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ORIGINAL ARTICLE

Rhinitis, Sinusitis and Upper Airway Disease

AM-301, a barrier-forming nasal spray, versus saline spray in seasonal allergic rhinitis: A randomized clinical trial

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Abstract

Rationale: Saline nasal sprays are frequently used in the management of seasonal allergic rhinitis (SAR) for the cleansing and clearing of aeroallergens from the nasal cavity. Also using a drug-free approach, AM-301 nasal spray is forming a thin film barrier on the nasal mucosa to prevent contact with allergens, trap them, and facilitate their discharge. A clinical trial compared the efficacy, safety, and tolerability of AM-301 and saline spray in SAR.

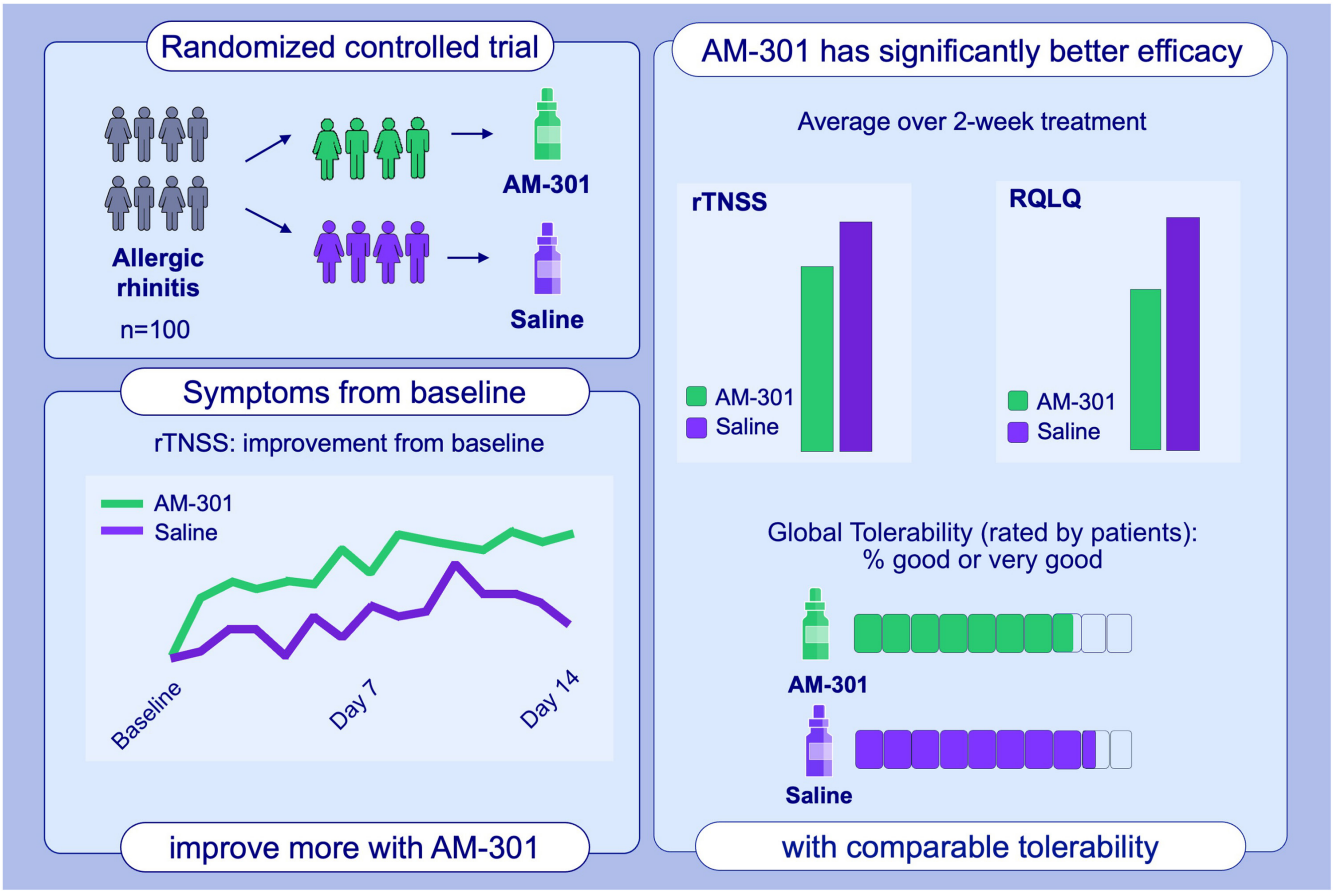
Methods: A total of 100 patients were randomized 1:1 to self-administer AM-301 or saline 3×daily for 2 weeks. Primary efficacy endpoint: reduction in mean daily reflective Total Nasal Symptom Score (rTNSS). Secondary efficacy endpoints: reduction in mean instantaneous TNSS and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), global impression of efficacy. Safety and tolerability: adverse events, relief medication use, symptom-free days, global impression of tolerability.

Results: AM-301-treated patients achieved a significantly lower rTNSS than the saline group (LS square means difference −1.1, 95% CI −1.959 to −0.241, $p = .013$) with improvement observed across all individual nasal symptoms. Likewise, all secondary endpoints showed statistical significance in favor of AM-301; for example, quality of life was significantly improved overall ($p < .001$) as well as for each individual RQLQ domain. Both treatments showed similarly good safety and tolerability. With AM-301, fewer patients used relief medication and more enjoyed symptom-free days compared to saline treatment.

