Efficacy and safety of stapokibart (CM310) in uncontrolled seasonal allergic rhinitis (MERAK): an investigator-initiated, placebo-controlled, randomised, double-blind, phase 2 trial

Yuan Zhang,[a,c,d,k] Bing Yan,[b,c,d,k] Zehua Zhu,[a,b,c,k] Xueyan Wang,[e] Xicheng Song,[f,g] Dongdong Zhu,[h,i] Tingting Ma,[e] Yu Zhang,[f,g] Cuida Meng,[h,i] Guangke Wang,[j] Chengshuo Wang,[b,c,d,**] and Luo Zhang[a,b,c,d,*]

[a]Department of Allergy, Beijing TongRen Hospital, Capital Medical University, Beijing 100005, China
[b]Department of Otolaryngology, Head and Neck Surgery, Beijing TongRen Hospital, Capital Medical University, Beijing 100730, China
[c]Beijing Institute of Otolaryngology, Beijing Laboratory of Allergic Diseases, Beijing Key Laboratory of Nasal Diseases, Key Laboratory of Otolaryngology Head and Neck Surgery, Ministry of Education, Capital Medical University, Beijing 100005, China
[d]Research Unit of Diagnosis and Treatment of Chronic Nasal Diseases, Chinese Academy of Medical Sciences, Beijing 100005, China
[e]Allergy Centre, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, China
[f]Department of Otorhinolaryngology, Head and Neck Surgery, Yantai Yuhuangding Hospital, Qingdao University, Yantai, Shandong 264000, China
[g]Shandong Provincial Clinical Research Centre for Otorhinolaryngologic Diseases, Yantai, Shandong 264000, China
[h]Department of Otolaryngology Head and Neck Surgery, China-Japan Union Hospital of Jilin University, Changchun, Jilin 130033, China
[i]Jilin Provincial Key Laboratory of Precise Diagnosis and Treatment of Upper Airway Allergic Diseases, Changchun, Jilin 130033, China
[j]Department of Otolaryngology, Head and Neck Surgery, Henan Provincial People's Hospital, People's Hospital of Zhengzhou University, People's Hospital of Henan University, Zhengzhou, Henan 450003, China

eClinicalMedicine
2024;69: 102467
Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.102467

Summary

Background There is no trial to assess the benefits of periodically using biologics during the pollen season in patients with uncontrolled seasonal allergic rhinitis (SAR), who have moderate-to-severe symptoms even after standard-of-care. This trial aimed to evaluate the efficacy and safety of the add-on administration of stapokibart, a humanised monoclonal antibody that targets interleukin-4 receptor alpha, in patients with uncontrolled SAR.

Methods In this investigator-initiated, randomised, double-blind, placebo-controlled trial, eligible patients received either stapokibart 600-300 mg weekly (QW), every 2 weeks (Q2W), or placebo QW for 4 weeks. All patients were given mometasone furoate nasal spray and loratadine throughout the trial. The primary endpoint was the mean change from baseline in daily reflective total nasal symptom score (rTNSS) during 2-week treatment. Secondary efficacy outcomes included: the mean change from baseline in daily rTNSS during 4-week treatment; the mean changes and the mean percentage changes from baseline during 2-week and 4-week treatment in 1) daily rTNSS and reflective total ocular symptom score (rTOSS), 2) morning (AM)/evening (PM) rTNSS and rTOSS, 3) AM instantaneous total nasal symptom score (iTNSS) and instantaneous total ocular symptom score (iTOSS), 4) individual nasal and ocular symptoms; the change from baseline in Rhinoconjunctivitis Quality of-Life Questionnaire score during 4-week treatment. Exploratory endpoints included the change of prespecified markers related to type 2 inflammation pre- and post-treatment. Safety, immunogenicity, and pharmacokinetics were also evaluated. This study is registered with www.clinicaltrials.gov (NCT05470647).

Findings Between August 17, 2022, and December 28, 2022, 92 patients with uncontrolled SAR were enrolled from 4 centres in China and randomly assigned to receive stapokibart 600-300 mg QW (n = 31), stapokibart 600-300 mg Q2W (n = 30), or placebo QW (n = 31), of whom 86 (93%) completed the study. Both stapokibart Q2W and QW did not significantly improve mean change from baseline in daily rTNSS compared with placebo in 2 weeks. The least-squares (LS) mean differences (97.5% confidence interval [CI]) compared with placebo were −1.0 (−2.3, 0.2) in stapokibart Q2W group (p = 0.065) and −0.2 (−1.5, 1.0) in stapokibart QW group (p = 0.67). For the secondary outcomes, compared with placebo, stapokibart Q2W presented significant improvements in the mean percentage change from baseline in daily rTNSS in 2 weeks (LS mean difference −12.9%, 95% CI −25.3%, −0.4%, p = 0.043), as well as AM iTNSS over 2 weeks (LS mean difference −17.4%, 95% CI −31.0%, −3.8%, p = 0.013) and 4 weeks

*Corresponding author. Department of Otolaryngology Head and Neck Surgery, Beijing TongRen Hospital, Capital Medical University, No. 1, Dongjiaominxiang, Dongcheng District, Beijing 100730, China.
**Corresponding author. Beijing Institute of Otolaryngology, No. 17, HouGouHuTong, DongCheng District, Beijing 100005, China.
E-mail addresses: dr.luozhang@139.com (L. Zhang), wangcs830@126.com (C. Wang).
[k]Contributed equally.

(LS mean difference −15.4%, 95% CI −29.0%, −1.9%, p = 0.026). Additionally, the nasal congestion score was significantly lower in stapokibart Q2W than placebo during 2-week (LS mean difference −0.4, 95% CI −0.7, −0.1, p = 0.014) and 4-week (LS mean difference −0.4, 95% CI −0.7, −0.04, p = 0.028) treatment. Treatment-emergent adverse events (TEAEs) occurred in 48% (15/31), 33% (10/30), and 61% (19/31) of patients receiving stapokibart QW, Q2W, and placebo, respectively. Most reported TEAEs were sinus bradycardia, hyperlipidaemia, and blood uric acid increased.

Interpretation In this phase 2 trial, both stapokibart regimens had an acceptable safety and tolerability profile but did not significantly improve daily rTNSS in patients with uncontrolled SAR. The efficacy of stapokibart in patients with uncontrolled SAR is being further investigated in ongoing phase 3 trials (clinicaltrials.gov, NCT05908032).

Funding Ministry of Science and Technology of the People's Republic of China; Ministry of Education of the People's Republic of China; National Natural Science Foundation of China; Chinese Academy of Medical Sciences.

Keywords: Co-seasonal application; Interleukin-4 receptor alpha; Monoclonal antibody; Seasonal allergic rhinitis; Uncontrolled

Research in context

Evidence before this study

The applications of monoclonal antibodies in patients with allergic rhinitis (AR) are limited. We searched the PubMed, EMBASE, and the Cochrane Library with the terms of "seasonal allergic rhinitis", "biologics", "monoclonal antibody", "omalizumab", "mepolizumab", "reslizumab", "benralizumab", "tezepelumab", "dupilumab", "lebrikizumab", "tralokinumab", "brodalumab", "ligelizumab", "randomised controlled trial" in English from database inception to Jun 2, 2022. Omalizumab has been found to be effective in reducing symptom severity and the need for rescue medication in patients with seasonal AR (SAR) when administered pre- and co-seasonally. However, there is no evidence to suggest the benefits of periodically using the biologics during the pollen season in patients with uncontrolled SAR, who have moderate-to-severe symptoms even after standard treatments.

Added value of this study

To the best of our knowledge, this is the first trial to assess the efficacy of a periodic add-on use of biologics for patients with uncontrolled SAR during pollen exposure phase. Stapokibart (CM310, a humanised monoclonal antibody that targets IL-4Rα) did not significantly improve daily reflective total nasal symptom score (rTNSS) in patients with uncontrolled SAR in the pollen period compared with placebo. However, compared with placebo, two doses of stapokibart showed a decrease in the mean percentage from baseline in rTNSS and reflective total ocular symptom score, as well as improved nasal congestion in patients with SAR who could not effectively control the symptoms with standard medication in the pollen period. Patients with peripheral blood eosinophil counts ≥300 cells/μL experienced a greater degree of improvement than those without.

Implications of all the available evidence

This phase 2 trial demonstrated the potential of stapokibart in treating uncontrolled SAR but without sufficient evidence. Stapokibart might be considered an effective and safe added-on treatment option during the pollen phase for patients with uncontrolled SAR for patients with peripheral blood eosinophil counts ≥300 cells/μL. The efficacy and safety of stapokibart for those patients are being evaluated in the ongoing phase 3 studies, in which a baseline blood eosinophil count of at least 300 cells/μL has been set as one of the inclusion criteria (clinicaltrials.gov, NCT05908032).

