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Stapokibart for moderate-to-severe seasonal allergic rhinitis: a randomized phase 3 trial

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Seasonal allergic rhinitis (SAR) places a significant socioeconomic burden, particularly on individuals with poorly managed recurrent and severe symptoms despite standard-of-care treatment. Stapokibart, a humanized monoclonal antibody that targets the interleukin (IL)-4 receptor subunit alpha, inhibits its interaction with both IL-4 and IL-13 in type 2 inflammation. Here we aim to assess the efficacy and safety of stapokibart as an add-on therapy in adults with moderate-to-severe SAR. The study was a phase 3 multicenter, randomized, double-blind, placebo-controlled clinical trial with 108 patients diagnosed with moderate-to-severe SAR and having baseline blood eosinophil counts ≥300 cells μl^{-1}. Participants were randomized (1:1) to receive 600 mg (loading dose) to 300 mg stapokibart subcutaneously or a placebo every 2 weeks for 4 weeks. The primary endpoint was mean change from baseline in daily reflective total nasal symptom score (rTNSS) over the first 2 weeks. Multiplicity-tested secondary endpoints included changes in rTNSS over 4 weeks, reflective total ocular symptom score and Rhinoconjunctivitis Quality of Life Questionnaire score over 2 weeks and 4 weeks. Compared with the placebo, stapokibart led to a significant improvement in the mean change from baseline in daily rTNSS during the 2-week (least-squares mean difference, −1.3; 95% confidence interval, −2.0 to −0.6; $P = 0.0008$) and 4-week (least-squares mean difference, −1.7; 95% confidence interval, −2.5 to −0.8; $P = 0.0002$) treatments. Stapokibart significantly improved the multiplicity-tested secondary endpoints. Treatment-emergent adverse events were comparable between the groups. Pharmacodynamics and exploratory analyses indicated that the observed improvements in outcomes during pollen season may be attributed to the reduction of type 2 inflammation in response to stapokibart treatment. The results of this trial show that pollen seasonal administration of stapokibart improved both nasal and ocular symptoms and quality of life in patients with moderate-to-severe SAR. ClinicalTrials.gov registration: NCT05908032.

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Allergic rhinitis (AR) is a persistent inflammatory condition of the nasal mucosa, mediated by immunoglobulin E (IgE) and triggered by aeroallergens. AR predominantly exhibits type 2 inflammatory signatures and can be categorized into seasonal (SAR) and perennial (PAR)[1,2]. Notably, SAR exhibits more severe and intense symptoms[3,4], prominent nasal inflammation[5] and decreased quality of life (QOL)[2], and is more challenging to control compared with PAR[6]. Furthermore, the expected consequences of future climate change encompass an increase in pollen levels and prolonged blooming seasons, leading to the projection that SAR is likely to become more widespread as a global health issue[7,8].

Despite receiving standard-of-care (SoC) treatment, including H1 antihistamines or intranasal corticosteroids, over 60% of patients with SAR are dissatisfied with their treatment owing to poor symptom control[6,9], highlighting a huge unmet need for effective therapeutic interventions. However, the encouraging efficacy of biologics in other type 2 inflammatory diseases of the respiratory tract suggests their potential use for SAR treatment. Previous RCT trials as well as meta-analysis studies have shown the significant efficacy of pre- and co-seasonal administration of omalizumab (an anti-IgE monoclonal antibody) in improving nasal and ocular symptoms, and QOL in patients with SAR during the pollen season[10–12]. Although some economic analyses conducted within asthma and chronic urticaria cohorts have concluded that omalizumab is a cost-effective treatment option when administered to specific patient groups[13,14], the cost ranging from US$10,000 to US$70,000 per year for the minimum to maximum dose significantly restricts its broader utilization across type 2 inflammations[15]. Administration with omalizumab as a preventive escalated therapy for the overall SAR population may potentially lead to overtreatment and is not deemed cost-effective. Furthermore, two studies investigated the effects of combination treatment with biological agents targeting interleukin (IL)-4 or IL-4 receptor subunit alpha (IL-4Rα) (specifically dupilumab and VAK694) and grass pollen subcutaneous immunotherapy (SCIT) on SAR[16,17]. In these two trials, in which nasal allergen challenges or allergen-induced skin late-phase response models were used as primary efficacy endpoints outside the pollen season, no significant differences were observed in the suppression of allergic responses between the combined anti-IL4 and SCIT treatment and SCIT monotherapy. Nevertheless, there has been an absence of clinical trials evaluating the efficacy of incorporating biologics as a seasonal add-on therapy to SoC treatment during the pollen season for patients with moderate-to-severe SAR.

Stapokibart (CM310) is a humanized antibody targeting IL-4Rα and effectively blocking its interaction with both IL-4 and IL-13 of type 2 inflammation. Our findings from a double-blind, randomized, placebo-controlled, phase 2 trial (the MERAK trial; ClinicalTrials.gov identifier: NCT05470647)[18] indicated that stapokibart was well tolerated and safe in the overall moderate-to-severe SAR population. Notably, it significantly reduced the daily reflective total nasal symptom score (rTNSS) in a subgroup of patients with blood eosinophil counts of at least 300 cells μl^{-1}, when exposed to pollen. Thus, we designed the PHECDA trial to confirm the efficacy and safety of stapokibart as seasonal add-on therapy to SoC treatment in adults with moderate-to-severe SAR and with a blood eosinophil count of at least 300 cells μl^{-1}.

Results

Patients

A total of 279 patients were assessed for eligibility between 10 August 2023 and 10 September 2023, of whom 108 were randomized to receive either stapokibart ($n = 50$) or placebo ($n = 58$). Exclusion of the 40 patients was based on 'investigators' discretion', permitting the investigator to consider patients ineligible for our study if they showed uncooperative behavior or had conditions potentially leading to protocol noncompliance or affecting evaluation outcomes. Of these, 29 had incomplete assessments by the end of enrollment, and 9 were excluded owing to poor compliance, 1 owing to SoC intolerance and 1 owing to anemia and abnormal renal function. One participant in the placebo group discontinued treatment early because of treatment-emergent adverse events (TEAEs) (Fig. 1). Two participants reported the use of medications that are prohibited by the protocol for managing pre-existing conditions (allergic conjunctivitis and asthma exacerbation), as major deviations from the protocol affecting efficacy evaluation, and subsequent continuous data were handled using the last observation carried forward (LOCF) method, while subsequent binary data were classified as nonresponse according to the composite variable strategy, as outlined in the Statistical Analysis Plan (SAP; see 'Statistical Analysis Plan' in Supplementary Information). Other minor deviations from the protocol are detailed in Supplementary Information 'Supplementary Table 1'. Data from all 108 participants were included in the efficacy analysis set.

The mean age of patients ($n = 108$) was 37.0 years, with 52.8% being female. The mean duration of SAR was 9.3 years, and the mean baseline blood eosinophil count was 540 cells μl^{-1}. The baseline mean rTNSS, reflective total ocular symptom score (rTOSS) and mean total Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score were similar between the two groups (Table 1).

Efficacy

Stapokibart significantly improved the mean change from baseline in daily rTNSS over a 2-week treatment (the primary efficacy endpoint), compared with placebo (least-squares (LS) mean difference, −1.3; confidence interval (CI), −2.0 to −0.6; $P = 0.0008$) (Table 2). Sensitivity analysis showed no significant interaction between centers and treatment groups ($P = 0.222$). Subgroup analyses favored stapokibart over placebo regarding the primary endpoint for all subgroups (Extended Data Fig. 1).

Secondary outcomes and results from the per-protocol analysis are detailed in Table 2, Fig. 2, Extended Data Tables 1–4 and Extended Data Figs. 2 and 3. Similarly, the mean percentage change concerning daily rTNSS over 2 weeks' treatment was greater with stapokibart versus placebo (LS mean difference, −13.5%; 95% CI, −21.9% to −5.1%; $P = 0.002$) (Extended Data Table 1). Furthermore, the efficacy of stapokibart was significantly evident over the 4-week treatment (LS mean difference in mean change from baseline in daily rTNSS over 4 weeks of treatment, −1.7; 95% CI, −2.5 to −0.8; $P = 0.0002$; and in mean percentage change, −17.4%; 95% CI, −26.8% to −8.0%; $P = 0.0004$) (Table 2 and Extended Data Table 1). Indeed, stapokibart led to greater improvements than placebo in multiple efficacy endpoints for nasal symptoms, including morning (a.m.) instantaneous total nasal symptom score (iTNSS), a.m. rTNSS and evening (p.m.) rTNSS as well as daily, a.m. and p.m. assessments of most individual nasal symptoms over the 2-week and 4-week treatment periods (Extended Data Table 1). Based on the time course of daily rTNSS, the onset of action was observed on day 4 (LS mean difference, −1.0; 95% CI, −1.8 to −0.2; $P = 0.017$), and the maximum effect was observed on day 14 (LS mean difference, −2.1; 95% CI, −3.1 to −1.1; $P = 0.0001$) over the 2-week treatment and day 18 (LS mean difference, −2.2; 95% CI, −3.3 to −1.1; $P < 0.0001$) over the 4-week treatment (Fig. 2 and Supplementary Information 'Supplementary Table 2'). The area under the curves (AUCs) of changes from baseline in daily rTNSS had improved in the stapokibart versus placebo group over the 2-week (LS mean difference, −19.1; 95% CI, −29.6 to −8.6; $P = 0.0005$) and 4-week treatment (LS mean difference, −47.4; 95% CI, −71.2 to −23.6; $P = 0.0002$) (Extended Data Table 2).

Stapokibart also resulted in greater improvements than placebo in daily ocular symptoms as indicated by significantly greater mean changes from baseline in the daily rTOSS over both the 2-week treatment (LS mean difference, −0.7; 95% CI, −1.3 to 0.0; $P = 0.039$) and 4-week treatment (LS mean difference, −0.8; 95% CI, −1.4 to −0.2; $P = 0.016$) (Table 2). The mean percentage change from baseline in

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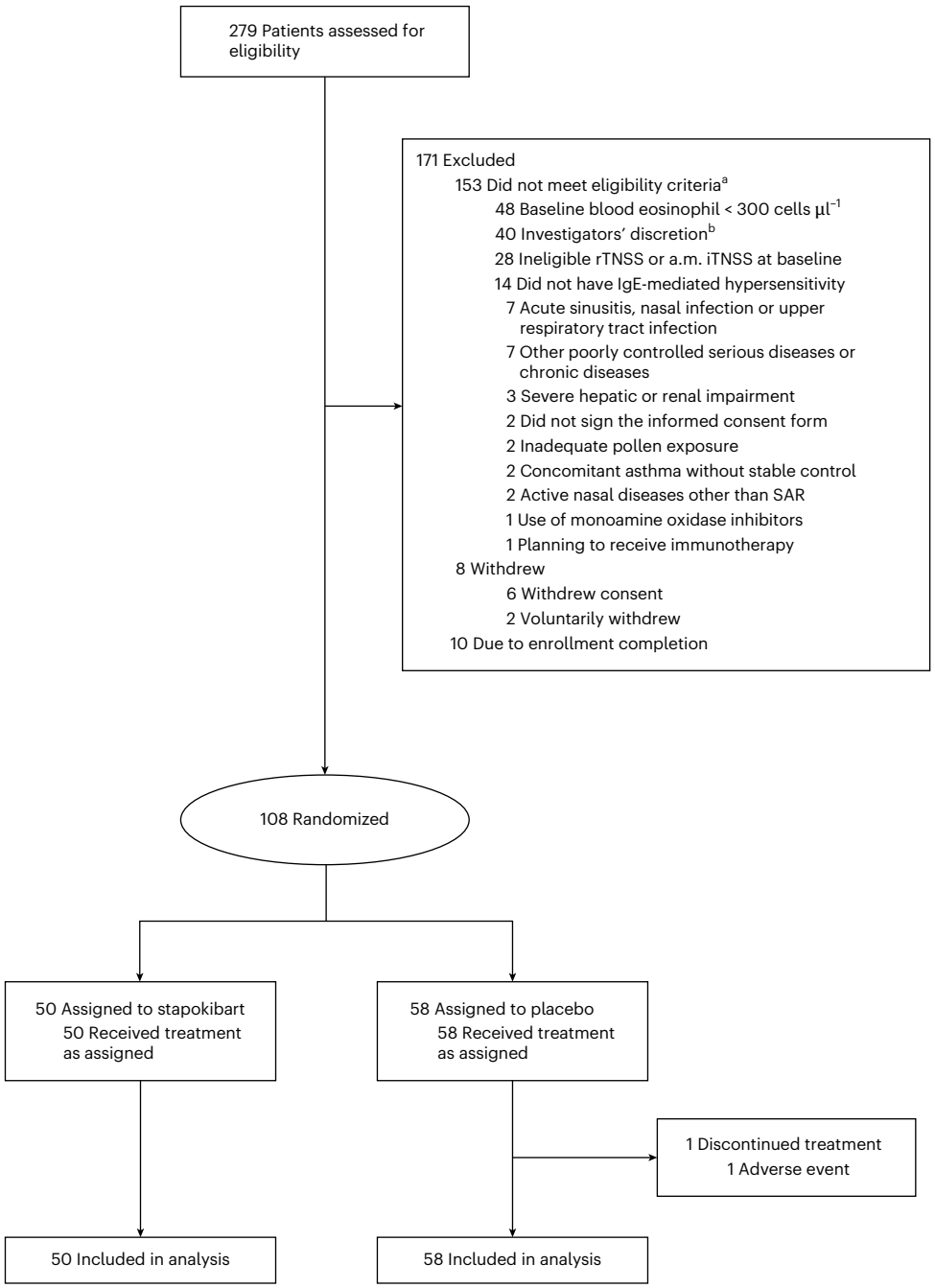

Fig. 1 | Consort diagram in the trial of stapokibart for moderate-to-severe seasonal AR. The flow chart depicts the process of patient screening, randomization and final analysis in the study. [a]Three patients had multiple reasons for not meeting the eligibility criteria, which resulted in nonadditive data. [b]Patients were excluded based on the following objective circumstances: had insufficient assessments until enrollment completion ($n = 29$), poor compliance ($n = 9$), unable to tolerate background treatment during screening ($n = 1$) and had anemia and abnormal renal function leading to safety concerns ($n = 1$).

daily rTOSS showed a similar trend (Extended Data Table 3). Consistently, the effect of stapokibart was greater than that of the placebo for other daily ocular symptom-associated endpoints, including a.m. rTOSS, p.m. rTOSS, a.m. instantaneous total ocular symptom score (iTOSS) and individual ocular symptom scores (Extended Data Table 3).