Conclusions: AM-301 was more effective than saline in improving SAR nasal symptoms and related quality of life while offering similar tolerability, demonstrating the benefits of a barrier approach.

KEYWORDS
allergic rhinitis, AM-301, drug-free, nasal spray, saline

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GRAPHICAL ABSTRACT

We compared the efficacy of two nonpharmacological nasal sprays (AM-301 and saline) in reducing symptoms of allergic rhinitis in a randomized, controlled clinical trial. A statistically significantly larger reduction in average rTNSS, iTNSS, and RQLQ scores was observed in patients treated with AM-301 compared to saline-treated patients. Tolerability of AM-301 was comparable to the one of saline.
Abbreviations: iTNSS, instantaneous Total Nasal Symptom Scores; rTNSS, reflective Total Nasal Symptom Score; SPT, Skin Prick Test; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.

1 | INTRODUCTION

Allergic rhinitis (AR) affects 20%–30% of adults and up to 40% of children in Europe and the United States, making AR the most common atopic condition and the second leading cause of chronic disease.[1] When poorly controlled, AR is recognized to have a major effect on quality of life, emotional well-being, sleep, daily activities, and productivity.[2-4] Treatment options include Allergen Immunotherapy (AIT) as sole causal treatment, as well as various pharmacological options, including the use of topical glucocorticoids, antihistamines, antileukotrienes, cromoglicic acid, and sympathomimetic decongestants for symptom relief.[5,6] The efficacy of drug-based treatments in achieving symptom relief depends on symptom severity, and their use is often accompanied by side effects.[5-18]

As an alternative or complement to drug-based therapies, patients may administer saline or seawater nasal sprays to cleanse and clear aeroallergens from the nasal cavity[19] and provide relief from nasal congestion by helping to remove excess mucus. Another drug-free treatment approach consists of creating a protective physical layer on top of the nasal mucosa in order to limit exposure to aeroallergens and subsequent activation of the cascade of pro-inflammatory cytokines responsible for the manifestation of allergic symptoms.[20] Such barrier products include lipid creams, cellulose powders, and other barrier-enforcing measures.[20]

AM-301 (marketed as Bentrio® in several countries) is a drug-free nasal spray based on a thixotropic gel emulsion that has been developed for the treatment of AR and possibly also certain viral infections. Upon application, the spray forms a thin film barrier on the nasal mucosa to prevent contact with allergens, trap them, and facilitate their discharge. AM-301's main ingredient is bentonite, a mineral clay widely known for its adsorbent, swelling, and rheological properties.[21-23] In a study with eight healthy volunteers, fluorescence-labeled AM-301 was shown to be broadly distributed within the nasal vestibule, inferior turbinate and on the septum, where inhaled aeroallergens tend to collect, for about 3.5 h.[24]

In two clinical trials AM-301 was tested in AR patients exposed under controlled conditions for 4 and 3 h, respectively, to grass pollen and house dust mites in challenge chambers.[25,26] Following single-dose pre-exposure administration, both studies showed an effective and persistent reduction in nasal symptoms. The present study sought to evaluate the efficacy, safety, and tolerability of AM-301 under real-life conditions in SAR patients in comparison to

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saline nasal spray, which is considered the current drug-free standard of care treatment.

2 | METHODS

2.1 | Patients

The study enrolled 100 males and females between 18 and 75 years of age with ≥2-year history of SAR, a positive skin prick test reaction or presence of specific IgE at baseline or within 12 months before enrolment, and a mean rTNSS score ≥5 at baseline. Detailed inclusion and exclusion criteria are listed in Table S1.

2.2 | Study design and treatment groups

Eligible patients were randomized at a 1:1 ratio to either treatment with AM-301 (Altamira Medica AG, Basel, Switzerland) or FESS® saline nasal spray (Care Pharmaceuticals Pty Ltd, Sydney, Australia) for 2 weeks. Levocabastine nasal spray (Zyrtec®, 10 mL) was made available as potential relief medication in case AR symptoms became unbearable. Local area weather and pollen counts were collected to monitor exposure to airborne allergens.

The trial involved eight recruiting sites in Australia that enrolled eligible patients during two allergy seasons between August 2021 and December 2022. It was registered on the Australian New Zealand Clinical Trials Registry (ACTRN12621001727831) and conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonisation, Good Clinical Practice guidelines, and the International Organization for Standardization (ISO) standard 14155, Clinical Investigation of Medical Devices. The study was approved by an appropriate independent ethics committee.

2.3 | Procedures

The study consisted of a screening visit, a treatment-free run-in period of 4–7 days, baseline assessments before randomization on Day 1, a phone call on Day 8, one on-site follow-up visit at treatment period end (Day 15), and a final follow-up phone call on Day 22. Throughout screening and treatment, patients rated the severity of AR symptoms (itchy nose, nasal congestion, runny nose, sneezing) daily in the evening in an electronic diary (reflective: worst experience during preceding 24 h, rTNSS, and instantaneous, iTNSS).[27] Baseline safety and eligibility assessments included vital signs, nasal mucosa examination, IgE / skin prick test, urine drug test, and urine pregnancy test for women of child-bearing age. The 28-item Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)[28] was administered at baseline and on Days 8 and 15; in addition, patients and investigators rated at Day 15 their global impressions of efficacy (in terms of improving allergic symptoms) and tolerability; response categories included "very good", "good", "moderate", and "poor".