Introduction

Allergic rhinitis (AR) is an inflammatory disease induced by an immunoglobulin E (IgE)-mediated reaction in the nasal mucosa, driven by type 2 inflammation. AR is characterised by sneezing, rhinorrhea, nasal congestion and nasal pruritus, which are often accompanied by ocular pruritus, redness and/or lacrimation. AR is a global health concern and currently affects up to 50% of the population worldwide[1,2] and the direct and indirect economic expenses incurred as a result are estimated to cost up to €50 billion per year,[1,3–5] suggesting a huge socio-economic burden. AR is classified into seasonal AR (SAR) and perennial AR (PAR) according to the type of allergen, with SAR primarily caused by outdoor pollen dispersal and affects an estimated 10–12% population.[6,7] It has been reported that ocular involvement and irritative symptoms (itching, sneezing, and rhinorrhea) were more frequent in SAR than in PAR.[8] Moreover, compared with PAR, more pronounced elevated levels of proinflammatory

cytokines in nasal secretions were observed in SAR, indicating a higher degree of inflammation.[9] Furthermore, studies have revealed that August and September are the months with the greatest amount of individuals consulting doctors for AR.[10,11]

Current management of AR encompasses patient education, allergen avoidance, pharmacotherapy, and allergen-specific immunotherapy.[12] Oral and/or intranasal H1 antihistamines, intranasal corticosteroids (INCS), and a combination of the two are effective first-line pharmacotherapies. Despite receiving standard-of-care (SoC), there are still some patients whose clinical symptoms cannot be effectively controlled, for instance, studies have indicated that more than 60% of patients with SAR using SoC regularly reported partial or poor symptom control.[10,13] In this sense, novel treatment options are needed to improve the effectiveness and adherence of patients whose symptoms are inadequately controlled with SoC, especially in SAR individuals.[14,15]

Type 2 inflammations are key factors to drive AR pathogenesis, therefore, biologics that target key molecules in type 2 inflammation are potential therapeutic approaches for patients with AR. Studies have shown that pre- and co-seasonal application of omalizumab (anti-IgE monoclonal antibody) can improve quality of life (QoL) and reduce the need for rescue medications in patients with SAR.[16–18] Nonetheless, the fly in the ointment is that it is unclear whether the use of omalizumab is essential for these patients, since all prior studies on omalizumab that included individuals had not gone through the SoC run-in screening stage. Considering the cost-effectiveness, it is suggested that biologics should be used as an additional treatment for those with uncontrolled SAR who cannot be adequately managed after SoC. However, no evidence has been presented to demonstrate the efficacy and safety of periodically utilizing biologics as an add-on treatment during the pollen season in patients with uncontrolled SAR so far.

In addition, it has been proposed that targeting the key proximal type 2 cytokines such as interleukin (IL)-4, IL-13, and IL-5, instead of the downstream products of the type 2 inflammation pathway like IgE, could be a more successful treatment of type 2 immunity-related diseases.[19] Monoclonal antibodies that target these key proximal type 2 signalling pathways have been shown to be novel and promising medical strategies for airway diseases that are not controlled by conventional treatment.[20] Nonetheless, there is still no evidence from high-quality research to demonstrate that targeting these pathways can treat AR effectively. Dupilumab, a monoclonal antibody that targets IL-4 receptor alpha (IL-4Rα) and thereby inhibits both IL-4 and IL-13 signalling pathways, was only reported to be effective in improving AR-associated nasal symptoms and QoL in a pivotal phase 2b study through the post-hoc analysis of the subgroup of asthma patients with comorbid PAR.[21] Another study reported that 16 weeks of treatment with dupilumab did not reduce the post-allergen challenge nasal symptoms in patients with SAR.[22]

This trial is the first to explore the periodic use of biologics in patients with uncontrolled SAR. Stapokibart (CM310), a humanised monoclonal antibody that targets IL-4Rα, is being used in this trial. In previous phase 2 clinical trials, stapokibart has shown a good safety profile and promising efficacy in adults with severe eosinophilic chronic rhinosinusitis with nasal polyps and moderate-to-severe atopic dermatitis.[23,24] This randomised, investigator-initiated multicentre study was designed to assess the efficacy, safety, pharmacodynamics, pharmacokinetics, and immunogenicity of stapokibart as an add-on to SoC (antihistamines and nasal corticosteroids) in treating moderate-to-severe symptoms of patients with SAR refractory to SoC during the fall pollen season.

Methods

Study design

An investigator-initiated, randomised, double-blind, placebo-controlled, multicentre, phase 2 trial (NCT05470647) was conducted at 6 study sites in China between August 17, 2022, and December 28, 2022. Details for the full protocol are available in the Appendix. Both the screening/run-in period and blinded treatment period were conducted during the fall pollen season. After a 7-day screening and run-in period, eligible individuals were randomised 1:1:1 to receive either stapokibart 300 mg weekly (QW) or every 2 weeks (Q2W), or placebo QW subcutaneously during a 4-week treatment period, followed by an 8-week follow-up period (Fig. 2). A 600-mg loading dose of stapokibart or a matching placebo was given on day 1. Patients who were treated with stapokibart Q2W received a matching placebo during the weeks when stapokibart was not administrated. Additionally, all participants in the three groups were given mometasone furoate nasal spray (MFNS, 100 μg per nostril once daily) and oral loratadine (10 mg once daily) throughout the trial.

This trial was done in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines issued by the National Medical Products Administration. All study documents and procedures were approved by the ethics committees at each trial centre. Informed consent was obtained from each patient before enrolment in the trial.

Participants

Eligible patients were aged 18–65 years, with a confirmed diagnosis of SAR and a clinical history of fall SAR for at least 2 years; had adequate pollen exposure during the pollen season; had IgE-mediated hypersensitivity to at least one pollen allergen found in the current environment; had a documented history of inadequate response to nasal corticosteroids or other

medications; had a morning (AM) instantaneous total nasal symptom score (iTNSS) of ≥6 points before screening; and had an AM iTNSS of ≥6 points and an average of the last 6 reflective TNSS (rTNSS) of ≥6 points at baseline visit after one-week run-in period with the treatment of MFNS and loratadine. In this trial, patients are required to acquire treatment by appointed nurses in the outpatient injections of each centre during the 4-week treatment phase. The full inclusion and exclusion criteria are listed in Appendix (protocol).

Randomisation and masking

Randomisation lists of patients and drugs were generated via SAS using stratified block randomisation method (strata factor: study site), respectively, and then imported into Interactive Web Response System (IWRS). The drug kit numbers (stapokibart or placebo) were provided by IWRS as required. The trial was blinded to all patients and trial personnel until a prespecified unblinding, except for the randomisation statisticians.

Assessments

The assessment of AR symptoms was generally based on the patient scores for four nasal symptoms (sneezing, rhinorrhea, nasal itching, and nasal obstruction), and three ocular symptoms (ocular itching, watery eyes, and eye redness); scored range of 0 (not at all) to 3 (severe). Each component was analyzed in a combined summed total nasal symptom score (TNSS, point range, 0–12) and total ocular symptom score (TOSS, point range, 0–9). The rTNSS and reflective TOSS (rTOSS) were ratings of the severity of symptoms over the previous 12 h and were performed in the AM and evening (PM). The daily rTNSS or rTOSS is the average of the PM assessment on the day and the AM assessment on the next day. The AM iTNSS and instantaneous TOSS (iTOSS) were assessed once daily (in the morning). The severity scales used for these four efficacy assessments are shown in Appendix (Efficacy Assessment Scale). In particular, (1) if one of the individual symptom scores is missing; the corresponding total score will be regarded as missing; (2) if both the AM and PM are missing, then the daily rTNSS/rTOSS will be regarded as missing; (3) if only one of the AM and PM is missing, then the daily rTNSS/rTOSS will be regarded as the non-missing score.

The baseline values of TNSS and TOSS-related total symptom scores, individual symptom scores, and PM scores were defined as the mean of the non-missing scores within the 3 days (Day −3 to Day-1) prior to randomisation. For AM scores, the baseline value is defined as the mean of the non-missing scores on the day of randomization (Day 1) and within the 2 days (Day −2 and Day −1) prior to randomisation.

For the overall evaluation of response to therapy, patients rated their perspectives of change in allergic symptoms at the end of the trial using the following 7-point categorical scale: significantly improved, moderately improved, mildly improved, no change, mildly worse, moderately worse, significantly worse. Patients' QoL was assessed twice via Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ). A detailed severity scale of RQLQ assessment was provided in Appendix (Efficacy Assessment Scale).

Outcomes

Primary endpoint was the mean change from baseline in daily rTNSS during 2-week treatment. Secondary efficacy variables included: the mean change from baseline in daily rTNSS during 4-week treatment; the mean changes from baseline in AM or PM rTNSS, AM iTNSS, individual nasal symptoms, daily rTOSS, AM or PM rTOSS, AM iTOSS, and individual ocular symptoms during 2-week and 4-week treatment; the mean percentage changes from baseline in daily rTNSS, AM iTNSS, daily rTOSS, and AM iTOSS during 2-week and the 4-week treatment; the change from baseline in RQLQ score during 4-week treatment; time to onset of action; time to maximum effect; and overall evaluation of response to therapy during the study.

Safety was assessed by monitoring adverse events (AEs), clinical laboratory parameters, physical examination, vital signs, and 12-lead electrocardiogram during the study period. Pharmacokinetics and immunogenicity of stapokibart were also studied.

An exploratory analysis was performed on patients with SAR to determine the duration of mild or no nasal and ocular symptoms (defined as the number of days during which patients had each item with a nasal and ocular symptom score of mild or none [i.e., an item score of ≤1]) during 2-week and 4-week treatment, which is clinically meaningful to patients with SAR. Additionally, the area under the curve (AUC) of change from baseline of daily rTNSS was also assessed. Changes of biomarkers in blood, nasal brushings, and nasal secretions were also determined pre-and post-treatment.