The stapokibart group also achieved longer mild symptoms or was free of nasal and ocular symptoms compared with the placebo group over the 4-week treatment (median difference, 4.0 days; 95% CI, 1.0–7.0; $P = 0.0005$) (Extended Data Fig. 2a). The proportion of participants achieving mild or no nasal symptoms was 26.0%, 42.0%, 52.0% and 64.0% at day 7, 14, 21 and 28 in the stapokibart group, respectively, while the proportion was 10.3%, 15.5%, 27.6% and 39.7%, respectively, in the placebo group (Extended Data Fig. 2b).

Stapokibart also showed significantly greater changes from baseline in the total RQLQ score than placebo at both week 2 (LS mean difference, −0.9; 95% CI, −1.4 to −0.4; $P = 0.0003$) and week 4 (LS mean difference, −1.0; 95% CI, −1.5 to −0.5; $P < 0.0001$) (Table 2). The differences versus placebo exceeded the minimal clinically important difference (MCID) of 0.5 point[19], and 88.0% and 100.0% of stapokibart-treated patients versus 67.2% and 79.3% of placebo-treated patients achieved a ≥0.5 reduction from baseline in RQLQ score at week 2 ($P = 0.012$) and 4 ($P = 0.0004$), respectively (Extended Data Table 4).

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Table 1 | Demographic and clinical characteristics of the patients at baseline

Characteristic	Stapokibart (*n*=50)	Placebo (*n*=58)	Overall (*n*=108)
Age, mean (s.d.) (years)	36.4 (8.4)	37.4 (8.8)	37.0 (8.6)
Sex, *n* (%)			
Female	29 (58.0)	28 (48.3)	57 (52.8)
Male	21 (42.0)	30 (51.7)	51 (47.2)
Han Chinese ethnic group, *n* (%)[a]	45 (90.0)	58 (100.0)	103 (95.4)
Body mass index, mean (s.d.) ($kg\,m^{-2}$)	24.3 (4.1)	25.4 (4.1)	24.9 (4.1)
Duration of SAR, mean (s.d.) (years)	9.2 (5.5)	9.4 (7.5)	9.3 (6.6)
Comorbid asthma, *n* (%)	7 (14.0)	10 (17.2)	17 (15.7)
Specific IgE positivity, *n* (%)			
Artemisia	41 (82.0)	54 (93.1)	95 (88.0)
Humulus	28 (56.0)	29 (50.0)	57 (52.8)
Ambrosia	31 (62.0)	40 (69.0)	71 (65.7)
Chenopodium	17 (34.0)	28 (48.3)	45 (41.7)
Baseline eosinophil count, mean (s.d.) (cells μl^{-1})	509 (191)	567 (214)	540 (204)
rTNSS, mean (s.d.)[b]	9.2 (1.4)	9.3 (1.4)	9.2 (1.4)
a.m. rTNSS, mean (s.d.)[b]	9.3 (1.5)	9.5 (1.4)	9.4 (1.5)
p.m. rTNSS, mean (s.d.)[b]	9.0 (1.5)	9.0 (1.5)	9.0 (1.5)
a.m. iTNSS, mean (s.d.)[b]	8.9 (1.7)	8.8 (1.7)	8.8 (1.7)
Individual nasal symptom score, mean (s.d.)[b]			
Nasal congestion	2.5 (0.4)	2.6 (0.4)	2.6 (0.4)
Runny nose	2.3 (0.4)	2.4 (0.4)	2.4 (0.4)
Nasal itching	2.2 (0.6)	2.1 (0.6)	2.1 (0.6)
Sneezing	2.2 (0.5)	2.2 (0.4)	2.2 (0.5)
rTOSS, mean (s.d.)[c]	6.2 (1.7)	6.6 (1.6)	6.4 (1.7)
Total RQLQ score, mean (s.d.)[d]	4.2 (0.9)	4.3 (1.1)	4.3 (1.0)

[a]Ethnic group was self-reported by the participants. [b]rTNSS is calculated by summing up the individual scores for nasal congestion, runny nose, nasal itching and sneezing reported over the past 12 h; separate scores are obtained for morning (a.m. rTNSS), evening (p.m. rTNSS) and the instantaneous morning before treatment (a.m. iTNSS); the individual nasal symptom score ranges from 0 (no symptom) to 3 points (severe); total scores range from 0 to 12, with lower scores indicating less severe nasal symptoms. [c]rTOSS is calculated by summing up the individual scores for itching and burning eyes, tearing and watering eyes, and eye redness reported over the past 12 h; the individual ocular symptom score ranges from 0 (no symptom) to 3 points (severe); total scores range from 0 to 9, with lower scores indicating less severe ocular symptoms. [d]RQLQ is a 28-item instrument specifically designed to assess the QOL status in adult patients with rhinoconjunctivitis; total scores range from 0 to 6, with lower scores indicating a higher QOL.

Moreover, the LS mean changes from baseline in all domains of the RQLQ score were greater in the stapokibart group than in the placebo group (all $P < 0.05$; Extended Data Fig. 3a,b).

Safety

TEAEs were reported in 26 (52.0%) patients in the stapokibart group and 27 (46.6%) in the placebo group (Table 3), all mild to moderate. Treatment-related TEAEs occurred in 7 (14.0%) patients in the stapokibart group and 5 (8.6%) in the placebo group. One patient in the placebo group discontinued treatment owing to two TEAEs (moderate night sweats and asthenia), which resolved spontaneously without treatment. No serious AEs or deaths occurred in either group. The most common TEAEs (≥5%) were upper respiratory tract infection, urinary tract infection, hyperuricemia, hyperlipidemia and cough.

Table 2 | Multiplicity-tested efficacy outcomes

Outcome[a]	Stapokibart (*n*=50)	Placebo (*n*=58)	LS mean difference	*P* value[a]
	LS mean (s.e.m.)	LS mean (s.e.m.)	(95% CI)	
Primary outcome				
Mean change from baseline in daily rTNSS during the 2-week treatment[b]	−3.6 (0.3)	−2.3 (0.3)	−1.3 (−2.0 to −0.6)	0.0008
Secondary outcome				
Mean change from baseline in daily rTOSS during the 2-week treatment[c]	−2.6 (0.3)	−1.9 (0.3)	−0.7 (−1.3 to 0.0)	0.039
Mean change from baseline in daily rTNSS during the 4-week treatment[b]	−4.9 (0.4)	−3.2 (0.4)	−1.7 (−2.5 to −0.8)	0.0002
Mean change from baseline in daily rTOSS during the 4-week treatment[c]	−3.7 (0.3)	−2.9 (0.3)	−0.8 (−1.4 to −0.2)	0.016
Change from baseline in total RQLQ score at week 2[d]	−2.5 (0.2)	−1.6 (0.2)	−0.9 (−1.4 to −0.4)	0.0003
Change from baseline in total RQLQ score at week 4[d]	−3.5 (0.2)	−2.5 (0.2)	−1.0 (−1.5 to −0.5)	<0.0001

[a]Listed in the order of hierarchical testing. All outcomes were analyzed using the ANCOVA model, with the baseline value of the given outcome, study site and treatment group as covariates. Differences in LS means and the corresponding 95% CI were calculated together with the *P* value (two sided). The overall type I error was controlled by step-down test procedures. All the data of a.m. and p.m. rTNSS and rTOSS in the 4 weeks of treatment were collected, and thus, there was no missing data-handling issue for rTNSS and rTOSS. Missing data for RQLQ were imputed by the LOCF method. [b]rTNSS is calculated by summing up the individual scores for nasal congestion, runny nose, nasal itching and sneezing reported over the past 12 h; the individual nasal symptom score ranges from 0 (no symptom) to 3 points (severe); total scores range from 0 to 12, with lower scores indicating less severe nasal symptoms. [c]rTOSS is calculated by summing up the individual scores for itching and burning eyes, tearing and watering eyes, and eye redness reported over the past 12 h; the individual ocular symptom score ranges from 0 (no symptom) to 3 points (severe); total scores range from 0 to 9, with lower scores indicating less severe ocular symptoms. [d]RQLQ is a 28-item instrument specifically designed to assess the QOL status in adult patients with rhinoconjunctivitis; total scores range from 0 to 6, with lower scores indicating a higher QOL. s.e.m., standard error of the mean.

Pharmacokinetics, pharmacodynamics and immunogenicity

The concentration–time trait of stapokibart was measured (Extended Data Fig. 4). The stapokibart group showed greater reductions in the concentrations of pharmacodynamic (PD) markers, including serum thymus and activation-regulated chemokine (TARC) (Extended Data Fig. 5a,b), serum total IgE (Extended Data Fig. 5c,d) and plasma eotaxin-3 (Extended Data Fig. 5e,f). The changes in counts (Extended Data Fig. 5g,h) and percentages (Extended Data Fig. 5i,j) of blood eosinophils were generally similar between groups. Treatment-emergent anti-drug antibodies were detected in 3 (6.0%) participants in the stapokibart group at week 12, whereas neutralizing antibodies were not detected.

Exploratory outcomes

The effects of stapokibart on both systemic and local levels of immunoglobulins (Ig), as well as on prespecified inflammatory biomarkers, implicated in the pathogenesis of SAR or associated with treatment response, were evaluated (Supplementary Tables 3 and 4). The stapokibart group showed significant reductions in median change and percentage change from the baseline of serum specific IgE (sIgE) levels

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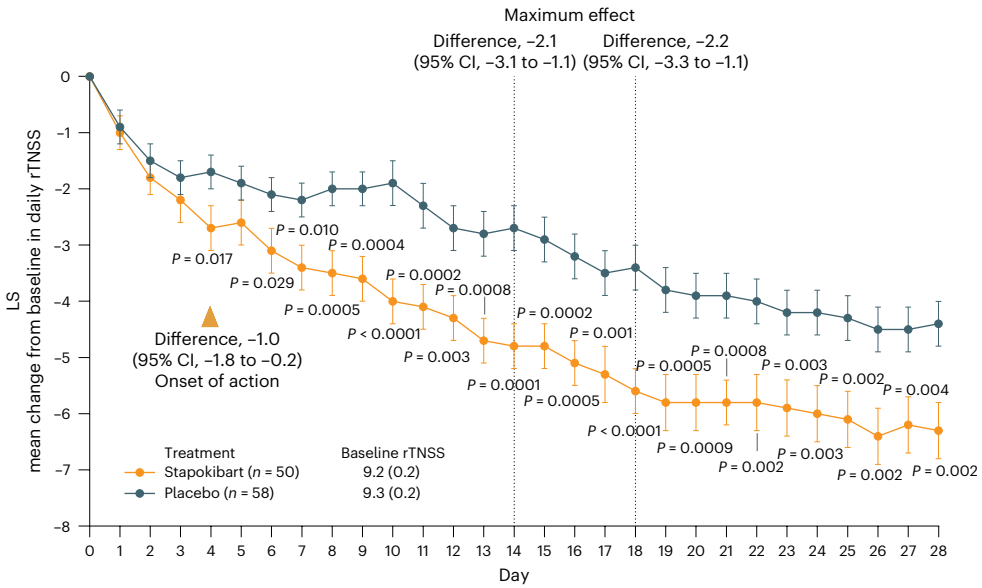

Fig. 2 | Change from baseline over time in daily rTNSS during the 4-week treatment period. Onset of action for stapokibart was observed on day 4 (orange triangle), and the maximum effect was observed on day 14 and day 18 (gray vertical dotted lines) over the 2- and 4-week treatment periods, respectively. The changes from baseline in daily rTNSS up to week 4 were analyzed through a mixed-effect model for repeated measures, with the baseline daily rTNSS as the covariate and the treatment group, study site, visit and treatment-by-visit interaction as fixed effects. LS mean changes are shown for 50 patients in the stapokibart group and 58 in the placebo group. The error bars indicate standard errors. Differences in LS means and the corresponding 95% CIs were calculated. *P* values were two sided and nominal, without adjustments for multiple comparisons. The rTNSS is used to assess the overall severity of nasal symptoms over the past 12 h on a scale from 0 to 12. Lower scores indicate less severe nasal symptoms.

Table 3 | Adverse events

Event	Number of patients (%)	
	Stapokibart (*n*=50)	Placebo (*n*=58)
Any TEAEs[a]	26 (52.0)	27 (46.6)
SAEs[b]	0	0
Treatment-related TEAEs	7 (14.0)	5 (8.6)
TEAEs leading to treatment discontinuation	0	1 (1.7)
TEAEs leading to death	0	0
TEAEs occurring in ≥5% of either group[c]		
Upper respiratory tract infection	9 (18.0)	7 (12.1)
Urinary tract infection	4 (8.0)	1 (1.7)
Hyperuricemia	2 (4.0)	4 (6.9)
Hyperlipidemia	1 (2.0)	4 (6.9)
Cough	1 (2.0)	3 (5.2)

The safety analysis set consisted of all patients who received at least one dose of the investigational drug or placebo. SAEs, serious adverse events. [a]Defined as any adverse event that occurred between the start of treatment and the completion of the study (or early withdrawal), which included adverse events that occurred before treatment but worsened in severity after treatment. [b]Defined as any of the following untoward medical events that occurred after a participant received an investigational product: resulted in death or life-threatening, permanent or significant disability or incapacity; need for hospitalization or prolongation of existing hospitalization; congenital anomaly or birth defect; and an important medical event, which may not be immediately life threatening, or lead to death or hospitalization, but required medical intervention to prevent one of the above conditions, was also generally considered serious. A hospitalization with a duration of less than 24 h (for example, admission to a day ward) was not reported as an SAE. [c]Defined according to Medical Dictionary for Regulatory Activities preferred terms.

against four pollen allergens over the 4-week period (Extended Data Fig. 6a,c), accompanied by observable trends toward reductions in sIgE levels in nasal secretions (Extended Data Fig. 6b,d), compared with the placebo group. Significant reductions in the levels of the Charcot–Leyden crystal protein (CLC) and cystatin SN (CST1), both biomarkers of type 2 inflammation, were observed in nasal secretions from the stapokibart treatment group compared with the placebo group (Extended Data Fig. 6e,f).