Patients self-administered the study treatment in 1 puff/nostril 3 times per day or as needed (not more than 8 puffs/nostril per day). They recorded compliance with treatment, use of relief medication, and time spent outdoors in the electronic diary.

2.4 | Endpoints

The difference in mean rTNSS over 14 treatment days between AM-301 and saline nasal spray was selected as the primary efficacy endpoint, in accordance with published FDA guidance for AR trials with drug products.[29] Secondary efficacy endpoints included differences in mean iTNSS, mean individual rTNSS and iTNSS items, the RQLQ and its individual domains at the average of Days 8 and 15 as well as global patient and investigator impressions of efficacy at Day 15.

Safety endpoints included the frequency of adverse events (AEs), global patient and investigator impressions of tolerability at Day 15, use of relief medication as well as the number of symptom-free days.

2.5 | Statistical analysis

All analyses were performed on the modified-intent-to-treat (MITT) population (all treated patients with at least one post-baseline efficacy assessment) using the software SAS®, version 9.2 (SAS Institute, Cary NC, USA). Efficacy analyses on TNSS and RQLQ endpoints were performed in an analysis of covariance (ANCOVA) model with baseline scores and average use of relief medication as covariates and treatment group as factors. A sample size of 50 patients per treatment group was estimated to provide 80.76% power to detect a treatment effect of 1.0 rTNSS points at the two-sided alpha level of 0.05, assuming a standard deviation of 1.75 points. Changes from baseline were analyzed using the Mann–Whitney test, and global efficacy and tolerability ratings using the Cochran-Mantel–Haenszel test.

3 | RESULTS

3.1 | Patient demographics and baseline characteristics

A total of 299 subjects were screened of whom 100 were randomized (50 to each treatment group; Figure 1). Mean patient age was 41.1 years; a slight majority of participants was female (53.1%). Mean baseline rTNSS was 6.8 points with 59% of patients showing moderate or severe symptom levels; the mean RQLQ was 2.9 points. Overall, patient demographics and baseline characteristics were similar across treatment groups (Table S2).

3.2 | Pollen exposure

Treatment occurred during the Australian pollen seasons between September 2021 and April 2022 and from September 2022 to

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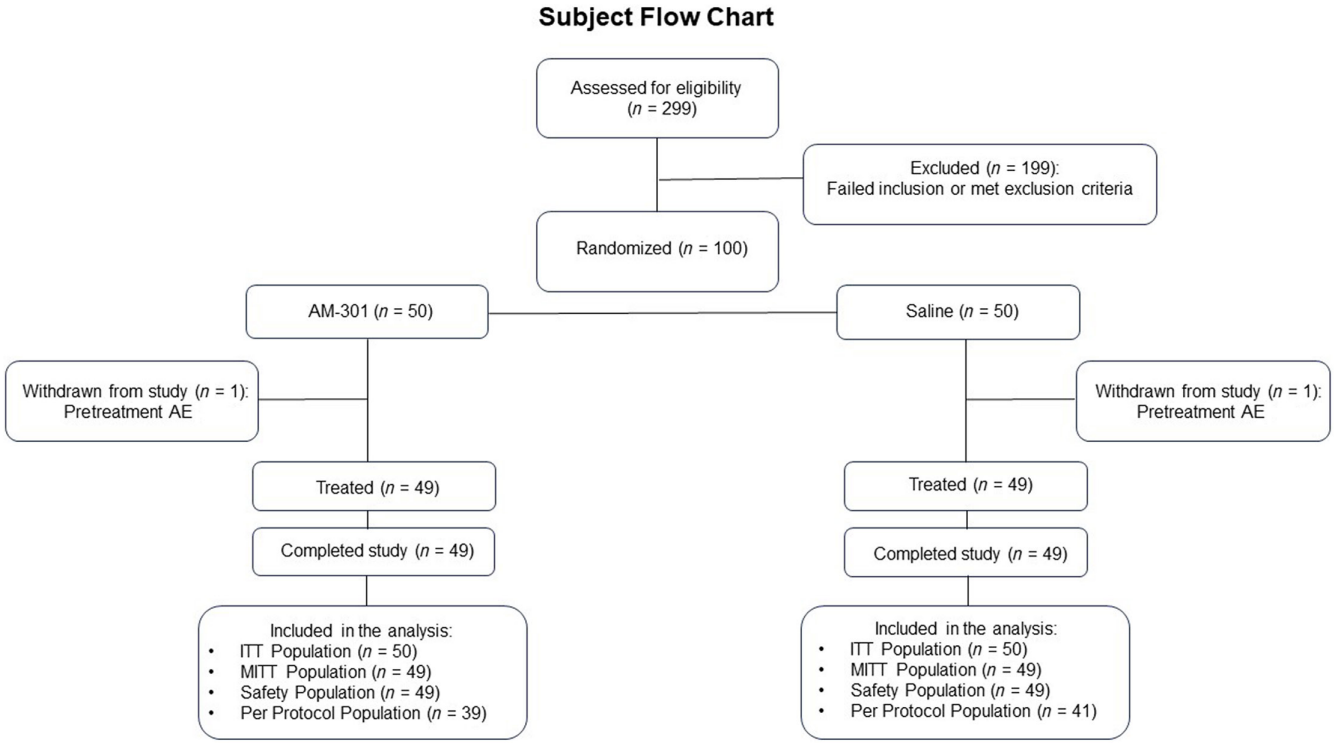


FIGURE 1 Subject flow chart. Schematic representation of the subject distribution. AE, adverse event; ITT, intent-to-treat; MITT, modified-intent-to-treat.