In addition, subgroup analyses according to baseline blood eosinophil (EOS) count (≥300 or <300 cells/μL) were performed on primary and secondary endpoints.

Statistical analysis

This study included two doses of stapokibart, superiority of either stapokibart dose over placebo on the primary endpoint (the mean change from baseline in daily rTNSS in 2 weeks) was considered a clinical trial success. To control the overall type I error (0.05) of the study, the type I error for each dose will be adjusted to 0.025 (=0.05/2). Based on PASS, a sample size of 24 patients per group will provide 85% power for primary endpoint between stapokibart and placebo groups, assuming an expected treatment effect of −1.95 (standard deviation [SD], 2.0), and the group ratio is 1:1.

Considering a dropout rate of 20%, a total of 90 patients were planned to be enrolled for the study.

Efficacy endpoints were analyzed on the full analysis set, which included all randomised patients who received the study drug at least once. The primary endpoint was analyzed using the analysis of covariance (ANCOVA) model, with the mean change from baseline in 2-week daily rTNSS as the dependent variable and baseline rTNSS, study site, and treatment group as the covariates. Least-squares (LS) mean differences between stapokibart and placebo groups, and the corresponding standard error (SE), 95% confidence interval (CI), and p value were calculated based on the ANCOVA model. In addition, the mean (SD) of the primary endpoint was also provided. Secondary efficacy variables and the AUC of change from baseline of daily rTNSS were analyzed using the same model as the primary endpoint. The duration of mild or no nasal and ocular symptoms was analyzed by one-way analysis of variance. Subgroup analyses for rTNSS, AM iTNSS, rTOSS, AM iTOSS, and RQLQ score were conducted according to baseline blood EOS counts.

Safety set included all randomised patients who received at least one dose of the study drug and was applied for safety analysis by treatment group as actually received. Pharmacodynamic analysis set, immunogenicity analysis set, and pharmacokinetic concentration set included all randomised patients who received any study drug and had at least one corresponding qualified result.

For primary endpoint and the mean change from baseline in TNSS- and TOSS-related total symptom scores and individual symptom scores, when the number of valid data was less than 12 days ($14 \times 0.8 = 11.2$) within 2-week treatment or less than 23 days ($28 \times 0.8 = 22.4$) within 4-week treatment, last observation carried forward method was used to impute missing score and further derive corresponding data. No imputation was performed for other missing values.

SAS version 9.4 was adopted for statistical analysis. The continuous endpoints were descriptively summarised by the number of subjects, mean, SD, median, interquartile range (IQR), minimum and maximum. Categorical variables were summarised by frequency and percentage. Statistical comparisons were two-sided at the 0.05 level of significance, unless otherwise specified. Detailed statistical methods are described in Appendix (Statistical Analysis Plan).

Role of the funding source

The research funding for the study did not influence the study design, data collection, data analysis, data interpretation, and manuscript preparation. We didn't pay to write this article by a pharmaceutical company or other agency. All the authors were not precluded from accessing data in the study and they accept responsibility to submit for publication.

Results

Patients

The patients begin to be screened in six centres once the concentration of the pollen is higher than 20 pollen/1000 mm^2 for 3 consecutive days in each centre. Finally, between August 17, 2022, and December 28, 2022, 172 patients were screened, of whom 93 patients from 4 centres were enrolled in the study (Fig. 1). One patient in the stapokibart 600-300 mg Q2W group withdrew consent and did not receive the first dose. Therefore, 92 patients received at least one dose of the study drug, and out of those, 86 completed the study (n = 30 for stapokibart QW, n = 29 for Q2W, and n = 27 for placebo). Baseline demographics and clinical characteristics of participants are shown in Table 1. The mean age at baseline was 37.0 (SD 8.9) years, and 51 (55%) of 92 were female. The mean SAR duration was 7.6 (SD 4.6) years. The mean (SD) baseline assessment scores were as follows: rTNSS (8.7 [1.9]), AM iTNSS (8.6 [2.1]), rTOSS (6.0 [2.0]), AM iTOSS (5.8 [2.1]), and total RQLQ score (4.0 [1.1]).

Primary endpoints

Stapokibart 600-300 mg QW or Q2W did not significantly improve daily rTNSS compared with placebo, but demonstrated a trend of improving daily rTNSS to a greater extent than placebo. The mean change from baseline in daily rTNSS in 2 weeks was −2.5 in placebo group, −2.8 in stapokibart QW group (LS mean difference −0.2 [97.5%CI −1.5, 1.0], p = 0.67), and −3.5 in Q2W group (LS mean difference −1.0 [97.5%CI −2.3, 0.2], p = 0.065) (Fig. 3A, Table 2).

Secondary endpoints

Table 2 shows the effect of stapokibart on nasal symptoms. Significant improvement in the mean percentage change from baseline in daily rTNSS was observed with stapokibart Q2W compared with placebo in 2 weeks (LS mean difference −12.9% [95% CI −25.3%, −0.4%], p = 0.043) (Table 2; Fig. 4A). In addition, significant improvement in the mean percentage changes from baseline in AM iTNSS in 2 weeks (LS mean difference −17.4% [95% CI −31.0%, −3.8%], p = 0.013) and 4 weeks (LS mean difference −15.4% [95% CI −29.0%, −1.9%], p = 0.026) were observed with stapokibart Q2W compared with placebo (Table 2; Fig. 4B). The LS mean difference between stapokibart Q2W and placebo was significant for nasal congestion in 2 weeks (LS mean difference −0.4 [95% CI −0.7, −0.1], p = 0.014) and 4 weeks (LS mean difference −0.4 [95% CI −0.7, −0.04], p = 0.028) (Fig. 4C). Other secondary outcomes of the effect of stapokibart on nasal symptoms are shown in Table 2.

Effects of stapokibart on ocular symptoms are shown in Table 3. Significant improvement in the mean percentage change from baseline in daily rTOSS was observed with stapokibart Q2W compared with placebo in 2 weeks (LS mean difference −14.6% [95%

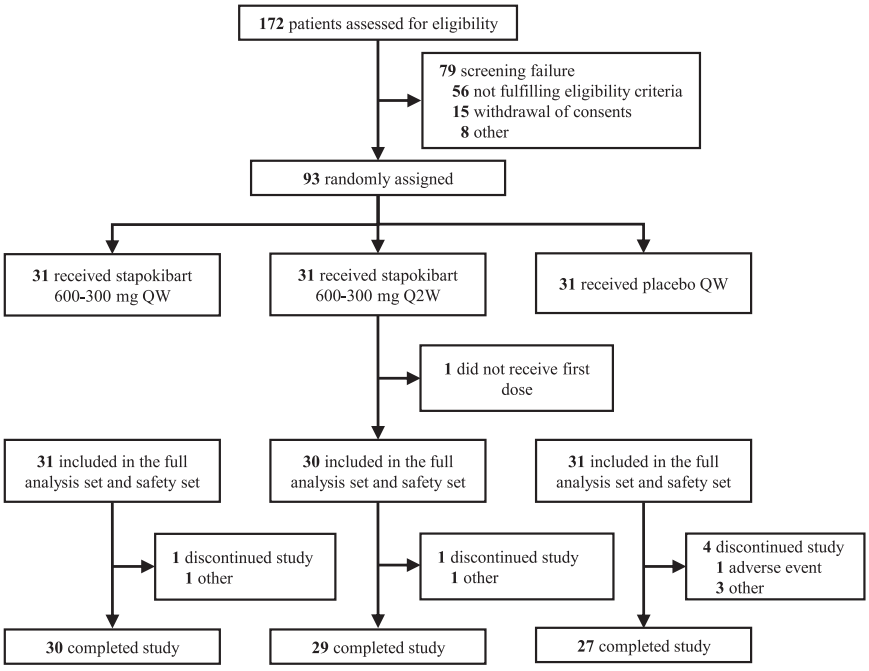

Fig. 1: Trial profile. QW = weekly. Q2W = every 2 weeks.

CI –28.5%, –0.6%], p = 0.041, Fig. 4D), and it was also observed in the mean change of AM iTOSS in 2 weeks (LS mean difference –1.0 [95% CI –1.9, –0.1], p = 0.038, Fig. 4E), and in the mean percentage change from baseline in AM iTOSS in 2 weeks (LS mean difference –29.0% [95% CI –48.4%, –9.6%], p = 0.0038) and 4 weeks (LS mean difference –19.1% [95% CI –35.2%, –3.0%], p = 0.021, Fig. 4F). Other secondary outcomes of the effect of stapokibart on ocular symptoms are shown in Table 3.

Stapokibart did not significantly alter the overall RQLQ score (LS mean difference –0.4 [95% CI –1.1, 0.2], p = 0.19) and four individual domains compared with placebo (Appendix pp 5–6). As for the outcome of time to onset of action, 4 h after taking the first administration of stapokibart, the LS mean (SE) changes from baseline in AM iTNSS were –1.1 (0.4) for stapokibart QW group, –2.6 (0.5) for stapokibart Q2W group, and –1.1 (0.5) for placebo group. The LS mean differences between the stapokibart Q2W group and placebo group at 4 h was –1.5 (95% CI –2.7, –0.3), p = 0.019. Fig. 3B demonstrates the time to maximum effect. Compared with the placebo group, the greatest reduction in the change from baseline in daily rTNSS was observed in the stapokibart QW and Q2W groups at 21 and 15 days, respectively (LS mean difference –0.9 [95% CI –2.4, 0.6, p = 0.23] and –1.5 [95% CI –3.3, 0.3, p = 0.096], respectively, Fig. 3B).