Nasal brushing performed at baseline and weeks 2 and 4 was evaluable for RNA sequencing (RNA-seq) analysis in 100 eligible patients who completed sample collections and provided samples of sufficient quality for analysis (Supplementary Table 1). Gene expression profiling at the point of disease progression posttreatment, relative to baseline levels, revealed that a set of genes showed significant downregulation in response to stapokibart compared with placebo (Fig. 3a). These genes are predominantly canonical type 2 inflammation biomarkers, including intelectin 1 (ITLN1), CST1, chloride channel accessory 1 (CLCA1), periostin (POSTN) CLC and others. Stapokibart-mediated inhibition of IL-4 and IL-13 could modulate genes pertinent to SAR, which were significantly enriched in pathways linked to immune regulation and inflammatory responses, showing attenuation at weeks 2 and 4 of treatment, as determined by functional enrichment analysis (Fig. 3b).

Discussion

Our study has indicated that, compared with treatment with placebo, treatment with stapokibart resulted in a significant reduction in daily nasal and ocular symptom scores during the pollen phase in patients with moderate-to-severe SAR and with high symptom loads despite receiving SoC. Furthermore, stapokibart treatment also resulted in significantly greater improvements in QOL and an increased percentage of SAR with no or only mild symptoms.

The preliminary data from our phase 2 MERAK trial have indicated the efficacy of stapokibart in moderate-to-severe SAR in patients with a blood eosinophil count of at least 300 cells μl^{-1} (ref. 18). Coincidentally, the trials of dupilumab, another biological agent targeting IL-4R, have consistently shown significant benefits for patients with other airway diseases characterized by elevated blood eosinophil counts[10,20–22]. In this regard, the PHECDA study has also investigated the efficacy of stapokibart in patients with moderate-to-severe SAR with high blood

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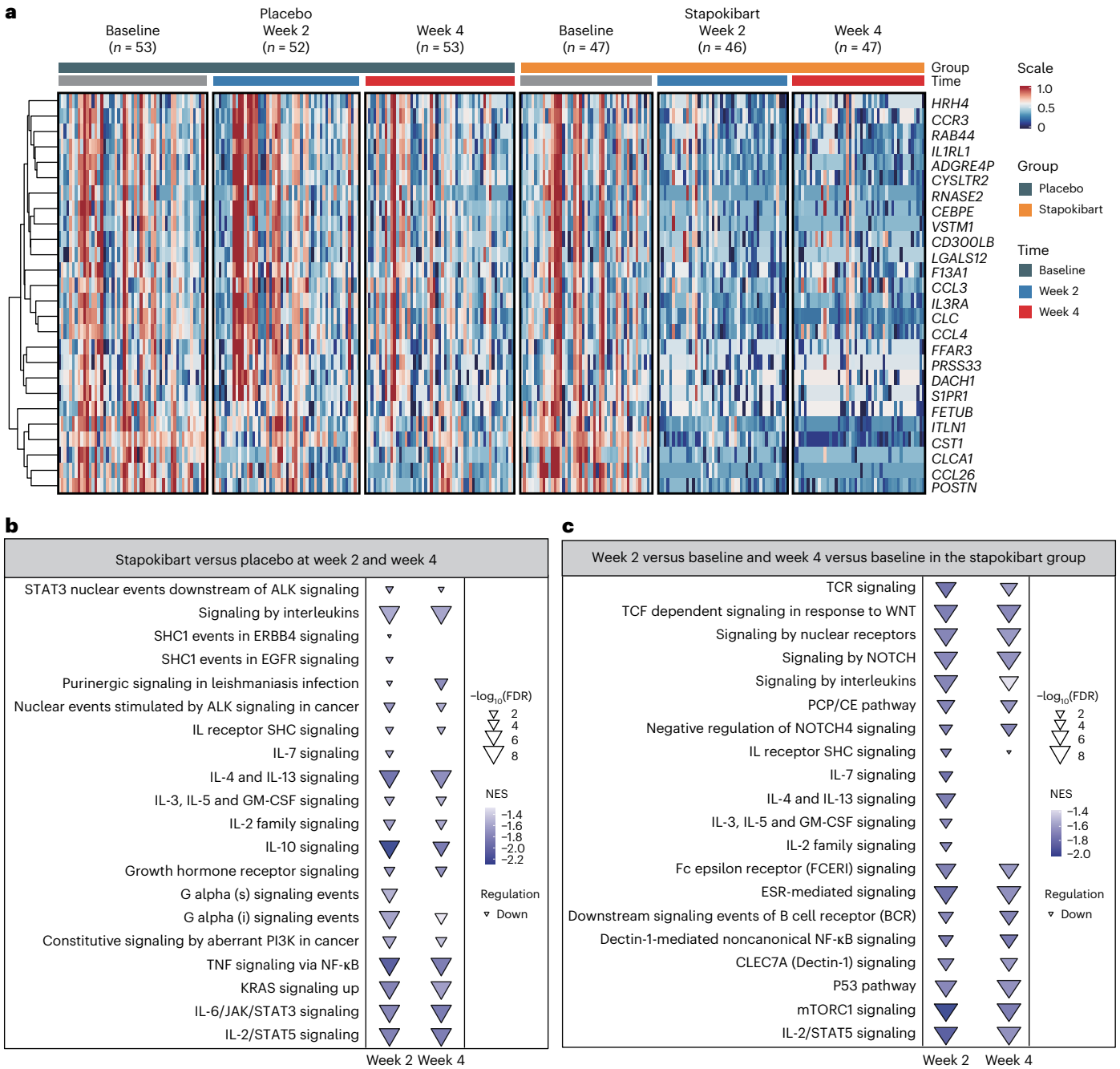

Fig. 3 | RNA-seq analysis of nasal brushing in study participants receiving stapokibart (n = 53) versus placebo (n = 47) at baseline and weeks 2 and 4. **a**, Heatmap illustrating the overlapping differentially expressed genes (absolute value $\log_2$(fold change) > 2 and q-value < 0.05) comparing post-stapokibart time points to baseline, as well as intergroup comparisons at each posttreatment time point. **b**, Normalized enrichment scores (NES) for the top 20 pathways that showed significant downregulation in posttreatment comparisons (weeks 2 and 4) between stapokibart and placebo. **c**, NES for the top 20 pathways that showed significant downregulation in a post-stapokibart comparison (at weeks 2 and 4) relative to baseline.

eosinophil counts and indicated that stapokibart resulted in early, substantial and clinically significant improvements toward multiple aspects of SAR, involving a persistent reduction in major nasal and ocular symptoms and RQLQ scores. Indeed, the between-group differences in rTNSS, the primary endpoint in our study, significantly exceed the recommended threshold for an MCID in studies on AR[23], and a higher percentage of stapokibart-treated patients (42.0% and 64.0%) achieved mild or no nasal symptoms (all individual symptom scores of ≤1 point) at weeks 2 and 4, respectively, compared with placebo-treated patients (15.5% and 39.7%, respectively). These findings for the greater efficacy of stapokibart are also supported by the observation that patients administered with this drug experienced a greater number of days with no or only mild nasal and ocular symptoms over the entire course of exposure to pollen. Indeed, a significantly greater treatment effect of stapokibart in the reduction of rTNSS was noted from day 4 to day 28, with the maximum effect observed on day 14 for the loading dose (600 mg) and on day 18 for the second dose (300 mg) of stapokibart. The effect of stapokibart throughout the 4-week treatment period suggests that it may be necessary to continuously suppress type 2 inflammation to maintain symptom control during pollen exposure. Distinct from the previous two trials investigating anti-IL-4 on SAR[16,17], our study evaluated therapeutic efficacy in patients showing

pronounced symptoms during natural pollen exposure, which were closed to real-world clinical conditions, thereby providing a more authentic assessment of treatment outcomes. Furthermore, our PHECDA trial, along with other studies involving biologics, indicates that a therapeutic strategy combining SoC is effective in the management of allergic disorders.

The baseline scores on the RQLQ in our study reflect the burden of QOL, which is exacerbated with increasing severity of AR[1,24,25]. RQLQ items include activity limitation and mental and physical functions in addition to the nasal and ocular symptoms. Both RQLQ total and domain scores showed significant and clinically meaningful improvements, consistent with the improvement in rTNSS observed in patients administered with stapokibart. The proportion of patients treated with stapokibart and achieving an improvement in the total RQLQ score above the MCID (0.5 points)[19] at weeks 2 and 4 of treatment was 88.0% and 100.0%, respectively, compared with 67.2% and 79.3%, respectively, for placebo. This finding contrasts with those of most RCTs investigating the effect of allergen-specific immunotherapy for SAR, which have reported a between-group difference in RQLQ of less than 0.5 (ref. 19), and suggests that stapokibart may provide the greatest clinical benefit to patients with moderate-to-severe SAR.

The observed improvements in outcomes during pollen season may be attributed to both systemic and local effects resulting from the reduction of type 2 inflammation in response to stapokibart treatment. Stapokibart significantly reduced serum TARC, plasma eotaxin-3, CLC and CST1 levels in nasal secretions during the 4-week treatment period. These biomarkers, which are upregulated by IL-4 and IL-13, serve as indicators of type 2 inflammation[26]. RNA-seq analysis of nasal brushing samples revealed a significant downregulation of a set of genes, predominantly associated with type 2 inflammation, following treatment with stapokibart compared with placebo. These genes may contribute to the efficacy of stapokibart in SAR patients who are inadequately controlled with SoC treatment. Transcriptomic evaluations from nasal brushing, incorporating stapokibart from the current study and dupilumab, indicate that IL-4Rα-targeted biologics augment SoC treatment by modulating transcriptional inflammatory pathways[27–29]. Stapokibart treatment resulted in a significant reduction in serum total IgE and sIgE levels over a 4-week period compared with placebo. Similar trends were observed in nasal secretions albeit without achieving statistical significance. In this respect, the observed significant difference between the groups suggests a potential additional antagonistic effect of stapokibart on the sustained peak seasonal allergen-induced IgE production. These findings are consistent with both the preclinical study of stapokibart[30] and clinical studies of dupilumab in allergic asthma and SAR[31,32]. However, these findings should be interpreted with caution, and further research is required to comprehensively characterize systemic and local humoral immune responses to stapokibart treatment.

The strength of the PHECDA trial lies in its well-designed timing for participant recruitment and evaluation of medical endpoints, aligning with pollen exposure in each center of Chinese pollen networks. The intervention and assessment were conducted with adequate exposure to pollen throughout the trial. Also, the 1-week run-in period for SoC treatment was implemented to ensure that all eligible patients had moderate-to-severe SAR and a baseline blood eosinophil count of at least 300 cells μl^{-1} was required, which ensured a targeted study focused on the specific population that would derive maximum benefit from stapokibart. Our study thus indicates that administration of stapokibart during the pollen season, along with the ability to selectively identify suitable patients, would facilitate the precise application of biologics in clinical practice and enhance the efficient utilization of medical resources.

The PHECDA study also has some limitations. First, it enrolled a relatively homogeneous Chinese population; therefore, the findings of our study need to be substantiated in individuals from different ethnic backgrounds and cultures, as well as different geographical locations with different types of pollen and climate, any of which may influence the outcome. Second, the study observed relatively high placebo responses, most likely due to increased adherence to standard background medications, as reported in other biologic asthma trials[33–35].

These findings show that stapokibart significantly improves both nasal and ocular symptoms and QOL in patients with moderate-to-severe SAR, while maintaining a favorable safety profile. Stapokibart presents an efficacious treatment choice for SAR patients who have not achieved satisfactory improvement with SoC treatment.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-025-03651-5.

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Methods

Study design

The PHECDA study was a phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial conducted at 18 centers across China. This trial was registered with ClinicalTrials.gov, NCT05908032, before the commencement of patient recruitment (registration date: 18 June 2023). The trial design and reporting adhered strictly to the protocol and SAP, both of which are provided in full in the 'Clinical Study Protocol' and 'Statistical Analysis Plan' sections of Supplementary Information (ref. 36). The study was conducted during the pollen season, which was defined as the period from the third day of three consecutive days when the daily pollen count was at least 20 per 1,000 mm^2 to the third day of three consecutive days when daily pollen count was less than 20 per 1,000 mm^2 (Supplementary Fig. 1). The study consisted of a 1-week screening and run-in period, a 4-week treatment period and an 8-week follow-up period.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol and amendments (Supplementary Information, 'Study Protocol Amendment Description') were developed collaboratively by the sponsors and principal investigators, and subsequently approved by the independent ethics committees of Beijing Tongren Hospital of Capital Medical University and the ethics committee of each participating center (see 'List of Investigators' in Supplementary Information). Written informed consent was signed by all participants before enrollment. The participants received compensation for commuting and blood collection.

Data collection was executed via an electronic data capture system, with subsequent analysis performed by independent statisticians from an external contract research organization, adhering rigorously to a predetermined SAP. This trial was designed as a short-term study, and previous clinical investigations of stapokibart showed a favorable safety profile[18,37,38]. The investigators meticulously oversaw the well-being and safety of the trial participants, documenting AEs, administering medical interventions and conducting follow-ups on AEs, in alignment with good clinical practice guidelines and the investigator's brochure. The China Center for Drug Evaluation provided continuous and thorough supervision throughout the entire trial. The established safety of stapokibart and robust procedures implemented to ensure the integrity, reliability and validity of the study data eliminated the necessity for a Data Safety Monitoring Board. All authors collectively resolved to submit the paper for publication and accept accountability for the precision and comprehensiveness of the analysis.