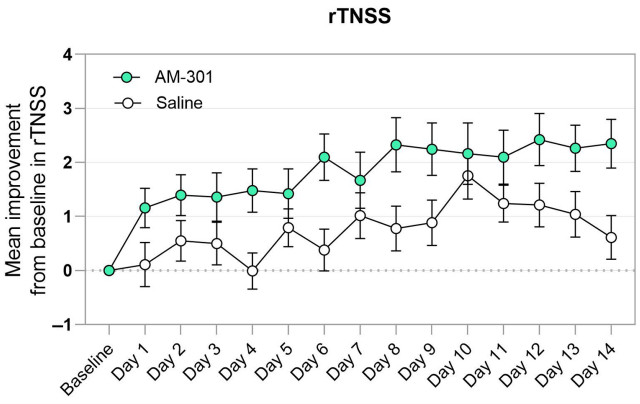


FIGURE 2 rTNSS improvement from baseline. Schematic representation of the time course of rTNSS improvement from baseline. Data are expressed as mean improvement per day.

January 2023. Across the locations and over time, daily pollen counts in grains/m^3 ranged from low (<20) to extreme (>100). The self-reported average time spent outdoors during the treatment period was 2.7 h/day.

3.3 | Efficacy outcomes

Nasal symptoms improved in both intervention groups during treatment, with the mean rTNSS decreasing on average by 1.8 points in the AM-301 and 0.77 points in the saline spray groups (Table S3, $p = .0111$). AM-301 treatment resulted consistently in a larger improvement from Day 1 on; at Day 14, the reduction in rTNSS from baseline was 2.3 points versus 0.61 points with saline spray treatment (Figure 2). The primary efficacy endpoint showed a statistically significantly lower mean rTNSS over the treatment period for the AM-301 group versus saline spray group (5.01 vs. 6.07 points) with a least square (LS) means difference in the ANCOVA model of −1.1 points (Table 1, 95% CI −1.959, −0.241; $p = .013$). Patients belonging to the same treatment group showed comparable rTNSS severity and improvement from baseline in the two pollen seasons (Figure S1).

A treatment effect in favor of AM-301 was also evident across all secondary efficacy endpoints. LS mean differences for *individual* nasal symptoms of the rTNSS averaged over the treatment period ranged from −0.24 to −0.32 points and reached statistical significance with p values ranging between 0.012 and 0.046 (Table S4 and Figure 3A). Like the rTNSS, the iTNSS decreased over the treatment period, although from lower baseline levels (Table S5; −1.7 points in the AM-301 group and −1.1 points in the saline spray group, $p = .124$). The difference in mean iTNSS in the ANCOVA model was −0.815 points in favor of AM-301 and statistically significant (Table 1, 95% CI −1.589, −0.042; $p = .039$). Among *individual* nasal symptoms of the iTNSS averaged over the treatment period, the difference in LS means for nasal itching was −0.27 points, reaching statistical significance ($p = .016$); differences for the three other items ranged from −0.17 to −0.19 points with p values between 0.064 and 0.120 (Table S6).

Health-related quality of life as measured by the RQLQ improved more in the AM-301 group than in the saline spray group; the change from baseline of 1.2 versus 0.4 points was statistically significant ($p < .01$). The difference in LS means in the ANCOVA model for the mean RQLQ level at Days 8 and 15 (1.68 vs. 2.38 points) was −0.7

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TABLE 1 Efficacy endpoints - reduction in rTNSS, iTNSS, and RQLQ.