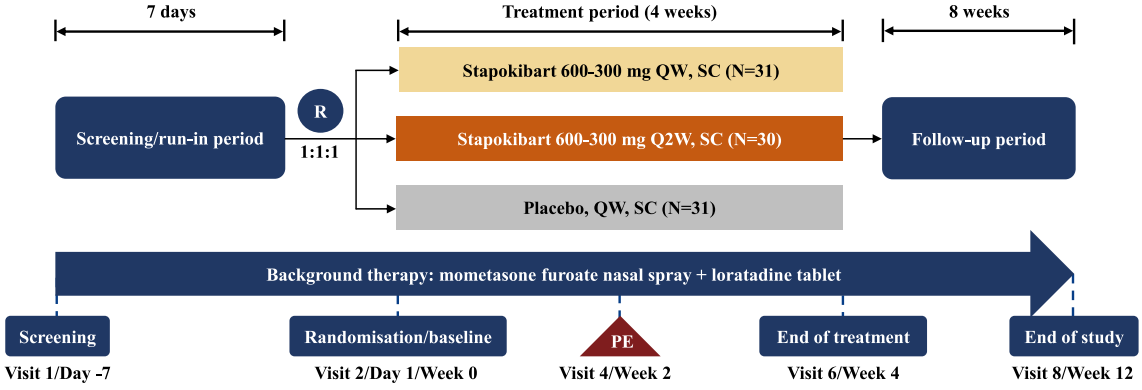

Fig. 2: Trial design. N = number. PE = primary endpoint. QW = weekly. Q2W = every 2 weeks. R = randomisation. SC = subcutaneous.

Characteristic	Stapokibart 600-300 mg QW (*n* = 31)	Stapokibart 600-300 mg Q2W (*n* = 30)	Placebo QW (*n* = 31)	Total (*n* = 92)
Age, years	36.8 (9.5)	37.9 (9.8)	36.3 (7.4)	37.0 (8.9)
Sex[a]				
Male	16 (52%)	12 (40%)	13 (42%)	41 (45%)
Female	15 (48%)	18 (60%)	18 (58%)	51 (55%)
Body mass index, kg/m^2	24.5 (3.1)	24.6 (3.4)	24.4 (3.7)	24.5 (3.4)
Duration of SAR, years	6.8 (4.0)	9.5 (5.4)	6.5 (3.8)	7.6 (4.6)
Baseline rTNSS	9.3 (2.0)	8.7 (2.1)	8.2 (1.6)	8.7 (1.9)
Baseline AM iTNSS	9.3 (2.1)	8.5 (2.2)	8.1 (1.9)	8.6 (2.1)
Baseline individual nasal symptom				
Rhinorrhea	2.4 (0.6)	2.2 (0.7)	2.1 (0.4)	2.2 (0.6)
Nasal congestion	2.5 (0.5)	2.3 (0.6)	2.1 (0.4)	2.3 (0.5)
Nasal itching	2.3 (0.6)	2.2 (0.6)	2.0 (0.5)	2.1 (0.6)
Sneezing	2.2 (0.7)	2.0 (0.6)	2.0 (0.6)	2.1 (0.6)
Baseline rTOSS	7.0 (1.9)	5.5 (2.2)	5.5 (1.8)	6.0 (2.0)
Baseline AM iTOSS	6.6 (2.0)	5.4 (2.2)	5.3 (2.0)	5.8 (2.1)
Baseline individual ocular symptom				
Ocular itching	2.6 (0.5)	2.2 (0.7)	2.1 (0.6)	2.3 (0.6)
Watery eyes	2.2 (0.8)	1.6 (0.9)	1.6 (0.8)	1.8 (0.8)
Eye redness	2.3 (0.8)	1.7 (0.9)	1.7 (0.7)	1.9 (0.8)
Baseline total RQLQ score	4.3 (0.9)	3.7 (1.2)	4.0 (1.2)	4.0 (1.1)
Sleep impairment	4.1 (1.3)	3.7 (1.7)	4.0 (1.5)	4.0 (1.5)
Daily activity[b]	4.4 (1.0)	3.7 (1.2)	3.9 (1.2)	4.0 (1.2)
Ocular symptoms	4.1 (1.2)	3.4 (1.5)	3.7 (1.5)	3.7 (1.4)
Emotional function	3.9 (1.3)	3.2 (1.5)	3.6 (1.6)	3.6 (1.5)
Baseline EOS counts				
<300/μL	13 (42%)	19 (63%)	17 (55%)	49 (53%)
≥300/μL	18 (58%)	11 (37%)	14 (45%)	43 (47%)
Comorbid asthma				
EOS counts of <300/μL	2 (7%)	2 (7%)	2 (7%)	6 (7%)
EOS counts of ≥300/μL	0	1 (3%)	1 (3%)	2 (2%)

Data are n (%) or mean (standard deviation), unless otherwise indicated. AM = morning. EOS = eosinophil. iTNSS = instantaneous total nasal symptom score. iTOSS = instantaneous total ocular symptom score. QW = weekly. Q2W = every 2 weeks. RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire. rTNSS = reflective total nasal symptom score. rTOSS = reflective total ocular symptom score. SAR = seasonal allergic rhinitis. [a]Sex was self-reported by the participants. [b]Daily activity involves non-nasal/ocular symptoms and practical problems.

Table 1: **Baseline demographic and clinical characteristics of patients.**

The overall rates of treatment-emergent AEs (TEAEs) were lower in stapokibart groups than those in placebo group (48% [15/31] in stapokibart QW and 33% [10/30] in stapokibart Q2W vs. 61% [19/31] in placebo; p = 0.099), with 9 patients experiencing drug-related TEAEs (13% [4/31] in stapokibart QW and stapokibart

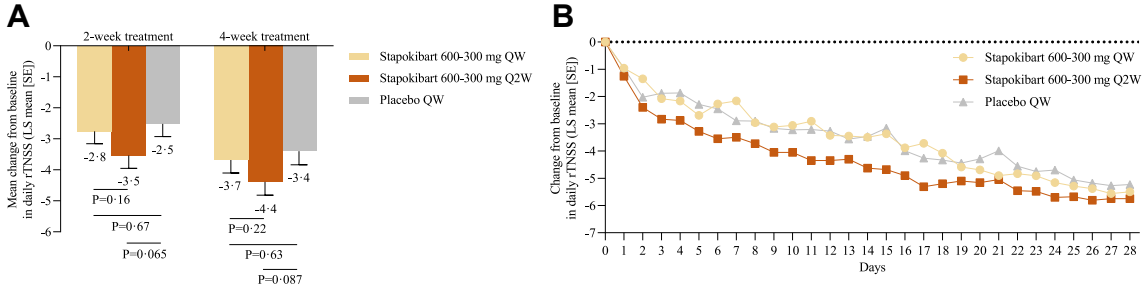

Fig. 3: Change in daily rTNSS. (A) Mean changes from baseline in daily rTNSS in 2-week and 4-week treatment. (B) Time course of daily rTNSS by treatment. LS = least-squares. QW = weekly. Q2W = every 2 weeks. rTNSS = reflective total nasal symptom score. SAR = seasonal allergic rhinitis. SE = standard error.