Population

A total of 108 eligible participants were enrolled, consisting of adults aged 18–65 years, female or male (self-reported) and with a clinical history of SAR with or without allergic conjunctivitis in the previous two pollen seasons[39]. The inclusion criteria included a positive serum weed-pollen-specific IgE test at the screening period, an adequate degree of exposure to pollen, history of being inadequately controlled by intranasal corticosteroids or more medications for SAR, at least 6 points for the baseline a.m. iTNSS and the average of the last 6 rTNSS assessments before randomization, at least 2 points for the nasal congestion score and score for any individual nasal symptom, and a baseline peripheral blood eosinophil count of at least 300 cells μl^{-1}. The application of all these inclusion criteria characterized the study population as being composed of individuals with moderate-to-severe SAR despite receiving SoC[12]. The key exclusion criteria included the recent use of any biologic and active nasal disease other than SAR that could potentially affect the efficacy assessment, such as acute or chronic sinusitis, non-AR, and upper respiratory tract or sinus infection. The details of the inclusion and exclusion criteria are available in Supplementary Methods.

Randomization and masking

Participants were randomized in a 1:1 ratio to receive either stapokibart or the matching placebo. Randomization was stratified by study site via an interactive web response system. A randomization statistician generated a randomization list of participants using the stratified block randomization method with a block size of 4, using the SAS, version 9.4. All participants were enrolled by investigators and specified personnel at each center, and assigned to the treatment group via the interactive web response system.

Stapokibart and a matching placebo were provided by the manufacturer in visually indistinguishable vials, and labels with the medication code were applied to the vials by statisticians and specified personnel blinded to the medication and not involved with the study. Similarly, investigators, site staff and all participants were also blinded to treatment assignment in a double-blind manner. The randomization statistician did not participate in any other work related to this study and was not allowed to disclose any information regarding randomization lists to any investigators or personnel involved with the study. Emergency unblinding or pharmacovigilance unblinding were not performed during the study.

Procedures

All patients received 100 µg of mometasone furoate nasal spray in each nostril and 10 mg of oral loratadine once daily during the run-in period (1 week) and throughout the treatment period (4 weeks). On day 1, participants received a loading dose (600 mg) of stapokibart or a matching placebo. In the subsequent 4 weeks, 300 mg of stapokibart or placebo was administered every 2 weeks. The study treatments were administered by subcutaneous injection by designated nurses at the outpatient clinic at each center throughout the 4-week treatment period. Patient visits were scheduled weekly from randomization until week 4, followed by follow-up visits at weeks 8 and 12.

Patients recorded self-assessed AR symptom scores daily in a paper diary during the entire 4-week treatment period. The total nasal symptom score (TNSS; range 0–12 points) was calculated as the sum of scores for nasal congestion, runny nose, nasal itching and sneezing, and the total ocular symptom score (TOSS; range 0–9 points) was the sum of scores for itching and burning eyes, tearing and watering eyes, and eye redness. Each symptom was scored from 0 (no symptom) to 3 points (severe). The rTNSS and rTOSS were used as assessments concerning symptom severity within the preceding 12-h period with the a.m. assessment administered before background treatment and the p.m. assessment conducted at a fixed time approximately 12 h post-treatment. The daily rTNSS and rTOSS were calculated as the average of the p.m. score obtained during the day and the a.m. score obtained on the following day. The a.m. iTNSS and iTOSS were self-assessed by each patient once daily in the morning before treatment. The severity scales used for rTNSS, iTNSS, rTOSS and iTOSS are shown in Supplementary Information ('Clinical Study Protocol'). The nasal and ocular related total and individual symptom scores of the baseline were determined as the average of the last six non-missing scores (p.m.: day −3 to day −1; a.m.: day −2, day −1 and day 1) before randomization. RQLQ was used to investigate patients' QOL at weeks 0, 2 and 4.

Outcomes

The primary efficacy endpoint was the mean change from baseline in daily rTNSS over a 2-week treatment period.

Secondary endpoints included mean change from baseline in rTNSS over 4 weeks of treatment; mean changes from baseline in rTNSS (a.m. and p.m. assessments), a.m. iTNSS, rTOSS (daily, a.m. and p.m. assessments), a.m. iTOSS and individual nasal (nasal congestion, runny nose, nasal itching and sneezing) and ocular (itching and burning eyes, tearing and watering eyes, and eye redness) symptom scores (daily, a.m. and p.m. assessments) over the 2-week and 4-week treatment; mean percentage changes from baseline in daily rTNSS, a.m. iTNSS, daily

rTOSS and a.m. iTOSS over the 2-week and 4-week treatment; change from baseline in the RQLQ score and the proportion of participants achieving ≥0.5 reduction from baseline in the RQLQ score, defined as the MCID[19] at weeks 2 and 4; time to onset of action; time to maximum effect over the 2- and 4-week treatment periods; AUCs of change from baseline in daily rTNSS over the 2- and 4-week treatment; and number of days during which participants had no or mild (score of ≤1 point) nasal and ocular symptoms over the 2- and 4-week treatment periods. The assessment details of efficacy endpoints are provided in Supplementary Methods.

Safety assessments involved AEs, vital signs, physical examination, 12-lead electrocardiogram and laboratory tests. AEs were coded according to the Medical Dictionary for Regulatory Activities.

Pharmacokinetics assessment was based on serum stapokibart concentrations. PD assessments included analysis of median change and percentage change from baseline in concentrations of serum human TARC, plasma eotaxin-3 and serum total IgE, and in blood eosinophil counts and percentages. The assessments of immunogenicity included assessment of anti-drug and neutralizing antibodies that may have developed during treatment. Blood samples for the assessment of pharmacokinetics, TARC, eotaxin-3 and total IgE were collected at weeks 0, 1, 2, 4 and 12; those for the analysis of blood eosinophil counts were collected at weeks 0, 2, 4, 8 and 12; and those for the analysis of immunogenicity were collected at weeks 0, 4 and 12.

Post hoc efficacy outcomes included the proportion of participants with no or mild nasal symptoms (all individual symptom scores ≤1 point) at each day during treatment.

Detection of serum stapokibart concentration and PD markers

Stapokibart serum concentration was quantified using an enzyme-linked immunosorbent assay (ELISA) with IL-4Rα as the capture reagent and a mouse anti-human IgG4 Fc-HRP antibody (catalog number 9200-05, Southern Biotech) for detection. Total serum IgE levels were measured via electrochemiluminescence immunoassay on a Cobas e601 analyzer (Roche), using the IgE II commercial kit (reference: 04827031190, Roche). Serum TARC concentrations were determined using the Quantikine ELISA Human CCL17/TARC Immunoassay kit (catalog number SDN00, R&D Systems). Plasma eotaxin-3 levels were analyzed with the Ella automated immunoassay system (catalog number SPCKC-PS-000486, Protein Simple).

Exploratory biomarker detection in serum and nasal secretions

Serum samples separated from peripheral whole blood and nasal secretions were collected at baseline and weeks 2, 4 and 12. The quantification of serum and nasal secretion protein biomarkers was conducted centrally. Samples were transported via a cold chain using dry ice and stored at temperatures below −60 °C. Nasal secretions were collected bilaterally from each patient. A scissored postoperative Merocel sinus sponge (2 × 0.7 × 0.5 cm; reference: 400402, Medtronic Xomed) was inserted into the superior fornix of each nostril parallel to the sagittal plane and maintained for 5–10 min. The sponge was carefully retrieved using Bayonet forceps and transferred into a 15-ml centrifuge tube containing 1 ml of 0.9% saline solution for secretion extraction. The sponges were then stored at 4 °C for 2 h before being transferred to a 5-ml syringe and centrifuged at 1,500 *g* for 15 min at 4 °C. Finally, the supernatants were collected and stored in aliquots at −80 °C until further analysis.

The sIgE levels for *Ambrosia* (catalog number R03412), *Artemisia* (catalog number R01512) and *Chenopodium* (catalog number R03506) (all from Haike Biotech) in both serum and nasal secretions were quantified using the ALLEOS 2000 system (HYCOR Biomedical). The sIgE levels for *Humulus* (catalog number E4WGY, Pharmacia Biotech) were assessed using the UniCAP system (Pharmacia Diagnostics). Other immunoglobulins, including total and *Artemisia*-specific IgA (catalog number 88-50600-88), IgG (catalog number 88-50550-88) and IgG4 (catalog number 88-50590-22), as well as total IgG2 (catalog number 88-50570-22), were quantified in both serum and nasal secretions using commercially available ELISA kits (all from Thermo Fisher Scientific). The assay plates were prepared with a coating of 5 μg ml^{-1} *Artemisia* antigen.

Serum and nasal secretion concentrations of CLC (catalog number SEC387Hu, Cloud-Clone) and histamine (catalog number CEA927Ge, Cloud-Clone), as well as CST1 (catalog number ARG81620, Arigobio) and apolipoprotein A-IV (catalog number ab214567, Abcam) in nasal secretions, were quantified using commercially available ELISA kits. The biomarkers detected in nasal secretions were normalized relative to the total protein concentration.

Nasal brushing RNA-seq processing and analysis

Bilateral nasal brushing was collected by swabbing the inferior turbinate of each nostril with a cytology brush. The brush samples were then placed into a 15-ml centrifuge tube containing 1 ml of RNAiso Plus (catalog number 9109, Takara Bio) and subsequently frozen at −80 °C. Total RNA was isolated using an RNeasy Mini Kit (catalog number 74106, Qiagen). RNA-seq libraries were constructed using the SMARTer Stranded Total RNA-Seq Kit v2 (catalog number 63441, Takara Bio). The purified libraries were quantified using a Qubit 2.0 Fluorometer (Life Technologies) and validated for insert size and molar concentration using an Agilent 2100 Bioanalyzer (Agilent Technologies). Cluster generation was performed on a cBot instrument with the library diluted to a final concentration of 10 pM, followed by sequencing on the Illumina NovaSeq 6000 platform (Illumina). Raw sequencing reads were preprocessed to remove rRNA reads, adapter sequences, short fragments and other low-quality reads. The cleaned reads were aligned to the human GRCh38 reference genome using HISAT2 software (version 2.0.4)[40], allowing up to two mismatches. Following genome alignment, StringTie (version 1.3.3b)[41] was used to estimate transcript counts with a reference annotation.

Differential gene expression analysis of nasal brushing RNA-seq count data was conducted using the limma/voom pipeline (version 3.54.2)[42]. The advantage of limma lies in its capability to incorporate a subject as a random effect, thereby accounting for baseline differences among individuals, which is crucial in this clinical context. The differential expression of genes induced by the treatment was evaluated by comparing the posttreatment time point to the baseline, as well as conducting intergroup comparisons at each time point. Genes showing an absolute value $\log_2$(fold change) > 2 and a Benjamini–Hochberg false discovery rate (FDR)-adjusted q-value < 0.05 were identified as differentially expressed. Min–max normalization was used to calculate Z-scores, thereby enhancing the visualization in heatmaps produced using the pheatmap package (version 4.9.0.2). Gene set enrichment analysis (GSEA) was conducted to evaluate the enrichment of differentially expressed genes in pathways from the MSigDB Hallmark and other pathway lists[43] using the clusterProfiler package (version 4.9.0.2). All statistical and computational analyses were performed in R (version 4.2.0). Scripts for RNA-seq downstream analysis can be found at https://doi.org/10.5281/zenodo.14958556 (ref. 44). No custom code was developed for this study.

Statistical analysis

Based on the results from the MERAK trial (NCT05470647)[18], the mean difference between the stapokibart and placebo groups in the primary endpoint (mean change from baseline in daily rTNSS over the 2-week treatment) was estimated at −1.50, with a common standard deviation (s.d.) of 2.43. With the two-sided $\alpha = 0.05$, a dropout rate of about 10% and a power of 85%, a total of 108 participants were planned to be included in this trial (allocation ratio 1:1).

Efficacy analyses were performed in the efficacy analysis set, defined as all randomized participants who have received at least

one dose of the study drug and recorded at least one efficacy data. The primary endpoint was analyzed using the analysis of covariance (ANCOVA) model, with the mean change from baseline in daily rTNSS over the 2-week treatment as the dependent variable and baseline rTNSS, study site and treatment group as covariates. The difference in LS means and the corresponding 95% CI were calculated together with the *P* value. All the data of the a.m. and p.m. rTNSS and rTOSS in the 4 weeks of treatment were collected, and thus, there was no missing data-handling issue for rTNSS and rTOSS. Missing data for RQLQ (one patient in the placebo group at week 2) was imputed by the LOCF method. To evaluate the center effect, sensitivity analysis was performed using ANCOVA with baseline rTNSS, study site, treatment group and interaction between study site and treatment group as covariates. In addition, subgroup analyses were performed by sex, weight, BMI, baseline daily rTNSS and baseline specific IgE classification. The other continuous efficacy endpoints over 2 or 4 weeks of treatment were analyzed with the same model.

The fixed-sequence step-down multiplicity procedure was applied to control the overall type I error for testing primary and selected secondary endpoints at a two-side 0.05 significance level. The widths of the confidence intervals for the between-group differences in other secondary endpoints were not adjusted for multiplicity. More details about statistical methods are described in Supplementary Methods.

The change and percentage change from baseline in continuous PD and exploratory biomarkers in serum and nasal secretions were descriptively summarized by group and group comparison was conducted by Wilcoxon rank-sum test.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The data supporting the findings of this trial are available in the article and Supplementary Information. The individual participant data are not accessible to the public owing to constraints related to patient confidentiality. All requests for additional data sharing should be directed to and reviewed by the lead clinical center, Beijing Tongren Hospital, as well as the trial sponsor, Keymed Biosciences (Chengdu) Co., Ltd. These entities will evaluate whether the requests are subject to any intellectual property or confidentiality restrictions. Requests may be submitted to Pub_data_request@keymedbio.com. A signed data access agreement with the sponsor is required before accessing shared data. Requests will be responded to in 3 months.