rTNSS	*n* Subjects	Estimate	SE	95% CI	*p*-Value
Over 14 days					
LS mean: AM-301	48	5.060	0.301	4.462, 5.659	
LS mean: Saline	47	6.160	0.305	5.555, 6.765	
LS mean difference AM-301 – Saline	95	−1.100	0.432	−1.959, −0.241	.013
Over Day 1 to Day 7					
LS mean: AM-301	48	5.393	0.293	4.811, 5.975	
LS mean: Saline	47	6.461	0.296	5.873, 7.049	
LS mean difference AM-301—Saline	95	−1.068	0.421	−1.904, −0.232	.013
Over Day 8 to Day 14					
LS mean: AM-301	48	4.704	0.343	4.022, 5.385	
LS mean: Saline	47	5.829	0.347	5.140, 6.517	
LS mean difference AM-301—Saline	95	−1.125	0.491	−2.101, −0.149	.024
iTNSS	***n* Subjects**	**Estimate**	**SE**	**95% CI**	***p*-Value**
Over 14 days					
LS mean: AM-301	48	2.878	0.271	2.340, 3.417	
LS mean: Saline	47	3.694	0.274	3.150, 4.238	
LS mean difference AM-301—Saline	95	−0.815	0.389	−1.589, −0.042	.039
Over Day 1 to Day 7					
LS mean: AM-301	48	3.186	0.281	2.628, 3.744	
LS mean: Saline	47	3.881	0.284	3.317, 4.445	
LS mean difference AM-301—Saline	95	−0.695	0.404	−1.498, 0.108	.089
Over Day 8 to Day 14					
LS mean: AM-301	48	2.539	0.301	1.942, 3.136	
LS mean: Saline	47	3.477	0.304	2.873, 4.081	
LS mean difference AM-301—Saline	95	−0.938	0.431	−1.795, −0.081	.032
RQLQ	***n* Subjects**	**Estimate**	**SE**	**95% CI**	***p*-Value**
Average Day 8 and Day 15					
LS mean: AM-301	36	1.682	0.141	1.400, 1.964	
LS mean: Saline	40	2.381	0.134	2.114, 2.684	
LS mean difference AM-301—Saline	76	−0.699	0.198	−1.093, −0.305	<.001
Day 8					
LS mean: AM-301	38	1.849	0.155	1.540, 2.158	
LS mean: Saline	41	2.469	0.149	2.172, 2.766	
LS mean difference AM-301—Saline	79	−0.620	0.219	−1.057, −0.184	.006
Day 15					
LS mean: AM-301	41	1.594	0.143	1.310, 1.878	
LS mean: Saline	43	2.352	0.139	2.075, 2.629	
LS mean difference AM-301—Saline	84	−0.758	0.201	−1.158, −0.357	<.001

Note: The analysis method is based on an ANCOVA model with baseline composite rTNSS/iTNSS/RQLQ score, average use of relief medication, and treatment group as covariates.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; MITT, modified-intent-to-treat; SE, standard error.

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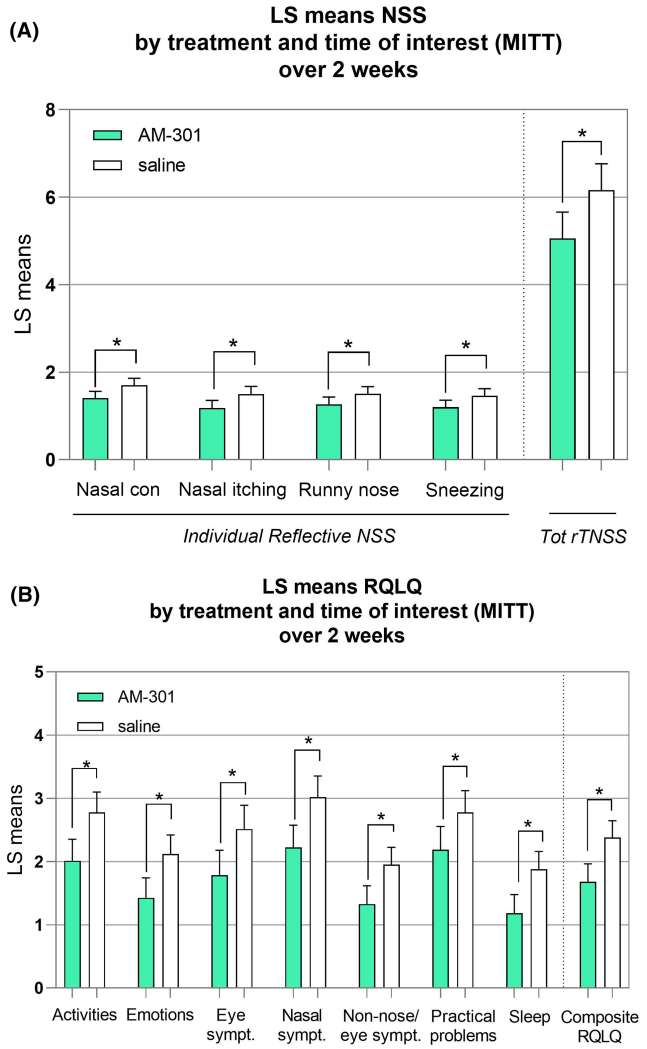


FIGURE 3 LS means NSS and RQLQ over 2 weeks. (A) The graph represents LS means of individual rNSS and total rTNSS. Data are expressed as LS means and 95% CI. (B) Graph represents LS means of individual RQLQ domains. Data are expressed as LS means and 95% CI. *$p < 0.05$

points and statistically significant (Table 1, 95% CI −1.093, −0.305; $p < .001$). The improvement in the AM-301 group exceeded that in the saline spray group in all individual domains with LS means differences ranging from −0.6 to −0.8 and p values ranging from .024 to .001 (Tables S7 and S8, Table 1 and Figure 3B).

Patient and investigator ratings for Global Impression of Efficacy were statistically significant in favor of AM-301 (both $p < .001$). Among AM-301 treated patients, 34.4% and 31.9% rated efficacy as "good" or "very good," respectively, compared with 22.4% and 6.1% for saline-treated patients, respectively (Figure 4A). "Poor" was the most frequent rating in the latter group (46.9%). Investigator ratings showed a similar distribution (Figure 4B).

3.4 | Safety and tolerability outcomes

Overall, both treatments were well tolerated and there was no statistically significant difference in patient and investigator ratings for Global Impression of Tolerability ($p = .416$ and .102, respectively). 31.9% and 44.7% of AM-301-treated patients rated tolerability as "good" or "very good," respectively, compared with 30.6% and 55.1% for saline-treated patients, respectively (Figure 4C). Tolerability was rated poor by 6.4% of patients in the AM-301 group and 10.2% of patients in the saline spray group. Investigator ratings overall were similar, albeit somewhat more favorable for saline nasal spray than AM-301 (Figure 4D).