Change from baseline	Overall (n = 92)		
	Stapokibart 600-300 mg QW (n = 31)	Stapokibart 600-300 mg Q2W (n = 30)	Placebo QW (n = 31)
Mean change in daily rTNSS			
2-week treatment			
Mean (SD)	−2.9 (1.8)	−3.6 (2.6)	−2.5 (1.8)
LS mean (SE)	−2.8 (0.4)	−3.5 (0.4)	−2.5 (0.4)
LS mean Diff. (97.5%CI)	−0.2 (−1.5, 1.0)	−1.0 (−2.3, 0.2)	
p value (vs. placebo)	0.67	0.065	
4-week treatment			
LS mean (SE)	−3.7 (0.4)	−4.4 (0.4)	−3.4 (0.4)
LS mean Diff. (95% CI)	−0.3 (−1.5, 0.9)	−1.0 (−2.1, 0.2)	
p value (vs. placebo)	0.63	0.087	
Mean percentage change in daily rTNSS, %			
2-week treatment			
LS mean (SE)	−33.5 (4.6)	−41.1 (4.7)	−28.2 (4.8)
LS mean Diff. (95% CI)	−5.3 (−18.1, 7.4)	−12.9 (−25.3, −0.4)	
p value (vs. placebo)	0.41	**0.043**	
4-week treatment			
LS mean (SE)	−43.4 (4.7)	−50.7 (4.8)	−38.3 (4.9)
LS mean Diff. (95% CI)	−5.1 (−18.2, 8.0)	−12.4 (−25.2, 0.5)	
p value (vs. placebo)	0.44	0.058	
Mean change in AM rTNSS			
2-week treatment			
LS mean (SE)	−2.8 (0.4)	−3.7 (0.4)	−2.6 (0.4)
LS mean Diff. (95% CI)	−0.2 (−1.3, 1.0)	−1.0 (−2.1, 0.1)	
p value (vs. placebo)	0.79	0.071	
4-week treatment			
LS mean (SE)	−3.7 (0.4)	−4.5 (0.4)	−3.5 (0.5)
LS mean Diff. (95% CI)	−0.2 (−1.4, 1.0)	−1.0 (−2.2, 0.2)	
p value (vs. placebo)	0.69	0.093	
Mean change in PM rTNSS			
2-week treatment			
LS mean (SE)	−2.7 (0.4)	−3.5 (0.4)	−2.5 (0.4)
LS mean Diff. (95% CI)	−0.2 (−1.3, 0.9)	−1.0 (−2.1, 0.1)	
p value (vs. placebo)	0.74	0.064	
4-week treatment			
LS mean (SE)	−3.6 (0.4)	−4.4 (0.4)	−3.4 (0.4)
LS mean Diff. (95% CI)	−0.2 (−1.3, 1.0)	−1.0 (−2.1, 0.2)	
p value (vs. placebo)	0.75	0.087	
Mean change in AM iTNSS			
2-week treatment			
LS mean (SE)	−2.8 (0.4)	−3.8 (0.4)	−2.5 (0.5)
LS mean Diff. (95% CI)	−0.3 (−1.4, 0.9)	−1.3 (−2.5, −0.1)	
p value (vs. placebo)	0.67	**0.030**	
4-week treatment			
LS mean (SE)	−3.7 (0.4)	−4.5 (0.5)	−3.4 (0.5)
LS mean Diff. (95% CI)	−0.3 (−1.5, 1.0)	−1.1 (−2.3, 0.1)	
p value (vs. placebo)	0.67	0.068	
Mean percentage change in AM iTNSS, %			
2-week treatment			
LS mean (SE)	−34.1 (5.0)	−44.5 (5.2)	−27.1 (5.2)
LS mean Diff. (95% CI)	−7.0 (−20.9, 6.9)	−17.4 (−31.0, −3.8)	
p value (vs. placebo)	0.32	**0.013**	
4-week treatment			
LS mean (SE)	−44.0 (5.0)	−52.6 (5.1)	−37.2 (5.2)

(Table 2 continues on next page)

Change from baseline	Overall (n = 92)		
	Stapokibart 600-300 mg QW (n = 31)	Stapokibart 600-300 mg Q2W (n = 30)	Placebo QW (n = 31)
(Continued from previous page)			
LS mean Diff. (95% CI)	−6.8 (−20.7, 7.0)	−15.4 (−29.0, −1.9)	
p value (vs. placebo)	0.33	**0.026**	
Mean change in individual nasal symptom			
Rhinorrhea			
2-week treatment			
LS mean (SE)	−0.7 (0.1)	−0.9 (0.1)	−0.7 (0.1)
LS mean Diff. (95% CI)	0.01 (−0.3, 0.3)	−0.2 (−0.5, 0.1)	
p value (vs. placebo)	0.94	0.29	
4-week treatment			
LS mean (SE)	−0.9 (0.1)	−1.1 (0.1)	−0.9 (0.1)
LS mean Diff. (95% CI)	−0.01 (−0.3, 0.3)	−0.2 (−0.5, 0.1)	
p value (vs. placebo)	0.95	0.24	
Nasal congestion			
2-week treatment			
LS mean (SE)	−0.7 (0.1)	−1.0 (0.1)	−0.6 (0.1)
LS mean Diff. (95% CI)	−0.1 (−0.5, 0.2)	−0.4 (−0.7, −0.1)	
p value (vs. placebo)	0.44	**0.014**	
4-week treatment			
LS mean (SE)	−0.9 (0.1)	−1.2 (0.1)	−0.8 (0.1)
LS mean Diff. (95% CI)	−0.1 (−0.4, 0.2)	−0.4 (−0.7, −0.04)	
p value (vs. placebo)	0.55	**0.028**	
Nasal itching			
2-week treatment			
LS mean (SE)	−0.7 (0.1)	−0.9 (0.1)	−0.7 (0.1)
LS mean Diff. (95% CI)	0.06 (−0.2, 0.4)	−0.2 (−0.5, 0.1)	
p value (vs. placebo)	0.69	0.24	
4-week treatment			
LS mean (SE)	−0.9 (0.1)	−1.1 (0.1)	−0.9 (0.1)
LS mean Diff. (95% CI)	0.04 (−0.3, 0.3)	−0.2 (−0.5, 0.1)	
p value (vs. placebo)	0.79	0.27	
Sneezing			
2-week treatment			
LS mean (SE)	−0.6 (0.1)	−0.8 (0.1)	−0.6 (0.1)
LS mean Diff. (95% CI)	−0.04 (−0.3, 0.2)	−0.2 (−0.5, 0.04)	
p value (vs. placebo)	0.78	0.097	
4-week treatment			
LS mean (SE)	−0.9 (0.1)	−1.0 (0.1)	−0.8 (0.1)
LS mean Diff. (95% CI)	−0.1 (−0.4, 0.2)	−0.2 (−0.5, 0.1)	
p value (vs. placebo)	0.61	0.14	
Mean change in AM individual nasal symptom			
Rhinorrhea			
2-week treatment			
LS mean (SE)	−0.7 (0.1)	−0.9 (0.1)	−0.8 (0.1)
LS mean Diff. (95% CI)	0.03 (−0.3, 0.4)	−0.2 (−0.5, 0.2)	
p value (vs. placebo)	0.86	0.29	
4-week treatment			
LS mean (SE)	−1.0 (0.1)	−1.1 (0.1)	−1.0 (0.1)
LS mean Diff. (95% CI)	0.0 (−0.3, 0.3)	−0.2 (−0.5, 0.1)	
p value (vs. placebo)	0.99	0.23	
Nasal congestion			
2-week treatment			

(Table 2 continues on next page)

Change from baseline	Overall (n = 92)		
	Stapokibart 600-300 mg QW (n = 31)	Stapokibart 600-300 mg Q2W (n = 30)	Placebo QW (n = 31)
(Continued from previous page)			
LS mean (SE)	−0.7 (0.1)	−1.0 (0.1)	−0.7 (0.1)
LS mean Diff. (95% CI)	−0.01 (−0.3, 0.3)	−0.4 (−0.7, −0.03)	
p value (vs. placebo)	0.93	**0.034**	
4-week treatment			
LS mean (SE)	−0.9 (0.1)	−1.2 (0.1)	−0.9 (0.1)
LS mean Diff. (95% CI)	−0.02 (−0.4, 0.3)	−0.3 (−0.7, −0.0)	
p value (vs. placebo)	0.068	**0.049**	
Nasal itching			
2-week treatment			
LS mean (SE)	−0.7 (0.1)	−0.9 (0.1)	−0.7 (0.1)
LS mean Diff. (95% CI)	0.0 (−0.3, 0.3)	−0.2 (−0.5, 0.1)	
p value (vs. placebo)	1.0	0.13	
4-week treatment			
LS mean (SE)	−0.9 (0.1)	−1.1 (0.1)	−0.9 (0.1)
LS mean Diff. (95% CI)	−0.02 (−0.3, 0.3)	−0.2 (−0.5, 0.1)	
p value (vs. placebo)	0.90	0.15	
Sneezing			
2-week treatment			
LS mean (SE)	−0.6 (0.1)	−0.9 (0.1)	−0.6 (0.1)
LS mean Diff. (95% CI)	0 (−0.3, 0.3)	−0.2 (−0.5, 0.1)	
p value (vs. placebo)	0.99	0.12	
4-week treatment			
LS mean (SE)	−0.9 (0.1)	−1.01 (0.1)	−0.8 (0.1)
LS mean Diff. (95% CI)	−0.1 (−0.4, 0.3)	−0.2 (−0.5, 0.1)	
p value (vs. placebo)	0.75	0.20	
Mean change in PM individual nasal symptom			
Rhinorrhea			
2-week treatment			
LS mean (SE)	−0.7 (0.1)	−0.9 (0.1)	−0.7 (0.1)
LS mean Diff. (95% CI)	0.04 (−0.3, 0.4)	−0.2 (−0.5, 0.1)	
p value (vs. placebo)	0.77	0.31	
4-week treatment			
LS mean (SE)	−0.9 (0.1)	−1.1 (0.1)	−0.9 (0.1)
LS mean Diff. (95% CI)	0.03 (−0.3, 0.3)	−0.2 (−0.5, 0.1)	
p value (vs. placebo)	0.86	0.25	
Nasal congestion			
2-week treatment			
LS mean (SE)	−0.7 (0.1)	−1.0 (0.1)	−0.6 (0.1)
LS mean Diff. (95% CI)	−0.2 (−0.5, 0.2)	−0.4 (−0.7, −0.1)	
p value (vs. placebo)	0.31	**0.0099**	
4-week treatment			
LS mean (SE)	−0.9 (0.1)	−1.2 (0.1)	−0.8 (0.1)
LS mean Diff. (95% CI)	−0.1 (−0.5, 0.2)	−0.4 (−0.7, −0.1)	
p value (vs. placebo)	0.49	**0.023**	
Nasal itching			
2-week treatment			
LS mean (SE)	−0.6 (0.1)	−0.9 (0.1)	−0.8 (0.1)
LS mean Diff. (95% CI)	0.1 (−0.2, 0.4)	−0.1 (−0.4, 0.2)	
p value (vs. placebo)	0.38	0.38	
4-week treatment			
LS mean (SE)	−0.9 (0.1)	−1.1 (0.1)	−1.0 (0.1)