Raw sequencing data have been uploaded to the Genome Sequence Archive in the National Genomics Data Center, China National Center for Bioinformation/Beijing Institute of Genomics, Chinese Academy of Sciences, under accession HRA009883, and the processed sequencing data have been uploaded to the OMIX, China National Center for Bioinformation/Beijing Institute of Genomics, Chinese Academy of Sciences, under accession OMIX008443. Approval for discretionary access control is required owing to policy constraints. Researchers may submit applications via the website, and typically, the review process by the database administrator and discretionary access control spans several weeks. The GRCh38 human reference genome datasets were procured from the GENCODE repository (http://www.gencodegenes.org). Gene sets were retrieved from the Molecular Signatures Database (https://www.gsea-msigdb.org/gsea/msigdb/human/collections.jsp#H). Source data are provided with this paper.

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Author contributions

L.Z. and C.W. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Y.Z., J. Li, M.W., Xian Li, B.Y., J. Liu, L.S., Z.C., Y.F., Weiwei Liu, Z. Xu, R.M., X.G., Wen Liu, J.X., X.R., Xuezhong Li, X.S., Y.Y., Y.W., Z. Xing, F.Q., J.P., Y.S., F.S., X.C., H.Y., G.Z., B.C., C.W. and L.Z. contributed to the study design, concept development, and acquisition, analysis and interpretation of data. Y.Z., J. Li, M.W., Xian Li, B.Y., H.Y., G.Z., B.C., C.W. and L.Z. drafted the paper. G.Z. performed statistical analyses. All authors performed critical revision of the paper for important intellectual content.

Competing interests

B.C. is a shareholder of Keymed Biosciences (Chengdu) Co., Ltd. G.Z. is an employee and shareholder of Keymed Biosciences (Chengdu) Co., Ltd. H.Y. is an employee of Keymed Biosciences (Chengdu) Co., Ltd. The other authors declare no competing interests.

Additional information

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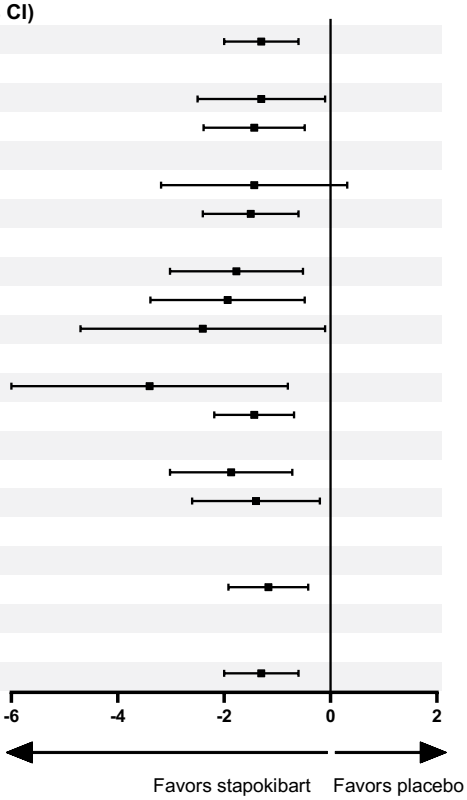
	Stapokibart (n)	Placebo (n)	LS mean difference (95% CI)
Overall	50	58	-1.3 (-2.0 to -0.6)
Sex			
Male	21	30	-1.3 (-2.5 to -0.1)
Female	29	28	-1.4 (-2.4 to -0.5)
Body weight, kg			
<60	20	13	-1.4 (-3.2 to 0.3)
≥60	30	45	-1.5 (-2.4 to -0.6)
Body mass index, kg m^{-2}			
<24	27	22	-1.8 (-3.0 to -0.5)
≥24 to <28	15	22	-1.9 (-3.4 to -0.5)
≥28	8	14	-2.4 (-4.7 to -0.1)
Baseline rTNSS			
<8	10	10	-3.4 (-6.0 to -0.8)
≥8	40	48	-1.4 (-2.2 to -0.7)
Baseline specific IgE			
Grade <4	26	33	-1.9 (-3.0 to -0.7)
Grade ≥4	24	25	-1.4 (-2.6 to -0.2)
ADA			
Positive	3	0	
Negative	47	58	-1.2 (-1.9 to -0.4)
Nab			
Positive	0	0	
Negative	50	58	-1.3 (-2.0 to -0.6)



Extended Data Fig. 1 | Subgroup analysis of mean change from baseline in daily rTNSS over 2-week treatment. Mean change from baseline in daily rTNSS over 2-week treatment in each subgroup was analyzed using the Analysis of Covariance (ANCOVA) model, with the baseline daily rTNSS, study site, and treatment group as covariates. Difference in LS means and the corresponding 95% CI were calculated. Baseline specific IgE: grade <4 refers to a concentration <17.5 kUA l^{-1}; grade ≥4 refers to a concentration ≥17.5 kUA l^{-1}. The ADA-positive subgroup includes all subjects with post-treatment present ADA or post-treatment enhanced ADA, and the ADA-negative subgroup included all subjects with either negative ADA or pre-existing ADA. The Nab-positive subgroup included all subjects with post-treatment Nab positivity, and the Nab-negative subgroup included all subjects with post-treatment Nab negativity. ADA, anti-drug antibody; CI, confidence interval; IgE, immunoglobulin E; LS, least-squares; Nab, neutralizing antibody; rTNSS, reflective total nasal symptom score.

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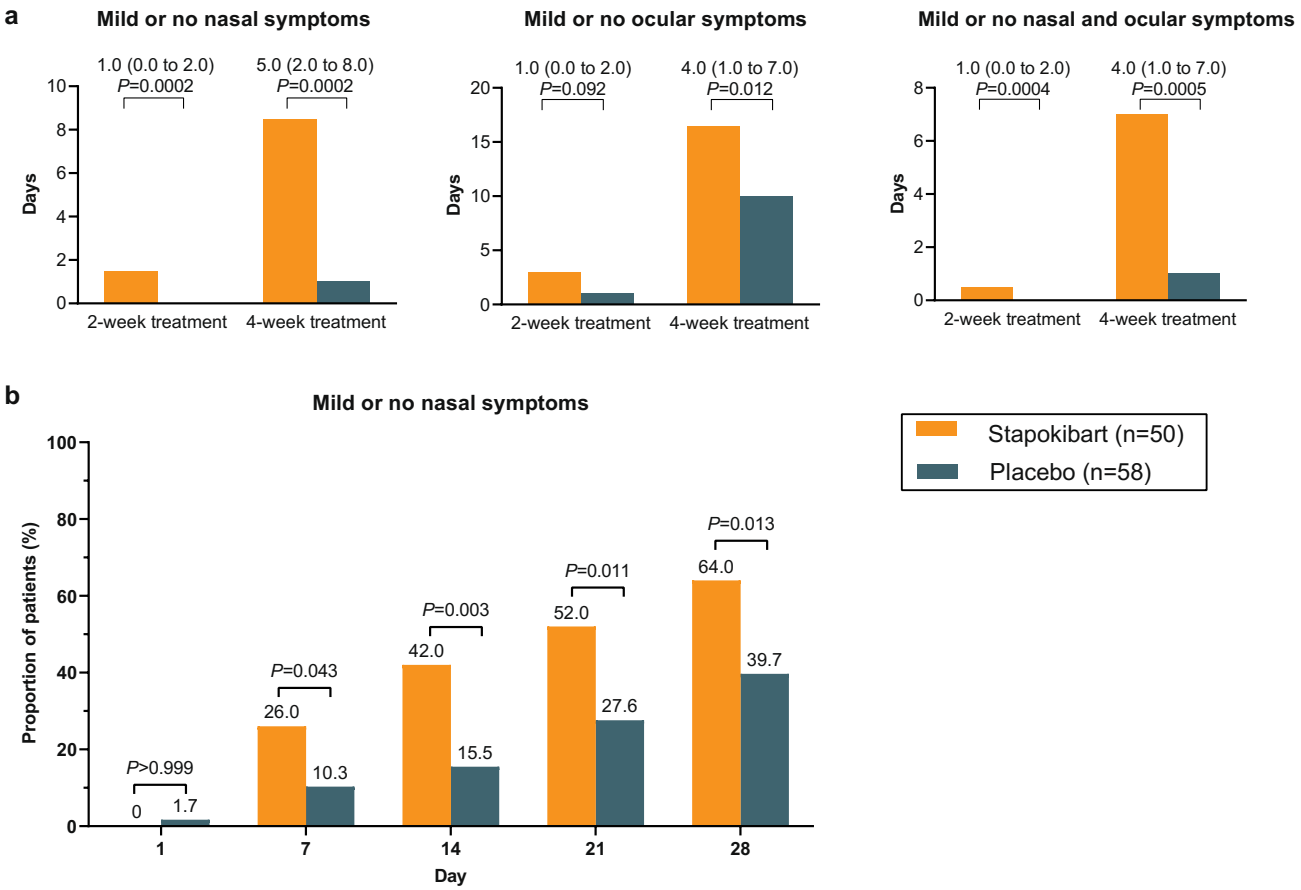

Extended Data Fig. 2 | Evaluation of mild or no symptoms. a, Median duration of mild or no nasal, ocular symptoms, and nasal and ocular symptoms over 2-week and 4-week treatment. The number of days with mild or no symptoms over 2 or 4 weeks of treatment was summarized for 50 patients in the stapokibart group and 58 in the placebo group, and the difference between groups was analyzed by Hodges-Lehmann method, together with its 95% CI. **b**, Proportion of patients with mild or no nasal symptoms at days 1, 7, 14, 21, and 28 (post-hoc analysis). Mild or no nasal symptoms were defined as all individual symptom scores of ≤ 1 point. The *P* values were two-sided and nominal, without adjustments for multiple comparisons.

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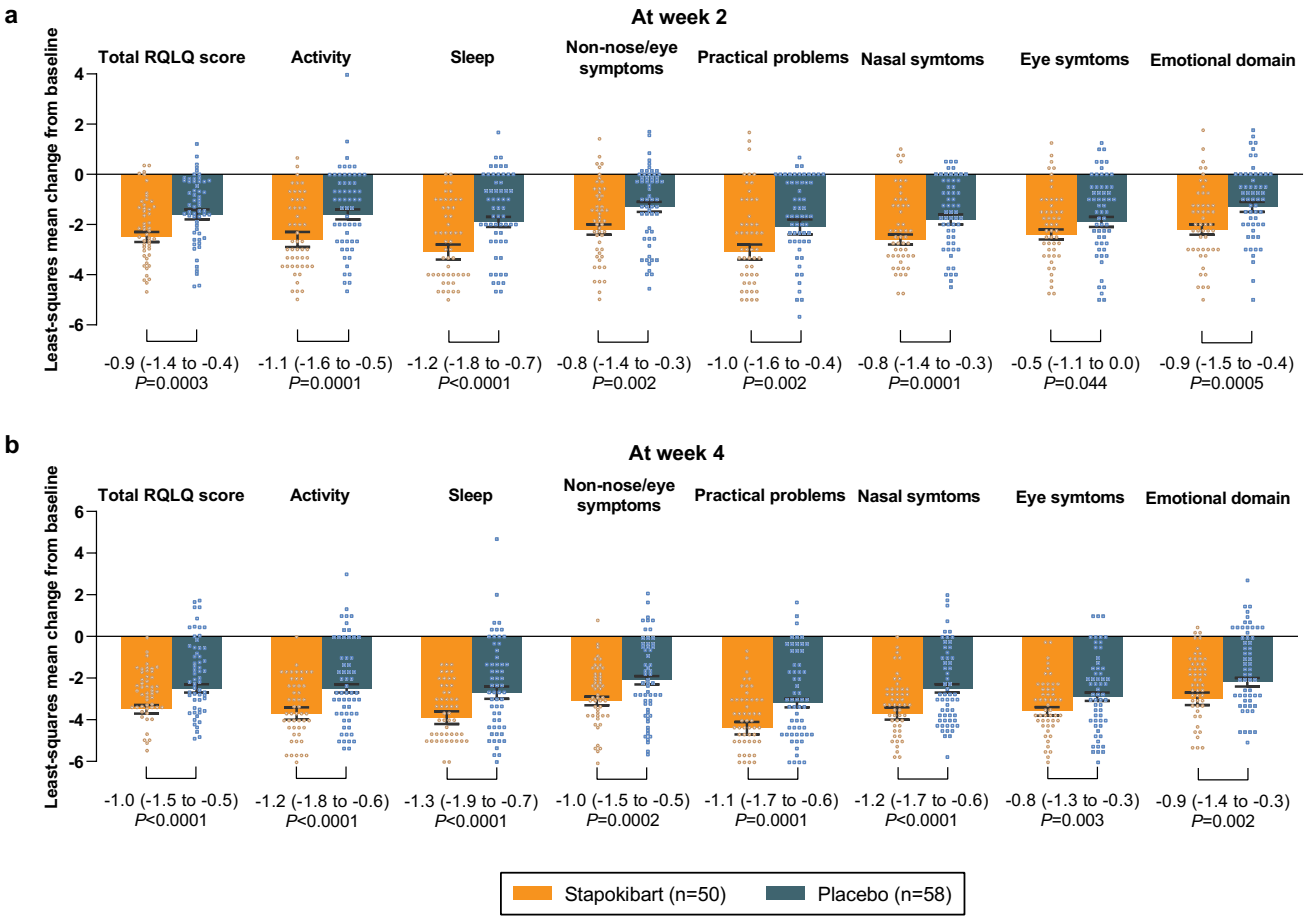

Extended Data Fig. 3 | Change from baseline in total RQLQ score and individual domains scores at 2-week (a) and 4-week treatment (b). Least-squares mean changes are shown for 50 patients in the stapokibart group and 58 in the placebo group; error bars indicate standard errors. Data are shown as differences in median value (95% confidence interval). Scatter points indicate change from baseline value for individual patient. The total RQLQ is used to assess the quality of life status in adult patients with rhinoconjunctivitis; total scores range from 0 to 6, with lower scores indicating a higher quality of life. The individual domain ranges from 0 (no trouble) to 6 points (extreme trouble). Data was analyzed using the Analysis of Covariance (ANCOVA) model, with the baseline RQLQ score, study site, and treatment group as covariates. Missing data for RQLQ was imputed by last observation carried forward method. Changes from baseline in total RQLQ score at week 2 and week 4 were multiplicity-tested efficacy outcomes with type I error controlled by step-down test procedures. *P* values for individual domains scores were two-sided and nominal, without adjustments for multiple comparisons. RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.

