it is essential to address that most AEs are mild and likely resolve with time. However, there is still a chance that patients will stop treatment because of AEs.

5 CONCLUSIONS

Our study confirms that HDM SLIT-tablet (ACARIZAX®) is a safe and well-tolerated treatment for HDM AR in daily clinical practice.

Adverse events are common but are mostly mild and decrease during the first year. Clinical scores (CARAT) improve, and symptomatic medication use decreases with treatment duration. If patients continue therapy, compliance rates are high and treatment satisfaction is good. However, with a stopping rate of 14.5% and 18.3% due to adverse events and motivational reasons, compliance remains the main concern when starting HDM SLIT-tablet.

Tables and Figure titles

TABLE 1 Baseline characteristics of patients

TABLE 2 Treatment related AEs

TABLE 3 Severity, outcome & study drug adjustments for treatment related AEs per visit

TABLE 4 Final evaluation of treatment satisfaction and tolerability

FIGURE 1 Study flow and follow-up

FIGURE 2 CARAT scores per visit and per allergic rhinitis and asthma status

Supporting information: Supplementary tables

TABLE E1 Ten most frequent adverse events by Preferred term and classification

TABLE E2 CARAT scores improved in all AR patients with or without asthma during HDM SLIT-tablet treatment

TABLE 1 Baseline characteristics of patients

Characteristic	Total (N=415)	Completed study n=277	Discontinued n=138	*P*-value for comparison
Age, years[++]	36.6 (12.2)	37.5 (12.2)	34.9 (12.0)	0.0388
Weight, kg[++]	77.0 (15.4)	77.1 (15.5)	77.0 (15.3)	0.9639
Height, cm[++]	173.8 (9.6)	174.1 (9.5)	173.1 (9.6)	0.2933
BMI[++]	25.5 (4.5)	25.4 (4.5)	25.8 (4.7)	0.3918
Female sex[§]	255 (61.4)	168 (60.6)	87 (63.0)	0.7151
Treated by general practitioner[§] (vs specialist)	116 (28.0)	68 (24.5)	48 (34.8)	0.03821
HDM-induced AR[§]	415 (100)	277 (100)	138 (100)	-
Years with HDM-induced AR[¶]	8 (1, 17)	8 (1, 18)	7 (1, 9.7)	0.1323
Asthma[§]	150 (36.1)	105 (37.9)	45 (32.6)	0.2899
Family history of allergy[§]	152 (27.2)	95 (34.4)	57 (41.3)	0.1978
Co-allergy status[§]				0.0737
Mono sensitized (only HDM) [§]	87 (21.0)	60 (21.7)	27 (19.6)	
One co-allergy[§]	100 (24.1)	57 (20.6)	43 (31.2)	
Two co-allergies[§]	124 (29.9)	91 (32.9)	33 (23.9)	
Three or more co-allergies[§]	104 (25.1)	69 (24.9)	35 (25.4)	
Type of co-allergies[§]				
Tree pollen[§]	177 (54.0)	123 (44.4)	54 (39.1)	0.3586
Grass pollen[§]	251 (76,5)	166 (59.9)	85 (61.6)	0.8254
Animal dander[§]	159 (48.5)	110 (39.7)	49 (35.5)	0.4698
Plant pollen[§]	10 (2.4)	8 (2.9)	2 (1.4)	0.5071
Fungus spores[§]	13 (3.1)	8 (2.9)	5 (3.6)	0.7667
Food[§]	34 (8.2)	24 (8.7)	10 (7.2)	0.7594
Other[§]	49 (11.8)	29 (10.5)	20 (14.5)	0.3006
Current immunotherapies use other than HDM SLIT-tablet[§]				0.05921
No other immunotherapy[§]	355 (85.5)	234 (84.5)	121 (87.7)	

Characteristic	Total (N=415)	Completed study n=277	Discontinued n=138	*P*-value for comparison
One immunotherapy§	47 (11.3)	37 (13.4)	10 (7.2)	
Two immunotherapies§	13 (3.1)	6 (2.2)	7 (5.1)	

Allergic rhinitis (AR); Body Mass Index (BMI); House dust mite (HDM); n is number of patients; ++mean (standard deviation, SD); ¶ median (interquartile range, IQR); § is number and proportion of patients n (%). *P* -value for comparison completed vs discontinued early by t-test or Chi square.