(Table 2 continues on next page)

Change from baseline	Overall (n = 92)		
	Stapokibart 600-300 mg QW (n = 31)	Stapokibart 600-300 mg Q2W (n = 30)	Placebo QW (n = 31)
(Continued from previous page)			
LS mean Diff. (95% CI)	0.1 (−0.2, 0.4)	−0.1 (−0.4, 0.2)	
p value (vs. placebo)	0.45	0.44	
Sneezing			
2-week treatment			
LS mean (SE)	−0.6 (0.1)	−0.8 (0.1)	−0.6 (0.1)
LS mean Diff. (95% CI)	−0.1 (−0.3, 0.2)	−0.2 (−0.5, 0.04)	
p value (vs. placebo)	0.74	0.098	
4-week treatment			
LS mean (SE)	−0.9 (0.1)	−1.0 (0.1)	−0.79 (0.11)
LS mean Diff. (95% CI)	−0.1 (−0.4, 0.2)	−0.2 (−0.5, 0.1)	
p value (vs. placebo)	0.60	0.11	

Data are least-squares mean (SE), unless otherwise indicated. Mean (standard deviation, SD) is descriptive statistics. p values were calculated for statistical comparison between stapokibart QW/Q2W and placebo by the ANCOVA model. AM = morning. ANCOVA = analysis of covariance. CI = confidence interval. Diff. = difference. iTNSS = instantaneous total nasal symptom score. LS = least-squares. PM = evening. QW = weekly. Q2W = every 2 weeks. rTNSS = reflective total nasal symptom score. SE = standard error. Bold values are statistically significant.

Table 2: **Effect of stapokibart on nasal symptoms.**

Q2W 10% [3/30] vs. 7% [2/31] in placebo) (Table 4). All TEAEs were mild or moderate in severity. The most common TEAEs occurring in ≥2 patients in either group were shown in Table 4. None of them were considered drug-related. Only one serious AE (SAE) was reported in a patient receiving placebo, which was considered unrelated to the study treatment. Additionally, one patient discontinued the study due to TEAE (palpitations). No deaths were reported. Of 92 patients who had at least one valid anti-drug antibody (ADA) assessment, only two (2%) patients tested positive for ADA: one in the stapokibart QW group had pre-existing ADA, and the other in the stapokibart Q2W group developed treatment-induced ADA. The concentration–time profile of stapokibart is seen in Appendix p 2.

Exploratory analyses

In exploratory analyses, patients receiving stapokibart 600-300 mg Q2W experienced more days of mild or no nasal and ocular symptoms than placebo in 2 weeks (LS

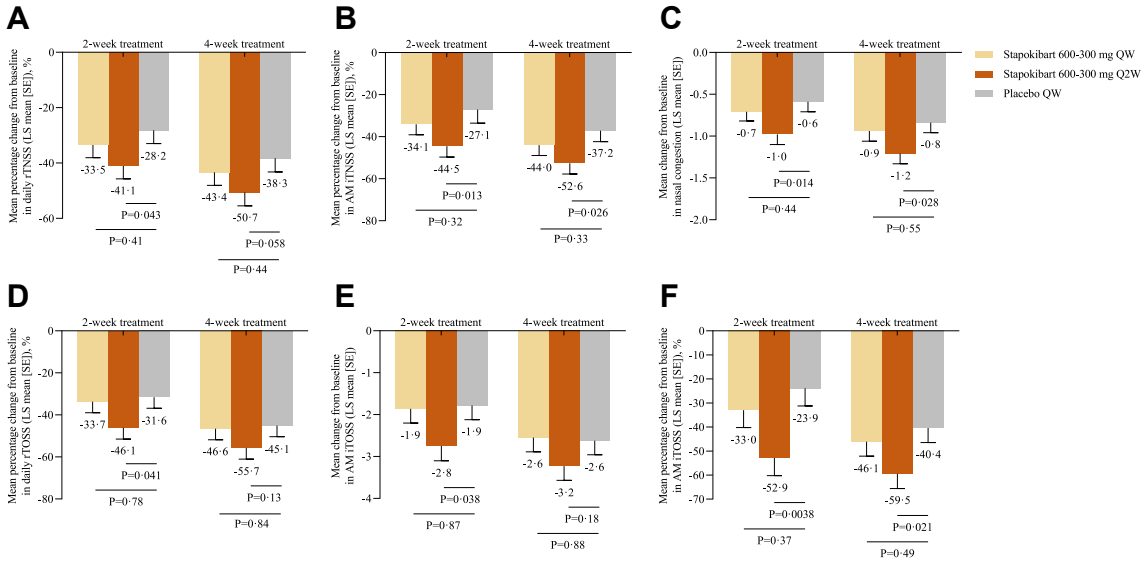

Fig. 4: Change in nasal and ocular symptoms. Mean changes or mean percentage changes from baseline in (A) daily rTNSS, (B) AM iTNSS, (C) nasal congestion, (D) daily rTOSS, and (E and F) AM iTOSS in 2-week and 4-week treatment. AM = morning. iTOSS = instantaneous total ocular symptom score. iTNSS = instantaneous total nasal symptom score. LS = least-squares. QW = weekly. Q2W = every 2 weeks. rTNSS = reflective total nasal symptom score. rTOSS = reflective total ocular symptom score. SAR = seasonal allergic rhinitis. SE = standard error.

Change from baseline	Overall (n = 92)		
	Stapokibart 600-300 mg QW (n = 31)	Stapokibart 600-300 mg Q2W (n = 30)	Placebo QW (n = 31)
Mean change in daily rTOSS			
2-week treatment			
LS mean (SE)	−2.0 (0.3)	−2.7 (0.3)	−2.0 (0.3)
LS mean Diff. (95% CI)	0.04 (−0.9, 0.9)	−0.7 (−1.5, 0.2)	
p value (vs. placebo)	0.94	0.14	
4-week treatment			
LS mean (SE)	−2.8 (0.3)	−3.3 (0.3)	−2.8 (0.3)
LS mean Diff. (95% CI)	0.1 (−0.8, 1.0)	−0.4 (−1.3, 0.4)	
p value (vs. placebo)	0.88	0.33	
Mean percentage change in daily rTOSS, %			
2-week treatment			
LS mean (SE)	−33.7 (5.3)	−46.1 (5.4)	−31.6 (5.3)
LS mean Diff. (95% CI)	−2.1 (−16.6, 12.5)	−14.6 (−28.5, −0.6)	
p value (vs. placebo)	0.78	**0.041**	
4-week treatment			
LS mean (SE)	−46.6 (5.3)	−55.7 (5.3)	−45.1 (5.3)
LS mean Diff. (95% CI)	−1.5 (−16.0, 13.0)	−10.6 (−24.5, 3.3)	
p value (vs. placebo)	0.84	0.13	
Mean change in AM rTOSS			
2-week treatment			
LS mean (SE)	−2.0 (0.3)	−2.8 (0.3)	−2.1 (0.3)
LS mean Diff. (95% CI)	0.02 (−0.9, 0.9)	−0.7 (−1.6, 0.2)	
p value (vs. placebo)	0.96	0.11	
4-week treatment			
LS mean (SE)	−2.8 (0.3)	−3.3 (0.3)	−2.9 (0.3)
LS mean Diff. (95% CI)	0.1 (−0.8, 1.0)	−0.5 (−1.4, 0.4)	
p value (vs. placebo)	0.84	0.29	
Mean change in PM rTOSS			
2-week treatment			
LS mean (SE)	−1.9 (0.3)	−2.6 (0.3)	−2.0 (0.3)
LS mean Diff. (95% CI)	0.2 (−0.7, 1.0)	−0.6 (−1.5, 0.3)	
p value (vs. placebo)	0.74	0.17	
4-week treatment			
LS mean (SE)	−2.7 (0.3)	−3.2 (0.3)	−2.8 (0.3)
LS mean Diff. (95% CI)	0.1 (−0.8, 1.0)	−0.4 (−1.3, 0.5)	
p value (vs. placebo)	0.79	0.36	
Mean change in AM iTOSS			
2-week treatment			
LS mean (SE)	−1.9 (0.3)	−2.8 (0.4)	−1.8 (0.3)
LS mean Diff. (95% CI)	−0.1 (−1.0, 0.9)	−1.0 (−1.9, −0.1)	
p value (vs. placebo)	0.87	**0.038**	
4-week treatment			
LS mean (SE)	−2.6 (0.3)	−3.2 (0.3)	−2.6 (0.3)
LS mean Diff. (95% CI)	0.1 (−0.9, 1.0)	−0.6 (−1.5, 0.3)	
p value (vs. placebo)	0.88	0.18	
Mean percentage change in AM iTOSS, %			
2-week treatment			
LS mean (SE)	−33.0 (7.3)	−52.9 (7.4)	−23.9 (7.3)
LS mean Diff. (95% CI)	−9.1 (−29.0, 10.9)	−29.0 (−48.4, −9.6)	
p value (vs. placebo)	0.37	**0.0038**	
4-week treatment			
LS mean (SE)	−46.1 (6.0)	−59.5 (6.1)	−40.4 (6.1)
LS mean Diff. (95% CI)	−5.8 (−22.3, 10.8)	−19.1 (−35.2, −3.0)	
p value (vs. placebo)	0.49	**0.021**	