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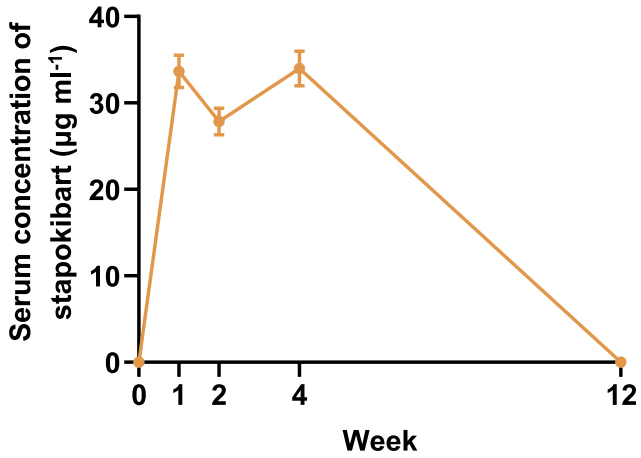

No. of patients					
Stapokibart	50	50	50	48	49

Extended Data Fig. 4 | Mean serum concentration of stapokibart over the course of the study period. Error bars denote standard errors.

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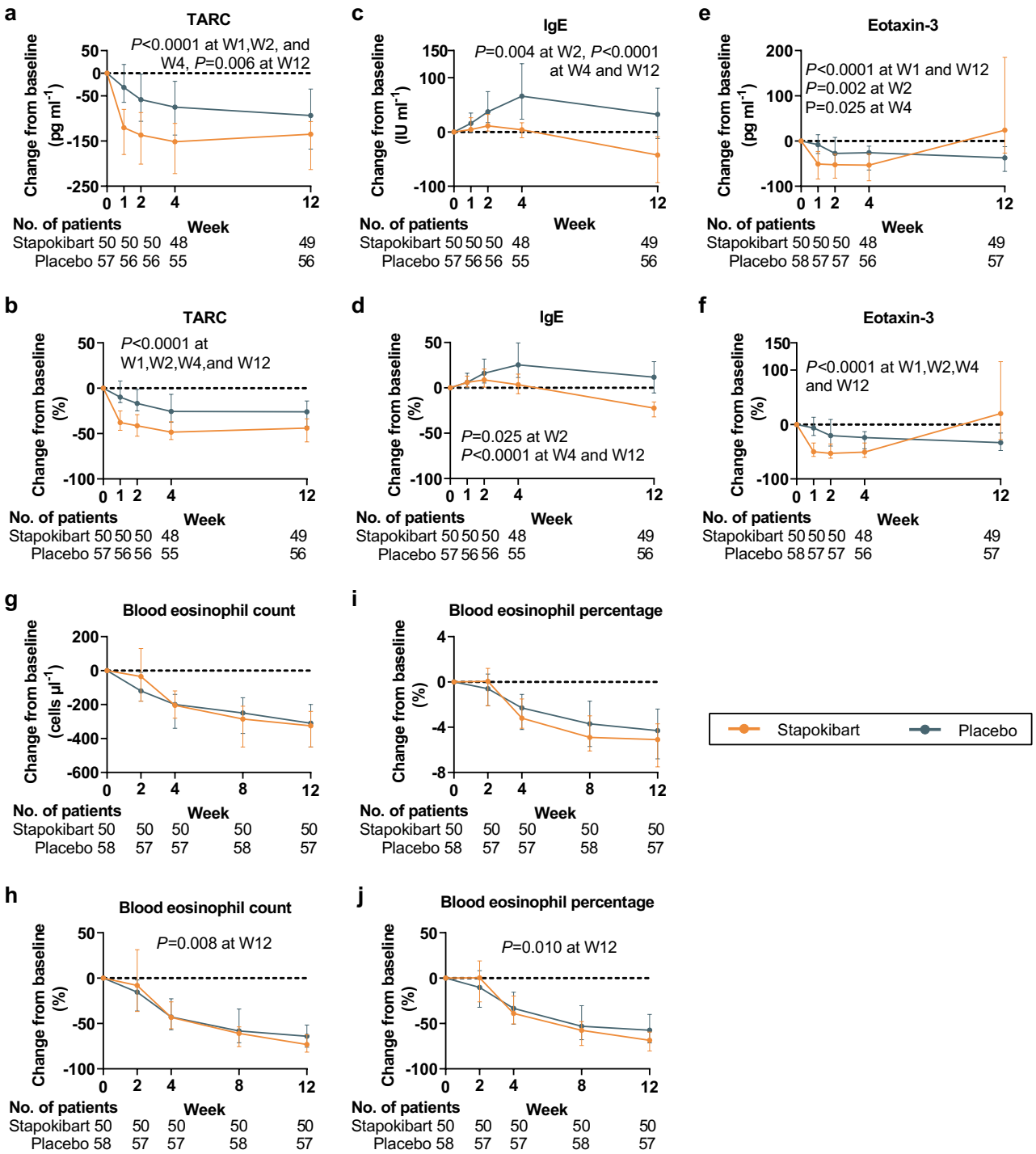

Extended Data Fig. 5 | Median change and percentage change from baseline over time in pharmacodynamic markers. a, b, Serum thymus and activation-regulated chemokine (TARC). **c, d**, Serum total immunoglobulin E (IgE). **e, f**, Plasma eotaxin-3. **g, h**, Blood eosinophil count. **i, j**, Blood eosinophil percentage. Comparisons between groups were analyzed using two-sided Wilcoxon rank-sum test, and *P* values were nominal without adjustments for multiple comparisons. Error bars denote interquartile ranges.

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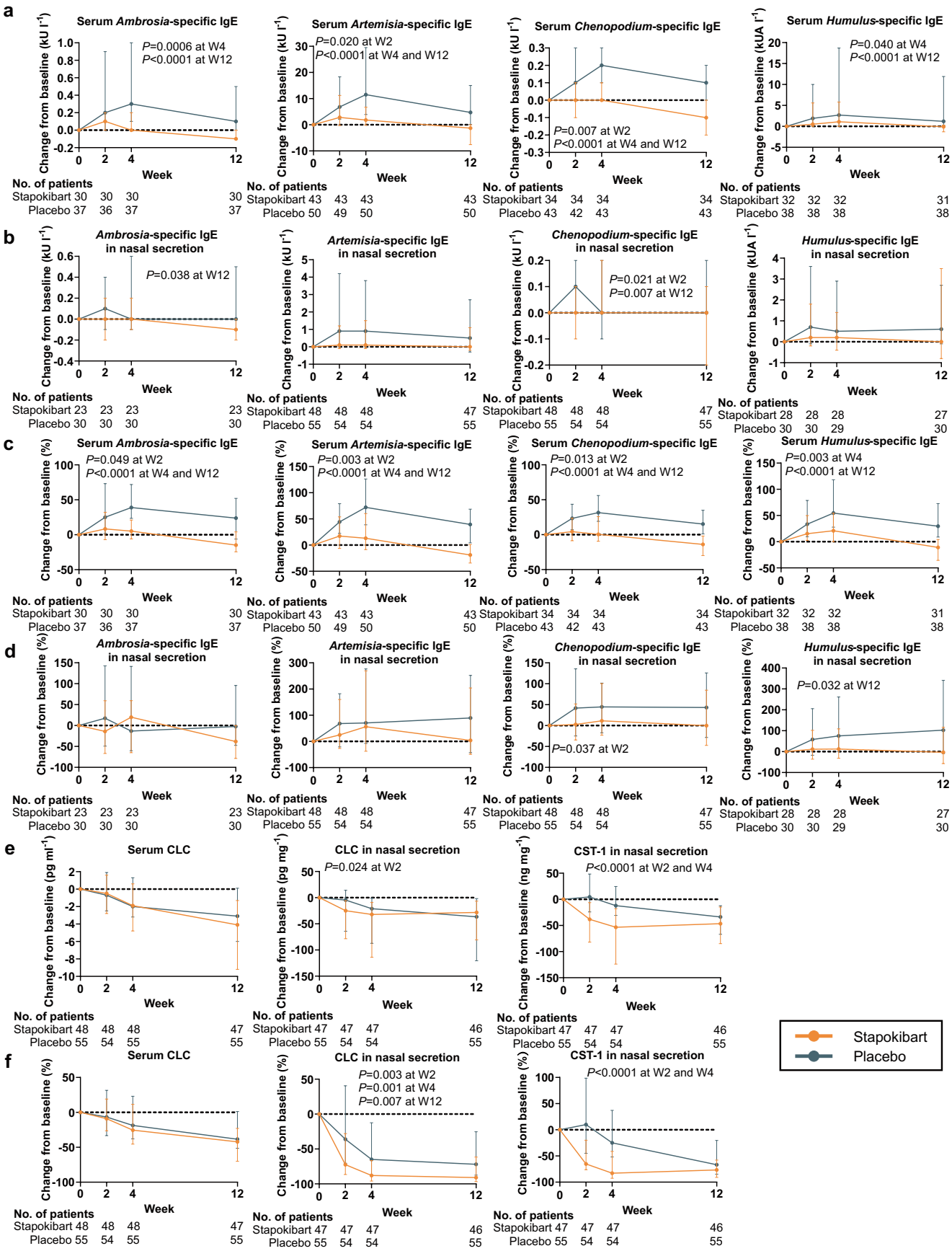

Extended Data Fig. 6 | See next page for caption.

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Extended Data Fig. 6 | Median change and percentage change from baseline over time in exploratory biomarkers in serum and nasal secretion. Changes of four grass pollen-specific immunoglobulin E (sIgE) in serum (**a, c**) and nasal secretion (**b, d**) were analyzed in patients with positive baseline sIgE (≥ 0.1 kU [kUA] l^{-1}). **e, f**, Charcot-Leyden Crystal Protein (CLC) in serum and nasal secretion; cystatin SN (CST-1) in nasal secretion. Comparisons between groups were analyzed using two-sided Wilcoxon rank-sum test, and *P* values were nominal without adjustments for multiple comparisons. Error bars denote interquartile ranges.

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Extended Data Table 1 | Effect of stapokibart and placebo on nasal symptoms over 2- and 4-week treatment

Outcomes[a]	Stapokibart (n = 50) LS Mean (s.e.m.)	Placebo (n = 58) LS Mean (s.e.m.)	LS mean difference (95% CI)	*P* value
Mean change from baseline in daily rTNSS[b]				
2-week treatment	-3.6 (0.3)	-2.3 (0.3)	-1.3 (-2.0 to -0.6)	0.0008
4-week treatment	-4.9 (0.4)	-3.2 (0.4)	-1.7 (-2.5 to -0.8)	0.0002
Mean percentage change from baseline in daily rTNSS, %				
2-week treatment	-38.4 (3.9)	-24.8 (3.5)	-13.5 (-21.9 to -5.1)	0.002
4-week treatment	-53.0 (4.4)	-35.6 (3.9)	-17.4 (-26.8 to -8.0)	0.0004
Mean change from baseline in a.m. rTNSS				
2-week treatment	-3.7 (0.4)	-2.4 (0.3)	-1.3 (-2.1 to -0.5)	0.001
4-week treatment	-5.1 (0.4)	-3.4 (0.4)	-1.7 (-2.5 to -0.8)	0.0002
Mean change from baseline in p.m. rTNSS				
2-week treatment	-3.4 (0.4)	-2.1 (0.3)	-1.3 (-2.0 to -0.5)	0.0009
4-week treatment	-4.7 (0.4)	-3.1 (0.4)	-1.7 (-2.5 to -0.8)	0.0002
Mean change from baseline in a.m. iTNSS				
2-week treatment	-3.4 (0.4)	-2.3 (0.3)	-1.2 (-1.9 to -0.4)	0.003
4-week treatment	-4.8 (0.4)	-3.3 (0.3)	-1.5 (-2.3 to -0.7)	0.0004
Mean percentage change from baseline in a.m. iTNSS, %				
2-week treatment	-39.0 (4.2)	-25.9 (3.7)	-13.1 (-22.0 to -4.1)	0.005
4-week treatment	-53.7 (4.5)	-37.3 (4.0)	-16.4 (-25.9 to -6.9)	0.0009
Mean change from baseline in individual nasal symptom				
Nasal congestion				
2-week treatment	-1.0 (0.1)	-0.5 (0.1)	-0.5 (-0.7 to -0.3)	<0.0001
4-week treatment	-1.4 (0.1)	-0.7 (0.1)	-0.6 (-0.9 to -0.4)	<0.0001
Runny nose				
2-week treatment	-0.9 (0.1)	-0.5 (0.1)	-0.3 (-0.5 to -0.2)	0.0007
4-week treatment	-1.2 (0.1)	-0.8 (0.1)	-0.4 (-0.6 to -0.2)	0.0004
Nasal itching				
2-week treatment	-0.8 (0.1)	-0.6 (0.1)	-0.2 (-0.5 to 0.0)	0.026
4-week treatment	-1.1 (0.1)	-0.8 (0.1)	-0.4 (-0.6 to -0.1)	0.003
Sneezing				
2-week treatment	-0.9 (0.1)	-0.7 (0.1)	-0.2 (-0.4 to 0.0)	0.088
4-week treatment	-1.2 (0.1)	-0.9 (0.1)	-0.3 (-0.5 to -0.1)	0.017
Mean change from baseline in a.m. individual nasal symptom				
Nasal congestion				
2-week treatment	-1.1 (0.1)	-0.5 (0.1)	-0.6 (-0.8 to -0.4)	<0.0001
4-week treatment	-1.4 (0.1)	-0.7 (0.1)	-0.7 (-0.9 to -0.4)	<0.0001
Runny nose				
2-week treatment	-1.0 (0.1)	-0.6 (0.1)	-0.4 (-0.6 to -0.2)	0.0009
4-week treatment	-1.3 (0.1)	-0.9 (0.1)	-0.4 (-0.7 to -0.2)	0.0005
Nasal itching				
2-week treatment	-0.8 (0.1)	-0.6 (0.1)	-0.2 (-0.4 to 0.0)	0.072
4-week treatment	-1.1 (0.1)	-0.8 (0.1)	-0.3 (-0.5 to -0.1)	0.010
Sneezing				
2-week treatment	-0.9 (0.1)	-0.7 (0.1)	-0.2 (-0.4 to 0.0)	0.120
4-week treatment	-1.2 (0.1)	-1.0 (0.1)	-0.3 (-0.5 to 0.0)	0.022
Mean change from baseline in p.m. individual nasal symptom				
Nasal congestion				
2-week treatment	-1.0 (0.1)	-0.5 (0.1)	-0.5 (-0.7 to -0.3)	<0.0001
4-week treatment	-1.3 (0.1)	-0.7 (0.1)	-0.6 (-0.8 to -0.3)	<0.0001
Runny nose				
2-week treatment	-0.8 (0.1)	-0.5 (0.1)	-0.3 (-0.5 to -0.1)	0.001
4-week treatment	-1.1 (0.1)	-0.7 (0.1)	-0.4 (-0.6 to -0.2)	0.0004
Nasal itching				
2-week treatment	-0.8 (0.1)	-0.5 (0.1)	-0.3 (-0.5 to -0.1)	0.016
4-week treatment	-1.1 (0.1)	-0.7 (0.1)	-0.4 (-0.6 to -0.2)	0.002
Sneezing				
2-week treatment	-0.8 (0.1)	-0.6 (0.1)	-0.2 (-0.4 to 0.0)	0.057
4-week treatment	-1.2 (0.1)	-0.9 (0.1)	-0.3 (-0.5 to -0.1)	0.010