Treatment Emergent Adverse Events (TEAEs) were reported in 21 (42.9%) of AM-301 treated patients and 16 (32.7%) of saline spray-treated patients (Table S9). TEAEs considered treatment-related were transitory and mostly mild in nature; most frequent occurrences were headache (AM-301: 5 patients, saline spray 6), oropharyngeal pain (5 patients vs. 1), epistaxis (saline: 3), throat irritation (AM-301: 2), migraine and tension headache (AM-301: 2) (Table S10). There were no serious AEs or severe TEAEs.

During treatment, 20.8% of patients required relief medication in the AM-301 group versus 31.9% in the saline spray group. Among those patients who used relief medication during run-in, a higher proportion abstained from it under AM-301 treatment than under saline spray treatment (68.7 vs. 26.6%). Symptom-free days during treatment were enjoyed by 59.2% of patients in the AM-301 group and 30.6% of patients in the saline group.

4 | DISCUSSION

The present study evaluated and compared two nasal sprays representing different drug-free treatment options to SAR—AM-301, which forms a physical barrier on the nasal mucosa to help avoid contact with airborne allergen particles and promote their discharge, and saline, which aims to wash out such particles and fluidify mucus and is usually considered standard of care in non-medicated allergic rhinitis management. Both treatment options resulted in a reduction of nasal symptoms over the course of the treatment period which exceeded 0.55 points on the rTNSS, a difference considered clinically meaningful.[30] The improvement set in from the first day of treatment, continued to grow in the course of the first week and essentially stabilized during the second week. Interestingly, the protective effect seemed to persist at least to some degree during the treatment-free observation period from Day 15 to 22 (data not shown), which may reflect some immune defense recovery of the mucosa while it is at least partially shielded during treatment.

Relative to saline nasal spray, treatment with AM-301 resulted consistently in a more pronounced improvement in TNSS, both for reflective and instantaneous ratings and also across the four individual nasal symptoms (nasal congestion, nasal itching, runny nose, and sneezing), with differences reaching robust statistical significance. The favorable TNSS outcomes were corroborated by superior global ratings of efficacy by both patients and investigators. Whereas a clear majority of AM-301-treated patients (65.9%) rated treatment efficacy as "good" or "very good," the most frequent assessment among saline-treated patients (46.9%) was "poor efficacy" and only

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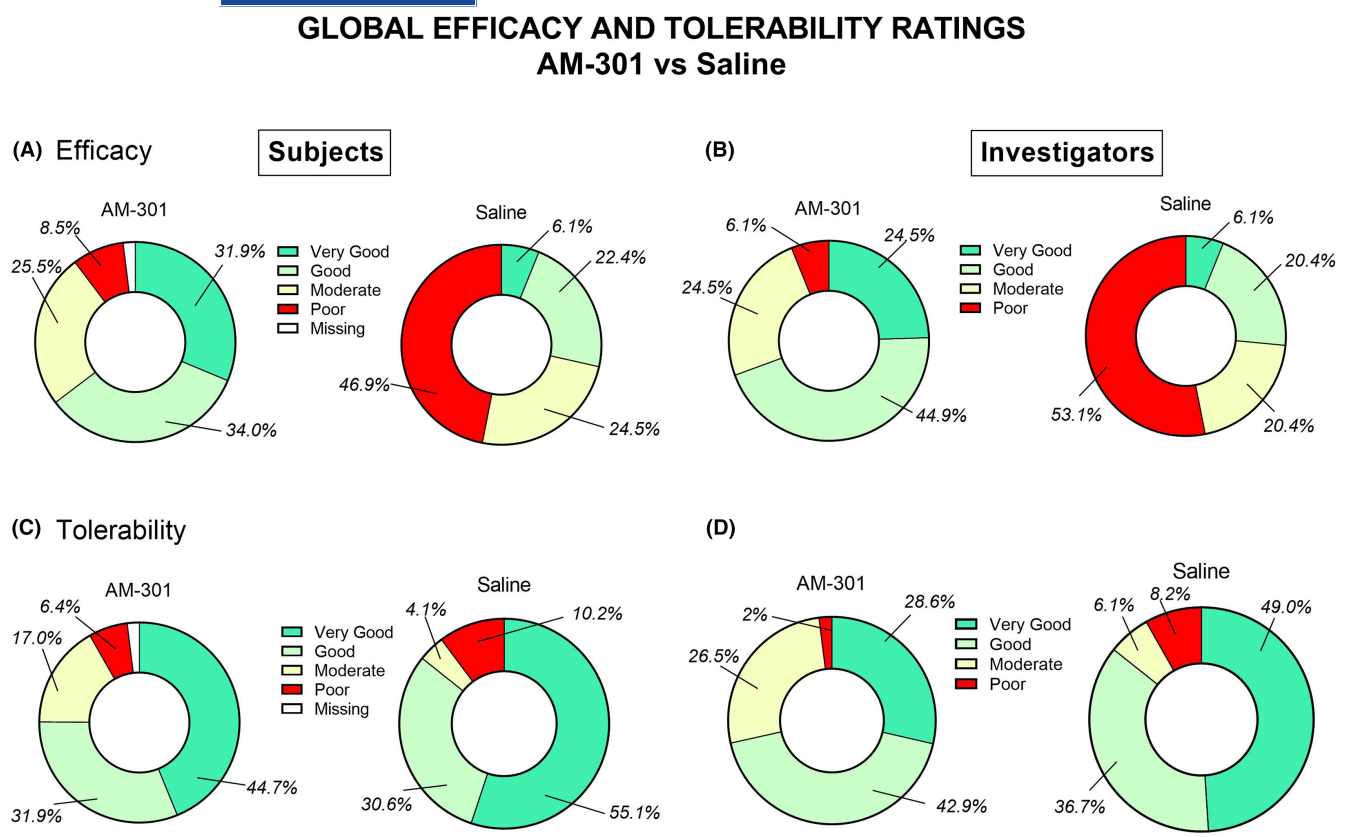