(Table 3 continues on next page)

Change from baseline	Overall (n = 92)		
	Stapokibart 600-300 mg QW (n = 31)	Stapokibart 600-300 mg Q2W (n = 30)	Placebo QW (n = 31)
(Continued from previous page)			
Mean change in individual ocular symptom			
Ocular itching			
2-week treatment			
LS mean (SE)	−0.7 (0.1)	−0.9 (0.1)	−0.7 (0.1)
LS mean Diff. (95% CI)	−0.1 (−0.4, 0.3)	−0.2 (−0.5, 0.1)	
p value (vs. placebo)	0.70	0.23	
4-week treatment			
LS mean (SE)	−1.1 (0.1)	−1.1 (0.1)	−1.0 (0.1)
LS mean Diff. (95% CI)	−0.1 (−0.4, 0.3)	−0.1 (−0.5, 0.2)	
p value (vs. placebo)	0.67	0.37	
Watery eyes			
2-week treatment			
LS mean (SE)	−0.6 (0.1)	−0.9 (0.1)	−0.7 (0.1)
LS mean Diff. (95% CI)	0.1 (−0.2,0.4)	−0.2 (−0.5, 0.1)	
p value (vs. placebo)	0.46	0.16	
4-week treatment			
LS mean (SE)	−0.8 (0.1)	−1.1 (0.1)	−0.91 (0.1)
LS mean Diff. (95% CI)	0.1 (−0.2, 0.4)	−0.2 (−0.5, 0.2)	
p value (vs. placebo)	0.50	0.31	
Eye redness			
2-week treatment			
LS mean (SE)	−0.6 (0.1)	−0.9 (0.1)	−0.6 (0.1)
LS mean Diff. (95% CI)	−0.01 (−0.3, 0.3)	−0.3 (−0.6, 0.1)	
p value (vs. placebo)	0.96	0.12	
4-week treatment			
LS mean (SE)	−0.9 (0.1)	−1.1 (0.1)	−0.9 (0.1)
LS mean Diff. (95% CI)	0.04 (−0.3, 0.4)	−0.1 (−0.4, 0.2)	
p value (vs. placebo)	0.78	0.38	
Mean change in AM individual ocular symptom			
Ocular itching			
2-week treatment			
LS mean (SE)	−0.8 (0.1)	−0.9 (0.1)	−0.7 (0.1)
LS mean Diff. (95% CI)	−0.1 (−0.4, 0.3)	−0.2 (−0.5, 0.1)	
p value (vs. placebo)	0.77	0.17	
4-week treatment			
LS mean (SE)	−1.1 (0.1)	−1.2 (0.1)	−1.0 (0.1)
LS mean Diff. (95% CI)	−0.1 (−0.4, 0.3)	−0.2 (−0.5, 0.2)	
p value (vs. placebo)	0.77	0.31	
Watery eyes			
2-week treatment			
LS mean (SE)	−0.6 (0.1)	−1.0 (0.12)	−0.7 (0.1)
LS mean Diff. (95% CI)	0.1 (−0.2, 0.4)	−0.2 (−0.6, 0.1)	
p value (vs. placebo)	0.51	0.13	
4-week treatment			
LS mean (SE)	−0.8 (0.1)	−1.1 (0.1)	−0.9 (0.1)
LS mean Diff. (95% CI)	0.1 (−0.2, 0.4)	−0.2 (−0.5, 0.1)	
p value (vs. placebo)	0.47	0.28	
Eye redness			
2-week treatment			
LS mean (SE)	−0.7 (0.1)	−0.9 (0.1)	−0.6 (0.1)
LS mean Diff. (95% CI)	−0.02 (−0.4, 0.3)	−0.3 (−0.6, 0.1)	

(Table 3 continues on next page)

Change from baseline	Overall (n = 92)		
	Stapokibart 600-300 mg QW (n = 31)	Stapokibart 600-300 mg Q2W (n = 30)	Placebo QW (n = 31)
(Continued from previous page)			
p value (vs. placebo)	0.90	0.094	
4-week treatment			
LS mean (SE)	−0.9 (0.1)	−1.1 (0.1)	−0.9 (0.1)
LS mean Diff. (95% CI)	0.04 (−0.3, 0.4)	−0.1 (−0.4, 0.2)	
p value (vs. placebo)	0.79	0.38	
Mean change in PM individual ocular symptom			
Ocular itching			
2-week treatment			
LS mean (SE)	−0.7 (0.1)	−0.8 (0.1)	−0.7 (0.1)
LS mean Diff. (95% CI)	−0.04 (−0.4, 0.3)	−0.2 (−0.5, 0.1)	
p value (vs. placebo)	0.79	0.30	
4-week treatment			
LS mean (SE)	−1.1 (0.1)	−1.1 (0.2)	−1.0 (0.1)
LS mean Diff. (95% CI)	−0.1 (−0.4, 0.3)	−0.1 (−0.4, 0.2)	
p value (vs. placebo)	0.68	0.42	
Watery eyes			
2-week treatment			
LS mean (SE)	−0.5 (0.1)	−0.9 (0.1)	−0.7 (0.1)
LS mean Diff. (95% CI)	0.2 (−0.1, 0.5)	−0.2 (−0.5, 0.1)	
p value (vs. placebo)	0.27	0.19	
4-week treatment			
LS mean (SE)	−0.8 (0.1)	−1.0 (0.1)	−0.9 (0.1)
LS mean Diff. (95% CI)	0.1 (−0.2, 0.5)	−0.2 (−0.5, 0.2)	
p value (vs. placebo)	0.40	0.34	
Eye redness			
2-week treatment			
LS mean (SE)	−0.6 (0.1)	−0.9 (0.1)	−0.6 (0.1)
LS mean Diff. (95% CI)	0.04 (−0.3, 0.4)	−0.2 (−0.6, 0.1)	
p value (vs. placebo)	0.81	0.14	
4-week treatment			
LS mean (SE)	−0.8 (0.1)	−1.1 (0.1)	−0.9 (0.1)
LS mean Diff. (95% CI)	0.1 (−0.2, 0.4)	−0.1 (−0.4, 0.2)	
p value (vs. placebo)	0.63	0.39	

Data are least-squares mean (SE), unless otherwise indicated. p values were calculated for statistical comparison between stapokibart QW/Q2W and placebo by the ANCOVA model. AM = morning. ANCOVA = analysis of covariance. CI = confidence interval. Diff. = difference. iTOSS = instantaneous total ocular symptom score. LS = least-squares. PM = evening. QW = weekly. Q2W = every 2 weeks. rTOSS = reflective total ocular symptom score. SE = standard error. Bold values are statistically significant.

Table 3: **Effect of stapokibart on ocular symptoms.**

mean difference 2.7 [95% CI 0.6, 4.8], p = 0.012) (Appendix pp 5–6).

The markers detected and their lower detection limits are shown in Appendix p 7. The changes from baseline in markers in serum, nasal secretions, and nasal brushings with significant differences between stapokibart treatment and placebo have been shown in Appendix pp 8–10. Blood thymus and activation-regulated chemokine (TARC) continued to decrease during 2- and 4-week Q2W stapokibart treatment period (during 2-week treatment, median [IQR], –15.4 pg/mL [–41.8, –3.4] in stapokibart Q2W vs. –1.5 pg/mL [–19.3, 8.4] in placebo, p = 0.0039; during 4-week treatment, median [IQR], –20.7 pg/mL [–33.6, –7.4] in Q2W vs. –8.6 pg/mL [–24.3, 0.5] in placebo, p = 0.029). Significant differences have also been observed in blood tumour necrosis factor alpha (TNF-α), transforming growth factor beta 2 (TGF-β2), 15(S)-hydroxyeicosatetraenoic acid (15[S]-HETE), and IgE between stapokibart and placebo groups, the detailed information has been shown in Appendix p 8. The protein level of IL-25, cystatin SN (CST1), and Charcot-Leyden crystal (CLC) in nasal secretions decreased significantly during the 2-week stapokibart treatment compared with placebo

	Stapokibart 600-300 mg QW (*n* = 31)	Stapokibart 600-300 mg Q2W (*n* = 30)	Placebo QW (*n* = 31)	p value
Total number of TEAEs	29	26	35	
Patients with:				
Any TEAEs	15 (48%)	10 (33%)	19 (61%)	0.099
Any study drug-related TEAEs	4 (13%)	3 (10%)	2 (7%)	0.76
Any SAEs	0	0	1 (3%)	1.00
TEAEs leading to discontinuation	0	0	1 (3%)	1.00
Death	0	0	0	1.00
Common TEAEs (≥2 patients in either group)				
Sinus bradycardia	2 (7%)	1 (3%)	3 (10%)	0.87
Hyperlipidaemia	2 (7%)	2 (7%)	1 (3%)	0.87
Blood uric acid increased	2 (7%)	1 (3%)	1 (3%)	1.00
Hyperuricaemia	2 (7%)	0	1 (3%)	0.77
Blood triglycerides increased	1 (3%)	1 (3%)	2 (7%)	1.00
Electrocardiogram T wave abnormal	0	0	2 (7%)	0.33
Ligament sprain	0	0	2 (7%)	0.33

Data are n (%), unless otherwise indicated. QW = weekly. Q2W = every 2 weeks. SAEs = serious adverse events. TEAEs = treatment-emergent adverse events. p values among the three groups were calculated by Fisher's exact test.