[a]All nasal symptom-related endpoints were analyzed using the Analysis of Covariance (ANCOVA) model, with the baseline value of the given outcome, study site, and treatment group as covariates. Difference in LS means and the corresponding 95% CI were calculated. Mean changes from baseline in daily rTNSS at week 2 and week 4 were multiplicity-tested efficacy outcomes with type I error controlled by step-down test procedures. *P* values for other outcomes were two-sided and nominal, without adjustments for multiple comparisons. If the number of days with valid data over the 2/4 weeks of treatment was less than 12 days (14 × 0.8=11.2)/23 days (28 × 0.8=22.4), the missing value was imputed by the last observation carried forward method. [b] rTNSS is calculated by summing up the individual scores for nasal congestion, runny nose, nasal itching and sneezing reported over the past 12 hours; separate scores are obtained for morning (a.m. rTNSS), evening (p.m. rTNSS) and the instantaneous morning before treatment (a.m. iTNSS); the individual nasal symptom score ranges 0 (no symptom) to 3 points (severe); total scores range from 0 to 12, with lower scores indicating less severe nasal symptoms. LS, least-squares; s.e.m., standard error of the mean; CI, confidence interval; rTNSS, reflective total nasal symptom score; iTNSS, instantaneous total nasal symptom score.

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Extended Data Table 2 | Area under the curve of change from baseline to weeks 2 and 4 in daily rTNSS

Outcome[a]	Stapokibart (n = 50)	Placebo (n = 58)	LS mean difference (95% CI)	*P* value
	LS mean (s.e.m.)	LS mean (s.e.m.)		
2-week treatment	-52.0 (4.9)	-33.0 (4.4)	-19.1 (-29.6 to -8.6)	0.0005
4-week treatment	-140.5 (11.2)	-93.1 (10.0)	-47.4 (-71.2 to -23.6)	0.0002

[a]The endpoints were analyzed using the Analysis of Covariance (ANCOVA) model, with the baseline daily rTNSS, study site, and treatment group as covariates. Difference in LS means and the corresponding 95%CI were calculated. *P* values were two-sided and nominal, without adjustments for multiple comparisons. All the data of a.m. and p.m. rTNSS in the 4 weeks of treatment were collected and thus no missing data handling issue for rTNSS. rTNSS, reflective total nasal symptom score; LS, least-squares; s.e.m., standard error of the mean; CI, confidence interval.

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Extended Data Table 3 | Effect of stapokibart and placebo on ocular symptoms over 2- and 4- week treatment

Outcome[a]	Stapokibart (n = 50)	Placebo (n = 58)	LS mean difference (95% CI)	*P* value
	LS mean (s.e.m.)	LS mean (s.e.m.)		
Mean change from baseline in daily rTOSS[b]				
2-week treatment	-2.6 (0.3)	-1.9 (0.3)	-0.7 (-1.3 to 0.0)	0.039
4-week treatment	-3.7 (0.3)	-2.9 (0.3)	-0.8 (-1.4 to -0.2)	0.016
Mean percentage change from baseline in daily rTOSS, %				
2-week treatment	-36.4 (5.7)	-28.4 (5.1)	-8.0 (-20.3 to 4.3)	0.200
4-week treatment	-54.2 (5.6)	-44.3 (5.0)	-9.9 (-22.0 to 2.2)	0.107
Mean change from baseline in a.m. rTOSS				
2-week treatment	-2.7 (0.3)	-2.0 (0.3)	-0.7 (-1.4 to -0.1)	0.030
4-week treatment	-3.9 (0.3)	-3.0 (0.3)	-0.8 (-1.5 to -0.2)	0.014
Mean change from baseline in p.m. rTOSS				
2-week treatment	-2.4 (0.3)	-1.8 (0.3)	-0.6 (-1.2 to 0.0)	0.053
4-week treatment	-3.5 (0.3)	-2.8 (0.3)	-0.8 (-1.4 to -0.1)	0.019
Mean change from baseline in a.m. iTOSS				
2-week treatment	-2.5 (0.3)	-1.8 (0.3)	-0.7 (-1.3 to -0.1)	0.028
4-week treatment	-3.6 (0.3)	-2.8 (0.3)	-0.8 (-1.4 to -0.2)	0.009
Mean percentage change from baseline in a.m. iTOSS, %				
2-week treatment	-36.8 (5.6)	-28.0 (5.0)	-8.8 (-20.9 to 3.3)	0.150
4-week treatment	-55.6 (5.4)	-44.7 (4.8)	-10.9 (-22.5 to 0.6)	0.064
Mean change from baseline in individual ocular symptom				
Itching/burning eyes				
2-week treatment	-0.8 (0.1)	-0.7 (0.1)	-0.2 (-0.4 to 0.0)	0.092
4-week treatment	-1.3 (0.1)	-1.0 (0.1)	-0.2 (-0.5 to 0.0)	0.030
Tearing/watering eyes				
2-week treatment	-0.9 (0.1)	-0.6 (0.1)	-0.3 (-0.5 to 0.0)	0.020
4-week treatment	-1.2 (0.1)	-0.9 (0.1)	-0.3 (-0.5 to -0.1)	0.010
Eye redness				
2-week treatment	-0.9 (0.1)	-0.7 (0.1)	-0.2 (-0.4 to 0.0)	0.062
4-week treatment	-1.2 (0.1)	-1.0 (0.1)	-0.3 (-0.5 to 0.0)	0.026
Mean change from baseline in a.m. individual ocular symptom				
Itching/burning eyes				
2-week treatment	-0.9 (0.1)	-0.7 (0.1)	-0.2 (-0.5 to 0.0)	0.036
4-week treatment	-1.3 (0.1)	-1.1 (0.1)	-0.3 (-0.5 to -0.1)	0.017
Tearing/watering eyes				
2-week treatment	-0.9 (0.1)	-0.7 (0.1)	-0.3 (-0.5 to 0.0)	0.026
4-week treatment	-1.3 (0.1)	-1.0 (0.1)	-0.3 (-0.5 to -0.1)	0.012
Eye redness				
2-week treatment	-0.9 (0.1)	-0.7 (0.1)	-0.2 (-0.5 to 0.0)	0.064
4-week treatment	-1.2 (0.1)	-1.0 (0.1)	-0.3 (-0.5 to 0.0)	0.029
Mean change from baseline in p.m. individual ocular symptom				
Itching/burning eyes				
2-week treatment	-0.7 (0.1)	-0.6 (0.1)	-0.1 (-0.3 to 0.1)	0.238
4-week treatment	-1.2 (0.1)	-1.0 (0.1)	-0.2 (-0.4 to 0.0)	0.059
Tearing/watering eyes				
2-week treatment	-0.8 (0.1)	-0.6 (0.1)	-0.3 (-0.5 to -0.1)	0.016
4-week treatment	-1.2 (0.1)	-0.9 (0.1)	-0.3 (-0.5 to -0.1)	0.009
Eye redness				
2-week treatment	-0.9 (0.1)	-0.6 (0.1)	-0.2 (-0.4 to 0.0)	0.067
4-week treatment	-1.2 (0.1)	-0.9 (0.1)	-0.3 (-0.5 to 0.0)	0.024

[a]All ocular symptom-related endpoints were analyzed using the Analysis of Covariance (ANCOVA) model, with the baseline value of the given outcome, study site, and treatment group as covariates. Difference in LS means and the corresponding 95% CI were calculated. Mean changes from baseline in daily rTOSS at week 2 and week 4 were multiplicity-tested efficacy outcomes with type I error controlled by step-down test procedures. *P* values for other outcomes were two-sided and nominal, without adjustments for multiple comparisons. If the number of days with valid data over the 2/4 weeks of treatment was less than 12 days (14 × 0.8=11.2)/23 days (28 × 0.8=22.4), the missing value was imputed by the last observation carried forward method. [b] rTOSS is calculated by summing up the individual scores for itching/burning eyes, tearing/watering eyes, and eye redness reported over the past 12 hours; separate scores are obtained for morning (a.m. rTOSS), evening (p.m. rTOSS) and the instantaneous morning before treatment (a.m. iTOSS); the individual nasal symptom score ranges 0 (no symptom) to 3 points (severe); total scores range from 0 to 9, with lower scores indicating less severe ocular symptoms. LS, least-squares; s.e.m., standard error of the mean; CI, confidence interval; rTOSS, reflective total ocular symptom score; iTOSS, instantaneous total ocular symptom score.

https://doi.org/10.1038/s41591-025-03651-5

Extended Data Table 4 | Proportion of participants achieving a ≥ 0.5 reduction from baseline in RQLQ score at weeks 2 and 4

Outcome[a]	No. of patients (%)		Difference (95% CI)	*P* value
	Stapokibart (n = 50)	Placebo (n = 58)		
At week 2	44 (88.0)	39 (67.2)	20.8 (5.7 to 35.8)	0.012
At week 4	50 (100.0)	46 (79.3)	20.7 (10.3 to 31.1)	0.0004

[a]Data shown are n (%), unless otherwise indicated. The proportion difference between groups and its 95% CI were computed by normal approximation method. *P* values were two-sided and nominal, without adjustments for multiple comparisons. Missing data was imputed as non-response. RQLQ, Rhinoconjunctivitis Quality of- Life Questionnaire; CI, confidence interval.

nature portfolio

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Last updated by author(s): Mar 3, 2025

Reporting Summary

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For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Clinical data was collected using Taimei eCollect V5.
Data analysis	All statistical analyses of clinical data were performed using SAS version 9.4. Raw RNA sequencing reads were preprocessed to remove rRNA reads, adapter sequences, short fragments, and other low-quality reads. The cleaned reads were aligned to the human GRCh38 reference genome using HISAT2 software (version 2.0.4), allowing up to two mismatches. Following genome alignment, StringTie (version 1.3.3b) was employed to estimate transcript counts with a reference annotation. Differential gene expression analysis of nasal brushing RNA-seq count data was conducted using the limma/voom pipeline (version 3.54.2). Genes exhibiting absolute value log2fold change> 2 and Benjamini–Hochberg false discovery rate (FDR) adjusted q-value < 0.05 were identified as differentially expressed. Min-Max normalization was utilized to calculate Z-scores, thereby enhancing the visualization in heatmaps produced using the pheatmap package (version 4.9.0.2). Gene Set Enrichment Analysis (GSEA) was conducted to evaluate the enrichment of differentially expressed genes in pathways from the MSigDB Hallmark and other pathway lists using the clusterProfiler package (version 4.9.0.2). All statistical and computational analysis was performed in R (version 4.2.0).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The data supporting the findings of this trial are available within the manuscript and its Supplementary Information. The individual participant data are not accessible to the public due to constraints related to patient confidentiality. All requests for additional data sharing should be directed to and reviewed by the lead clinical center, Beijing TongRen Hospital, as well as the trial sponsor, Keymed Biosciences (Chengdu) Co., Ltd. These entities will evaluate whether the requests are subject to any intellectual property or confidentiality restrictions. Requests may be submitted to Pub_data_request@keymedbio.com. A signed data access agreement with the sponsor is required before accessing shared data. Requests will be responded to in threemonths.
Raw sequencing data have been uploaded to the Genome Sequence Archive (GSA) in National Genomics Data Center, China National Center for Bioinformation / Beijing Institute of Genomics, Chinese Academy of Sciences under accession HRA009883, and the processed sequencing data have been uploaded the OMIX, China National Center for Bioinformation / Beijing Institute of Genomics, Chinese Academy of Sciences under accession OMIX008443. Approval for discretionary access control (DAC) is required due to policy constraints. Researchers may submit applications via the website, and typically, the review process by the database administrator and DAC spans several weeks. The GRCh38 human reference genome datasets were procured from the GENCODE repository (http://www.gencodegenes.org). Gene sets were retrieved from the Molecular Signatures Database (MSigDB, https://www.gsea-msigdb.org/gsea/msigdb/human/collections.jsp#H)