TABLE 2 Treatment related AEs

	Over total study period	**Initial visit**
Patients attending visit	N=415	n=415
Subjects with any AE^{++}	271 (65.3)	215 (51.8)
Subjects with any moderate or severe AE^{++}	96 (23.1)	42 (10.1)
AEs per patient§	3 (2;5)	2 (1;3)
Subjects per specific category of AEs^{++}	**Subjects per specific category of AEs^{++}**	**Subjects per specific ca**
Oral allergy reactions^{++}	243 (58.6)	203 (48.9)
Gastrointestinal reactions^{++}	39 (9.4)	12 (2.9)
Airway reactions^{++}	51 (12.3)	27 (6.5)
-Lower airway reactions^{++}	26 (6.3)	14 (3.4)
-Upper airway reactions^{++}	35 (8.4)	13 (3.1)
Skin reactions^{++}	20 (4.8)	6 (1.4)
General reactions^{++}	28 (6.7)	12 (2.9)
Other^{++}	59 (14.2)	18 (4.3)

$^{++}$n (%) is number and proportion of patients;§ median (interquartile range); AE: adverse event. The most frequent AEs by preferred term are listed in**Table E1** .

TABLE 3 Severity, outcome & study drug adjustments for treatment related AEs per visit

AE characterization by	**Initial visit**	**1 week**	**3 months**	**1 year**
Total number of AEs per visit moment	441	255	98	26
Severity of AEs	*Severity of AEs*	*Severity of AEs*	*Severity of AEs*	*Severity of AEs*
Mild	343 (77.8)	149 (58.4)	50 (51.0)	12 (46.2)
Moderate	92 (20.9)	63 (24.7)	33 (33.7)	6 (23.1)
Severe	2 (0.5)	41 (16.1)	10 (10.2)	7 (26.9)
Unknown	4 (0.9)	2 (0.8)	5 (5.1)	1 (7.7)
Course / Outcome	*Course / Outcome*	*Course / Outcome*	*Course / Outcome*	*Course / Outcome*
Recovered	390 (88.4)	179 (70.2)	75 (76.5)	19 (73.1)
Recovered with residual symptoms	3 (0.7)	5 (2.0)	2 (2.0)	0 (0)

AE characterization by	Initial visit	1 week	3 months	1 year
No recovery	8 (1.8)	23 (9.0)	4 (4.1)	1 (3.8)
Fatal	0 (0)	0 (0)	0 (0)	0 (0)
Unknown	40 (9.1)	48 (18.8)	17 (17.3)	6 (23.1)
Study drug adjustment	*Study drug adjustment*	*Study drug adjustment*	*Study drug adjustment*	*Study drug adjustment*
No	428 (97.1)	193 (75.7)	76 (77.6)	16 (61.5)
Temporary interrupted	6 (1.4)	15 (5.9)	8 (8.2)	0 (0)
Stopped	6 (1.4)	47 (18.4)	14 (14.3)	9 (34.6)
Unknown	1 (0.2)	0 (0)	0 (0)	1 (3.8)

AEs: adverse events. Number of AEs and proportion (%) of AEs ongoing at respective study visits. First administration at initial visit.

TABLE 4 Final evaluation of treatment satisfaction and tolerability

Treatment tolerability	Very well	Well	Moderately	Poorly tolerated	No response
Patient (n=357)	121 (33.9)	145 (40.6)	28 (7.8)	63 (17.6)	58
Physician (n=362)	117 (32.3)	173 (47.8)	44 (12.2)	28 (7.8)	53
Treatment satisfaction	**Very satisfied**	**Satisfied**	**Not satisfied**	**Very dissatisfied**	**No response**
Patients (n=356)	85 (23.9)	174 (48.9)	78 (21.9)	19 (5.3)	59
Physicians (n=360)	84 (23.3)	204 (56.7)	63 (17.5)	9 (2.5)	55

n is number of patients. Frequencies of a selected answer and proportions (%) of total responding patients and observing physicians, respectively.

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