***Table 4*: Summary of adverse events.**

(Appendix p 9). CST1 decreased in both stapokibart QW and Q2W treatment (median [IQR], −223.4 [−468.9, −67.7] in QW, −221.1 [−340.3, −62.0] in Q2W and 26.5 [−17.9, 120.7] in placebo, ng/mL, p = 0.0019 and 0.00070 respectively). IL-25 decreased in stapokibart Q2W treatment (median [IQR], −2.9 [−37.1, 0.0] in Q2W and 0.0 [0.0, 0.0] in placebo, pg/mL, p = 0.045). CLC decreased in stapokibart QW treatment (median [IQR], −223.0 [−459.5, −40.1] in QW and 0.0 [−83.8, 0.0] in placebo, ng/mL, p = 0.0046). The mRNA level of CST1 and CLC in nasal brushings decreased significantly in stapokibart QW and Q2W treatment during 2- and 4-week compared with placebo, while the level of arachidonate 15-lipoxygenase (ALOX15) decreased in stapokibart Q2W during 2- and 4-week and in QW during 4-week treatment (Appendix p 10).

Subgroup analyses

Nearly half of the study population had a baseline blood EOS count of ≥300 cells/μL (Table 1), thus we further stratified patients with blood EOS count. In patients with baseline blood EOS count of ≥300 cells/μL subgroup, the mean change from baseline in daily rTNSS was significantly greater for stapokibart Q2W than for placebo in 2 weeks (LS mean difference −1.9 [95% CI −3.2, −0.5], p = 0.0095) (Appendix p 3 and p 11). Significant improvements in the secondary efficacy endpoints were observed with stapokibart Q2W compared with placebo, including the mean changes from baseline in daily rTNSS in 4 weeks, AM rTNSS in 2 weeks, PM rTNSS in 2 weeks, AM iTNSS in 2 weeks, and the mean percentage changes from baseline in daily rTNSS and AM iTNSS in 2 weeks and 4 weeks (Appendix p 4 and pp 11–17). The LS mean difference between stapokibart Q2W and placebo was significant for nasal congestion in 2 weeks and 4 weeks (Appendix p 4 and pp 11–17). Stapokibart QW also showed similar trends but less extent of improvement than stapokibart Q2W (Appendix pp 3–4 and pp 11–17).

In the subgroup with a baseline blood EOS count of ≥300 cells/μL, patients receiving stapokibart Q2W experienced more days of mild or no ocular symptoms than placebo in 2 weeks, and mild or no nasal and ocular symptoms than placebo in 2 weeks (Appendix pp 16–17). Also, in the baseline blood EOS count ≥300 cells/μL subgroup, AUC of change from baseline of daily rTNSS vs. time was significantly larger in the patients receiving stapokibart Q2W than in the placebo group in 2 weeks (p = 0.0099) and 4 weeks (p = 0.049) (Appendix p 16). The efficacy results of patients with a baseline blood EOS count of <300 cells/μL are seen in Appendix pp 18–21. No significant difference was noticed in the overall evaluation of response as well as the overall RQLQ score and four individual domains to therapy among the subgroup analysis (Appendix pp 16–17 and p 21).

Discussion

Stapokibart 600-300 mg QW or Q2W did not significantly improve mean change from baseline in daily rTNSS compared with placebo. However, this trial indicated that two doses of stapokibart 600-300 mg Q2W during the pollen period effectively improve mean

percentage change from baseline in daily rTNSS, AM iTNSS, rTOSS and AM iTOSS in 2 weeks in patients with SAR, particularly for those with baseline blood EOS count of ≥300 cells/μL. Additionally, stapokibart was found to be safe and well-tolerated in patients with uncontrolled SAR.

To the best of our knowledge, this is the first trial to assess the efficacy of a periodic add-on use of biologics for patients with uncontrolled SAR during the pollen exposure phase. Previous studies on biologics enrolled patients with SAR have not gone through the SoC run-in screening stage, which cannot confirm whether the study population is currently subjects with uncontrolled or "refractory" SAR. Therefore, it is also not possible to confirm the necessity of using biologics in these patients. In the present study, the setting of a 1-week SoC run-in period serves the goal of ensuring that the subjects involved in this study are truly patients with uncontrolled SAR who need treatment with biologics to obtain further benefit. Moreover, in the previous add-on study design of omalizumab on AR, oral antihistamines were used throughout the treatment period while INCS was only used in severe pollen scattering season.[17] This may increase the therapeutic efficacy difference between biologics and placebos to some extent. In contrast, here we choose the combination of oral antihistamines and INCS as the background SoC throughout the entire treatment period and we concluded that stapokibart could improve nasal and ocular symptoms in patients with uncontrolled SAR particularly those with high blood EOS counts. Except for omalizumab, current biological agents for type 2 inflammation have not been studied well in AR, as stated in the Introduction.[21,22]

Subgroup analyses have also revealed patients with baseline blood EOS count ≥300 cells/μL experienced significant improvements in nasal symptoms, ocular symptoms, and quality of life compared with patients with baseline blood EOS count <300 cells/μL. This is consistent with the mechanisms of stapokibart which targets IL-4-induced inflammation. Similar conclusions were drawn in a phase 3 trial of asthma, LIBERTY ASTHMA QUEST, in which, asthma patients with a baseline blood EOS count ≥300 cells/μL experienced the greatest clinical benefits from dupilumab. Therefore, in the ongoing phase 3 trial of stapokibart in SAR, patients' baseline blood EOS level has been established as one of the inclusion criteria.

After 4 weeks of treatment, the total IgE level in the stapokibart QW group was significantly lower than in the placebo group, while similar trends were observed in the Q2W group but without statistical significance. However, both stapokibart QW and Q2W groups showed significant decreases compared to the placebo group after 12 weeks of observation. Although the predictive value of serum IgE in the efficacy of monoclonal antibodies such as omalizumab or dupilumab in the treatment of AR is unknown, previous studies have suggested that serum total IgE is not a reliable marker to predict the outcome of AR treated with allergen immunotherapy.[25,26] Due to the limited volume of nasal secretion, we have not been able to detect IgE in nasal secretion in this study, but we will consider this important issue in future research.

Stapokibart was generally well tolerated and had an acceptable safety profile for the treatment of patients with SAR. No significant differences were observed among stapokibart QW, Q2W and placebo groups. All TEAEs in the stapokibart group were mild to moderate and had been resolved or were in the process of being resolved at the last visit. One patient in the placebo group experienced acute cholecystitis, which was not considered drug-related serious AE. This case of acute cholecystitis was caused by gallstones obstruction in the cystic duct.

A linear dose-response relationship was not observed in this study. This phenomenon remains unexplained despite the well-maintained balance of baseline clinical characteristics among the three groups. Notably, non-linear dose-response relationships have been previously noted with other monoclonal antibodies.[27–30] For instance, higher numerical improvement in disease severity was reported in pediatric atopic dermatitis patients treated with dupilumab at 2 mg/kg QW vs. 4 mg/kg QW despite saturation of the IL-4 receptor at both regimens (R668-AD-1412).[30] In addition, similar more numerical improvement in low-dose group (200 mg Q2W) compared with high-dose group (300 mg Q2W) was also reported in patients with moderate-to-severe asthma.[31]

There are some limitations to this trial. A relatively small sample size may have limited the power of detecting a difference between groups. Only the primary analysis was adjusted for multiplicity, all other p-values were nominal. Additionally, the stratification of patients with blood EOS was not prespecified. However, these limitations of this exploratory study will provide a basis and valuable experience for future SAR studies involving stapokibart.

In conclusion, stapokibart was well tolerated and has the potential to improve nasal/ocular symptoms as an added-on treatment in patients with moderate-to-severe uncontrolled SAR, particularly in patients with a baseline EOS count of ≥300 cells/μL.

Contributors

All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. LZ and CW contributed to study design, data collection and interpretation; LZ and CW also contributed to preparation and review of the report. YZ, BY, ZZ, XW, XS, DZ, TM, YZ, CM, and GW contributed to data collection, analysis, and interpretation. LZ and CW accessed and verified the data.

Data sharing statement

Data requests should be addressed by E-mail to the corresponding authors. The trial protocol will be made available.

Declaration of interests

LZ was supported by grants from the Ministry of Science and Technology of the People's Republic of China; the Ministry of Education of

the People's Republic of China and the Chinese Academy of Medical Sciences; CW declares support from the National Natural Science Foundation of China.

Acknowledgements

This work was supported by the National Key R&D Program of China (2022YFC2504100) from the Ministry of Science and Technology of the People's Republic of China; Changjiang Scholars and Innovative Research Team (IRT13082) from the Ministry of Education of the People's Republic of China; National Natural Science Foundation of China (82025010); CAMS Innovation Fund for Medical Sciences (2019-I2M-5-022) from Chinese Academy of Medical Sciences. We thank Keymed Biosciences (Chengdu) Limited for providing stapokibart for this study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102467.

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