FIGURE 4 Global impression of efficacy and tolerability by subjects and investigators. Schematic representation of the overall ratings of efficacy and tolerability expressed as percentage of subjects or investigators giving "very good", "good", "moderate" or "poor" ratings of the performance of AM-301 and saline in terms of efficacy (A, B) and tolerability (C, D).

a minority among them (28.6%) considered the treatment as "good" or "very good."

Superior treatment outcomes for the AM-301 group were also apparent for health-related quality of life as measured by the RQLQ, being statistically highly significant. Unlike the saline group, the improvement by the end of the treatment period clearly exceeded 0.5 points (reaching 1.2 vs. 0.4 points), which was proposed as a minimal clinically important difference by the developers of the instrument.[31] Importantly, improvement from baseline and superiority for AM-301 over saline nasal spray were observed across all seven RQLQ domains, including eye symptoms, which are frequently observed in SAR.[32] Such secondary treatment effects have been reported also with intranasal corticosteroids, presumably due to a reduction in neurogenic inflammation spreading from the nasal cavity to the ocular surface.[33] By forming a protective film on the nasal mucosa and reducing the potential for the release of inflammatory mediators such as histamine as the starting point for neurogenic inflammation, AM-301 may help to reduce eye symptoms by physical rather than pharmacological action. Further, there was a larger improvement observed with AM-301 for non-nose/eye symptoms and sleep problems. A meta-analysis showed evidence for higher risks of sleep problems in AR patients, including nocturnal dysfunctions, including insomnia, nocturnal enuresis, restless sleep, sleep-disordered breathing, obstructive sleep apnea, and snoring.[34]

Since the covariate for baseline rTNSS, iTNSS, and RQLQ in the ANCOVA model was statistically highly significant ($p < .001$), we checked in a post hoc analysis whether SAR severity—using the TNSS classification[27]—was distributed similarly among treatment groups. This being confirmed, we could exclude that potential differences in SAR severity influenced treatment outcomes. Whereas the *absolute* size of the treatment effect shown on the rTNSS was minimal for "mild" cases, it was much larger for "moderate" and "severe" cases, reaching 1.4 and 2.7 points, respectively, thus driving outcomes for the overall population. A similar observation was made for the RQLQ outcomes.

The efficacy outcomes from the present study are consistent with those from previous clinical evaluations of AM-301 and reinforce them. Under controlled exposure to grass pollen or house dust mites in challenge chambers for 4 and 3 h, respectively,[25,26] prior treatment with AM-301 alleviated the increase in TNSS on average by 1.1 points compared to no treatment. The change in TNSS tended to be larger in the present study than in the previous challenge studies, which suggests a cumulative effect from continued use. Interestingly, both the present study and the grass pollen challenge study showed the most pronounced effects on nasal itching and nasal congestion among the four TNSS items.

In the challenge studies the protective effect of AM-301 was maintained essentially for the whole duration of allergen challenge.

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A separate study in healthy volunteers demonstrated the presence of AM-301 for 3.5 h in the nasal cavity.[24] Although study participants in the present study were free to administer AM-301 up to 8 times per day, the mean frequency of administration was 2.8× (median 2.8×). With 3–4 h of protection following each administration, the recommended 3 applications per day provide coverage for 9–12 h, which seems to be sufficient and appropriate under average 'real world' conditions.

The protective barrier provided by AM-301 is established rapidly within the nasal cavity—within 1 min following spray application, as shown previously.[24] This feature coupled with continuous protection and broad coverage of relevant parts of the nasal cavity was probably essential for the swift and pronounced improvement in nasal symptoms following treatment initiation in the present study. In contrast, the effects of saline nasal spray appear to be more limited as it is present for only about 1 h and provides narrower distribution and less coverage within the nasal cavity.[23] Although allowed, study participants did not dose saline spray more frequently than three times daily to compensate for the short nasal residence time; rather there was a trend for more frequent use of (medicated) relief medication in the group.

Safety and tolerability of both treatments overall was favorable with a slight advantage for saline nasal spray, probably owing to its simple, physiologic formulation as well as the shorter exposure within the nasal cavity. Nevertheless, one in 10 saline-treated patients rated tolerability as only "poor" which was higher than for the AM-301 group (1 in 16). Whether this reflects actual tolerability issues, for example, arising from the presence of a preservative in the saline formulation or rather a perceived lack of efficacy, remains open. Following the observation of transient burning in a previous study with AM-301,[25] all preservatives had been removed from the formulation. Accordingly, no more burning sensation was reported in the present study.