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Sex was self-reported by the participants. In adults, SAR is equally common in both sexes. Female participants accounted for 58% of the stapokibart group and 48.3% of the placebo group. Subgroup analyses favored stapokibart over placebo regarding the primary endpoint in both male and female participants (Extended Data Fig 1).
Reporting on race, ethnicity, or other socially relevant groupings	In China, no significant differences in the prevalence of SAR were observed among Han and other races. Han Chinese ethinic group accounted for 90% of the stapokibart group and 100% of the placebo group.
Population characteristics	Demographic and clinical characteristics of the participants at baseline are presented in Table 1.
Recruitment	A total of 279 patients were assessed for eligibility between August 10, 2023, and September 10, 2023 at 18 medical centers across China according to the study protocol; of whom 108 were randomized to receive either stapokibart (n = 50) or placebo (n = 58). Eligible participants were adults aged from 18 to 65 years with a clinical history of SAR with or without allergic conjunctivitis in the previous two pollen seasons. The inclusion criteria included positive serum weed pollen-specific IgE test at the screening period; adequate degree of exposure to pollen; history of inadequately controlled to intranasal corticosteroids (INCS) or more medications for SAR; at least 6 points for the baseline a.m. iTNSS and average of the last six rTNSS assessments prior to randomization; at least 2 points for nasal congestion score and score for any individual nasal symptom; and a baseline peripheral blood eosinophil count of at least 300 cells/μl. The application of all these inclusion criteria characterized the study population as being comprised of individuals with moderate-to-severe SAR despite receiving SoC. The key exclusion criteria included the recent use of any biologic; active nasal disease other than SAR which could potentially affect the efficacy assessment, such as acute/chronic sinusitis, non-allergic rhinitis, upper respiratory tract, or sinus infection. The details of inclusion and exclusion criteria are available in the Supplementary Information.
Ethics oversight	This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol and amendments (see Supplementary Information, 'Study Protocol Amendment Description') were developed collaboratively by the sponsors and principal investigators, and subsequently approved by the independent ethics committees of Beijing Tongren Hospital of Capital Medical University and the ethics committee of each participating center (see List of Investigators in Supplementary information). Written informed consent was signed by all the participants before enrollment. Participants received compensation for commuting and blood collection.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Based on the results from the MERAK trial (NCT05470647), the mean difference between the stapokibart and placebo groups in the primary endpoint (mean change from baseline in daily rTNSS over 2-week treatment) was estimated as -1.50, with a common standard deviation (s.d.) of 2.43. With the two-sided α = 0.05, a dropout rate of about 10%, and a power of 85%, a total of 108 participants were planned to be included in this trial (allocation ratio 1:1).
Data exclusions	There were no data exclusions to report.
Replication	We did not conduct a replication of the study to assess reproducibility due to its nature as a multicenter clinical trial. However, we have meticulously detailed all procedures to facilitate replication.
Randomization	Randomization was stratified by study site via an interactive web response system (IWRS). A randomization statistician generated a randomization list of participants employing the stratified block randomization method with a block size of 4, using the SAS, version 9.4. All participants were enrolled by investigators and specified personnel at each center, and assigned to the treatment group via the IWRS.
Blinding	Stapokibart and matching placebo were provided by the manufacturer in visually indistinguishable vials, and labels with the medication code were applied to the vials by statisticians and specified personnel blinded to the medication and not involved with the study. Similarly, investigators, site staff and all participants were also blinded to treatment assignment in a double-blind manner. The randomization statistician did not participate in any other work related to this study and was not allowed to disclose any information regarding randomization lists to any investigators or personnel involved with the study. Emergency unblinding or pharmacovigilance unblinding were not performed during the study.

Behavioural & social sciences study design

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Study description	*Briefly describe the study type including whether data are quantitative, qualitative, or mixed-methods (e.g. qualitative cross-sectional, quantitative experimental, mixed-methods case study).*
Research sample	*State the research sample (e.g. Harvard university undergraduates, villagers in rural India) and provide relevant demographic information (e.g. age, sex) and indicate whether the sample is representative. Provide a rationale for the study sample chosen. For studies involving existing datasets, please describe the dataset and source.*
Sampling strategy	*Describe the sampling procedure (e.g. random, snowball, stratified, convenience). Describe the statistical methods that were used to predetermine sample size OR if no sample-size calculation was performed, describe how sample sizes were chosen and provide a rationale for why these sample sizes are sufficient. For qualitative data, please indicate whether data saturation was considered, and what criteria were used to decide that no further sampling was needed.*
Data collection	*Provide details about the data collection procedure, including the instruments or devices used to record the data (e.g. pen and paper, computer, eye tracker, video or audio equipment) whether anyone was present besides the participant(s) and the researcher, and whether the researcher was blind to experimental condition and/or the study hypothesis during data collection.*
Timing	*Indicate the start and stop dates of data collection. If there is a gap between collection periods, state the dates for each sample cohort.*
Data exclusions	*If no data were excluded from the analyses, state so OR if data were excluded, provide the exact number of exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established.*
Non-participation	*State how many participants dropped out/declined participation and the reason(s) given OR provide response rate OR state that no participants dropped out/declined participation.*
Randomization	*If participants were not allocated into experimental groups, state so OR describe how participants were allocated to groups, and if allocation was not random, describe how covariates were controlled.*

Ecological, evolutionary & environmental sciences study design

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Study description	*Briefly describe the study. For quantitative data include treatment factors and interactions, design structure (e.g. factorial, nested, hierarchical), nature and number of experimental units and replicates.*
Research sample	*Describe the research sample (e.g. a group of tagged Passer domesticus, all Stenocereus thurberi within Organ Pipe Cactus National Monument), and provide a rationale for the sample choice. When relevant, describe the organism taxa, source, sex, age range and any manipulations. State what population the sample is meant to represent when applicable. For studies involving existing datasets,*

describe the data and its source.

Sampling strategy	*Note the sampling procedure. Describe the statistical methods that were used to predetermine sample size OR if no sample-size calculation was performed, describe how sample sizes were chosen and provide a rationale for why these sample sizes are sufficient.*
Data collection	*Describe the data collection procedure, including who recorded the data and how.*
Timing and spatial scale	*Indicate the start and stop dates of data collection, noting the frequency and periodicity of sampling and providing a rationale for these choices. If there is a gap between collection periods, state the dates for each sample cohort. Specify the spatial scale from which the data are taken*
Data exclusions	*If no data were excluded from the analyses, state so OR if data were excluded, describe the exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established.*
Reproducibility	*Describe the measures taken to verify the reproducibility of experimental findings. For each experiment, note whether any attempts to repeat the experiment failed OR state that all attempts to repeat the experiment were successful.*
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Blinding	*Describe the extent of blinding used during data acquisition and analysis. If blinding was not possible, describe why OR explain why blinding was not relevant to your study.*

Did the study involve field work? ☐ Yes ☐ No

Field work, collection and transport

Field conditions	*Describe the study conditions for field work, providing relevant parameters (e.g. temperature, rainfall).*
Location	*State the location of the sampling or experiment, providing relevant parameters (e.g. latitude and longitude, elevation, water depth).*
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Disturbance	*Describe any disturbance caused by the study and how it was minimized.*

Reporting for specific materials, systems and methods

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Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	*Describe all antibodies used in the study; as applicable, provide supplier name, catalog number, clone name, and lot number.*
Validation	*Describe the validation of each primary antibody for the species and application, noting any validation statements on the manufacturer's website, relevant citations, antibody profiles in online databases, or data provided in the manuscript.*

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	*State the source of each cell line used and the sex of all primary cell lines and cells derived from human participants or vertebrate models.*
Authentication	*Describe the authentication procedures for each cell line used OR declare that none of the cell lines used were authenticated.*
Mycoplasma contamination	*Confirm that all cell lines tested negative for mycoplasma contamination OR describe the results of the testing for mycoplasma contamination OR declare that the cell lines were not tested for mycoplasma contamination.*
Commonly misidentified lines (See ICLAC register)	*Name any commonly misidentified cell lines used in the study and provide a rationale for their use.*

Palaeontology and Archaeology

Specimen provenance	*Provide provenance information for specimens and describe permits that were obtained for the work (including the name of the issuing authority, the date of issue, and any identifying information). Permits should encompass collection and, where applicable, export.*
Specimen deposition	*Indicate where the specimens have been deposited to permit free access by other researchers.*
Dating methods	*If new dates are provided, describe how they were obtained (e.g. collection, storage, sample pretreatment and measurement), where they were obtained (i.e. lab name), the calibration program and the protocol for quality assurance OR state that no new dates are provided.*

☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

Ethics oversight	*Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.*

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	*For laboratory animals, report species, strain and age OR state that the study did not involve laboratory animals.*
Wild animals	*Provide details on animals observed in or captured in the field; report species and age where possible. Describe how animals were caught and transported and what happened to captive animals after the study (if killed, explain why and describe method; if released, say where and when) OR state that the study did not involve wild animals.*
Reporting on sex	*Indicate if findings apply to only one sex; describe whether sex was considered in study design, methods used for assigning sex. Provide data disaggregated for sex where this information has been collected in the source data as appropriate; provide overall numbers in this Reporting Summary. Please state if this information has not been collected. Report sex-based analyses where performed, justify reasons for lack of sex-based analysis.*
Field-collected samples	*For laboratory work with field-collected samples, describe all relevant parameters such as housing, maintenance, temperature, photoperiod and end-of-experiment protocol OR state that the study did not involve samples collected from the field.*
Ethics oversight	*Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.*

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Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT05908032
Study protocol	The study protocol, statistical analysis plan, and all amendments were provided as Supplementary Information with the manuscript.
Data collection	Patients were screened and enrolled at 18 medical centers across China between August 10, 2023 and September 10, 2023. The last participant's last visit occurred on December 12, 2023.

Outcomes

The primary efficacy endpoint was the mean change from baseline in daily rTNSS over a 2-week treatment period.
Secondary endpoints included mean change from baseline in daily reflective total ocular symptom score (rTNSS) over 4 weeks of treatment; mean changes from baseline in rTNSS (a.m. and p.m. assessments), a.m. iTNSS, reflective total ocular symptom score (rTOSS) (daily, a.m., and p.m. assessments), a.m. instantaneous TOSS (iTOSS), and individual nasal (nasal congestion, runny nose, nasal itching, and sneezing) and ocular (itching/burning eyes, tearing/watering eyes, and eye redness)symptom scores (daily, a.m., and p.m. assessments) over 2-week and 4-week treatment; mean percentage changes from baseline in daily rTNSS, a.m. iTNSS, daily rTOSS, and AM iTOSS over 2-week and 4-week treatment; change from baseline in Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score and the proportion of participants achieving ≥0.5 reduction from baseline in RQLQ score, defined as the minimal clinically important difference (MCID)14 at week 2 and 4; time to onset of action; time to maximum effect over 2- and 4-week treatment periods; area under the curve (AUC) of change from baseline in daily rTNSS over 2- and 4-week treatment; and number of days during which participants had no or mild (score of ≤1 point) nasal and ocular symptoms over 2- and 4-week treatment periods. The assessment details of efficacy endpoints are provided in the Supplementary Methods and the protocol.
Safety assessments involved adverse events (AEs), vital signs, physical examination, 12-lead electrocardiogram, and laboratory tests. AEs were coded according to the Medical Dictionary for Regulatory Activities. Pharmacokinetic (PK) and pharmacodynamic (PD) assessments are described in the Supplementary Methods.
Post-hoc efficacy outcomes included the proportion of participants with no or mild nasal symptom (all individual symptom scores ≤1 point) at each day during treatment.

Dual use research of concern

Policy information about dual use research of concern

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

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☐	☐	Crops and/or livestock
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☐	☐	Any other significant area

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Does the work involve any of these experiments of concern:

No	Yes	
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☐	☐	Confer resistance to therapeutically useful antibiotics or antiviral agents
☐	☐	Enhance the virulence of a pathogen or render a nonpathogen virulent
☐	☐	Increase transmissibility of a pathogen
☐	☐	Alter the host range of a pathogen
☐	☐	Enable evasion of diagnostic/detection modalities
☐	☐	Enable the weaponization of a biological agent or toxin
☐	☐	Any other potentially harmful combination of experiments and agents

Plants

Seed stocks

Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.

Novel plant genotypes

Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.

Authentication

Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.

ChIP-seq

Data deposition

☐ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links *May remain private before publication.*	*For "Initial submission" or "Revised version" documents, provide reviewer access links. For your "Final submission" document, provide a link to the deposited data.*
Files in database submission	*Provide a list of all files available in the database submission.*
Genome browser session (e.g. UCSC)	*Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.*

Methodology

Replicates	*Describe the experimental replicates, specifying number, type and replicate agreement.*
Sequencing depth	*Describe the sequencing depth for each experiment, providing the total number of reads, uniquely mapped reads, length of reads and whether they were paired- or single-end.*
Antibodies	*Describe the antibodies used for the ChIP-seq experiments; as applicable, provide supplier name, catalog number, clone name, and lot number.*
Peak calling parameters	*Specify the command line program and parameters used for read mapping and peak calling, including the ChIP, control and index files used.*
Data quality	*Describe the methods used to ensure data quality in full detail, including how many peaks are at FDR 5% and above 5-fold enrichment.*
Software	*Describe the software used to collect and analyze the ChIP-seq data. For custom code that has been deposited into a community repository, provide accession details.*

Flow Cytometry

Plots

Confirm that:

☐ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☐ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☐ All plots are contour plots with outliers or pseudocolor plots.

☐ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	*Describe the sample preparation, detailing the biological source of the cells and any tissue processing steps used.*
Instrument	*Identify the instrument used for data collection, specifying make and model number.*
Software	*Describe the software used to collect and analyze the flow cytometry data. For custom code that has been deposited into a community repository, provide accession details.*
Cell population abundance	*Describe the abundance of the relevant cell populations within post-sort fractions, providing details on the purity of the samples and how it was determined.*
Gating strategy	*Describe the gating strategy used for all relevant experiments, specifying the preliminary FSC/SSC gates of the starting cell population, indicating where boundaries between "positive" and "negative" staining cell populations are defined.*

☐ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type	*Indicate task or resting state; event-related or block design.*

Design specifications

Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.

Behavioral performance measures

State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).

Acquisition

Imaging type(s)

Specify: functional, structural, diffusion, perfusion.

Field strength

Specify in Tesla

Sequence & imaging parameters

Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle.

Area of acquisition

State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.

Diffusion MRI ☐ Used ☐ Not used

Preprocessing

Preprocessing software

Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).

Normalization

If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.

Normalization template

Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.

Noise and artifact removal

Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).

Volume censoring

Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.

Statistical modeling & inference

Model type and settings

Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).

Effect(s) tested

Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference

Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.

(See Eklund et al. 2016)

Correction

Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).

Models & analysis

n/a	Involved in the study
☐	☐ Functional and/or effective connectivity
☐	☐ Graph analysis
☐	☐ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).

Graph analysis

Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).

Multivariate modeling and predictive analysis

Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.