Overall, the evidence accumulated from four clinical trials including the present one shows that a barrier-forming spray like AM-301 can provide effective and lasting improvement in nasal and nonnasal symptoms of SAR even without any active pharmacological ingredient. Importantly, treatment effects set in rapidly, which compares favorably with the slower onset, for example, of oral antihistamines, and they were in particular observed among patients with moderate or severe nasal symptoms, which means that a drug-free treatment such as the AM-301 sprays could even be considered an alternative to medicated treatments. Importantly, none of the AM-301-treated patients in this study experienced dryness of the nose, contrary to what is frequently reported for a variety of medicated topical treatments, such as corticosteroids or antihistamines.[5,11,12] Further, AM-301 treatment may also be used as a complement to medicated treatments, providing for potential additive or synergistic effects. Unlike the saline nasal spray group, AM-301 treated patients did cut back on use of relief medication in the present study.

It is commonly understood that saline nasal spray may not be the most efficacious, but certainly one of the best-tolerated treatment options in SAR management. However, the present study demonstrated that the equally drug-free barrier concept of AM-301 could achieve significantly better efficacy with a broadly similar tolerability profile. Whereas the simplicity of the formulation and comparatively low cost of saline nasal spray may be another important consideration for the choice of treatment especially in case of mild SAR symptoms, the potential additional gain in symptomatic relief and health-related quality of life suggest that AM-301 may be an appropriate drug-free treatment option especially for more severe SAR conditions.

This study has some possible limitations. One of them is the absence of a placebo control group. Although a double-blind placebo-controlled design represents the gold standard in clinical trials, the nature of AM-301 renders such approach unfeasible. Since its formulation does not contain any pharmacologically active ingredient, testing against a classic placebo preparation lacking active substance was not an option. On the other hand, intranasal application of another gel emulsion or even a different formulation type was no option either since some kind of barrier effect could not be ruled out[35] and blinding might be difficult to maintain due to differences in appearance or sensation. However, through randomization, the use of a control group and inclusion of 100 patients, the trial appears adequately designed to test for a systematic difference in treatment outcomes. Randomization worked as intended since treatment groups are comparable in terms of baseline demographics and sensitization levels (Table S2). Further, it appears unlikely that subjects had systematically inflated expectations of treatment benefits given the well-known effects of saline nasal spray on one hand and the absence of real-life SAR data for the novel treatment AM-301 on the other hand. Similar outcomes on global treatment efficacy (and tolerability) for both subject and investigator ratings provided independent verification.

Another possible limitation of the study arises from the different pollen exposure levels among patients. Indeed, pollen monitoring revealed some important differences in aerial pollen concentrations between some of the study regions and over time. Although patients were asked to record their daily outdoor activity time, precise monitoring of exposure was not possible. However, given the size of the study population as well as the randomization of treatments, it appears unlikely that outcomes were impacted in any meaningful way. Actually, coverage of a broad range of allergen exposure may also be considered representative of real-life conditions and strengthen the value of the results.

One major challenge for the study was the COVID-19 pandemic which significantly lengthened its duration. Enrollment was negatively impacted as the presence of an ongoing SARS-CoV-2 infection was an exclusion criterion, and SAR patients were generally less exposed to aeroallergens due to staying more at home and the mandatory use of face masks. Therefore, the study could not be completed over one allergy season but had to be extended to a second season.

In conclusion, the present study demonstrated that the drug-free, barrier-forming nasal spray AM-301 is significantly more

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effective in providing symptomatic relief to SAR sufferers and in enhancing health-related quality of life than saline nasal spray while offering a similar safety and tolerability profile.

AUTHOR CONTRIBUTIONS

Study planning and design (TM, SB), study management (VF), study oversight (SD, FDL, JL, AMG, ZN, CR), manuscript writing (VF, TM) with contributions from all other co-authors.

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CONFLICT OF INTEREST STATEMENT

SB was the principal investigator in another study related to AM-301 which was funded by the sponsor of the present clinical trial. In addition, he reports consulting fees from ALK Abello, Allergopharma, Allergy Therapeutics, Bencard Allergie, Sanofi, GSK, Novartis, Stryker, Viatris, and MSD. Honoraria for presentations from ALK Abello, Allergopharma, Allergy Therapeutics, AstraZeneca, Bencard Allergie, HAL Allergy, Thermo Fisher Scientific, Viatris, Sanofi, GSK and Novartis. Other nonfinancial interests: Chair of the working group for clinical immunology, allergology, and environmental medicine of the German Society of Otorhinolaryngology, Head and Neck Surgery; Chair of the German CRS-Registry, Board Member of the AeDA. SD, FDL, JL, AMG, ZN, and CR have no conflicts of interest to declare. VF is an employee of an affiliate of Altamira Medica AG and holds stock options in Altamira Therapeutics Ltd. TM is the CEO of Altamira Medica AG and of its parent company Altamira Therapeutics Ltd. Altamira Medica AG has a patent application for AM-301.

DATA AVAILABILITY STATEMENT

Study data cannot be shared openly to protect study participant privacy.

INFORMED CONSENT STATEMENT

Informed consent was obtained from all subjects involved in the study prior to treatment start.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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