Efficacy and safety of CM310 in severe eosinophilic chronic rhinosinusitis with nasal polyps (CROWNS-1): a multicentre, randomised, double-blind, placebo-controlled phase 2 clinical trial

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Summary

Background **Severe eosinophilic chronic rhinosinusitis with nasal polyps (ECRSwNP) remains the most relapsed subtype of uncontrolled CRSwNP. CM310, a humanised anti-interleukin (IL)-4 receptor alpha monoclonal antibody, inhibits IL-4 and IL-13 signaling which underlying eosinophilic inflammation. This study aims to evaluate the efficacy and safety of CM310 in patients with severe ECRSwNP.**

Methods **A multicentre, randomised, double-blind, and placebo-controlled phase 2 clinical trial was conducted. 56 eligible adult patients with severe ECRSwNP were randomised 1:1 to receive subcutaneously either CM310**

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(300 mg) or placebo every 2 weeks under the background therapy of mometasone furoate nasal spray (MFNS) for 16 weeks, with 8 weeks of follow-up. Coprimary endpoints included the changes from baseline in nasal polyp score (NPS) and nasal congestion score (NCS) at week 16. Key secondary endpoints included sinus Lund-Mackay CT score, change in sinus volume occupied by disease, University of Pennsylvania Smell Identification Test score, 22-item Sino-nasal Outcome Test score, and total symptom score. Safety, pharmacodynamics, and changes in type 2 inflammation biomarkers were assessed. This study is registered with ClinicalTrials.gov, NCT04805398.

Findings Between April 6, 2021, and March 18, 2022, 27 patients respectively in both the CM310 and placebo groups completed the study. Findings suggested that CM310 improved the coprimary efficacy endpoints of decreasing nasal polyp size and alleviating nasal congestion compared with the placebo. Least squares (LS) mean differences (CM310 vs placebo) of change from baseline in NPS and NCS at week 16 were −2.1 (95% CI −2.9, −1.4; $p < 0.0001$) and −0.9 (95% CI −1.4, −0.5; $p < 0.0001$), respectively. Sinus CT scan revealed that Lund-Mackay CT score (LS mean difference [95% CI] −7.6, [−9.4, −5.8]; $p < 0.0001$) and sinus volume occupied by disease (LS mean difference [95% CI] −37%, [−47%, −28%]; $p < 0.0001$) were significantly improved with CM310 compared with placebo. In addition, CM310 significantly relieved the daily symptoms of patients with CRSwNP and improved their quality of life reflected by the improvements in the TSS (−2.6 [95% CI −3.5, −1.6]), UPSIT (10.4 [95% CI 6.8, 14.0]) and SNOT-22 score (−19.1 [95% CI −29.8, −8.5]). Compared with placebo, CM310 administration significantly reduced type 2-related biomarkers including the serum TARC and total IgE, and tissue eosinophils. The most common adverse events were upper respiratory tract infection, blood cholesterol increased, and tinnitus, but none were considered drug-related.

Interpretation These findings support CM310 as an effective additional treatment option to the standard of care in patients with severe ECRSwNP.

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Keywords: Chronic rhinosinusitis with nasal polyps; RCT; Placebo-controlled; Double-blind; Anti-interleukin-4 receptor alpha monoclonal antibody

Research in context

Evidence before this study

Monoclonal antibodies have been demonstrated to be novel effective therapies for uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP). Severe eosinophilic CRSwNP (ECRSwNP) is identified as the most recurrent form of nasal polyps, characterised by mucosal/blood eosinophilia and a high rate of comorbid asthma. To evaluate the existing studies on ECRSwNP treatment, we searched PubMed, Embase, The Cochrane Library, ClinicalTrials.gov, and FDA.gov, using the search terms "antibodies", "Dupilumab", "Mepolizumab", "Omalizumab", "Reslizumab", "Benralizumab", "Tezepelumab", "Etokimab", "Lebrikizumab", "Tralokinumab", "AK001", "Astegolimab", "anti-immunoglobulin E", "anti-interleukin-4", "anti-interleukin-13", "anti-interleukin-4 receptor", "anti-interleukin-5", "anti-interleukin-5 receptor", "anti-interleukin-13", "anti-interleukin-33", "anti-thymic stromal lymphopoietin", "nasal polyp", "rhinosinusitis" for any articles published or trials recruited before October 29, 2020, with no language or time restrictions. Dupilumab, Omalizumab, and Mepolizumab are all efficacious in reducing polyp burden, ameliorating patients' nasal symptoms, and improving patients' quality of life regardless of blood eosinophil levels. No trials were identified that evaluated the safety and efficacy of antibodies in patients with severe ECRSwNP, particularly those diagnosed based on mucosal eosinophilia. Furthermore, there is yet no evidence to suggest the impact of antibodies on eosinophils in polyp tissue.

Added value of this study

To the best of our knowledge, this is the first trial to evaluate the efficacy of monoclonal antibodies in patients with severe ECRSwNP. The newly developed anti-IL-4Rα monoclonal antibody, CM310, was trialled and revealed rapid and substantial benefits for patients with severe ECRSwNP. These advantages included reducing polyp size, diminishing sinus opacification, relieving symptoms, and improving quality of life. Moreover, this is the first time that anti-IL-4Rα monoclonal antibody has been shown to significantly reduce local eosinophilic inflammation.

Implications of all the available evidence

This study suggests CM310 as an effective add-on treatment to the standard of care for those with severe ECRSwNP. Whether the high number of patients with tissue eosinophilia is responsible for the efficacy of CM310 in this study will be further examined in the ongoing phase 3 of CM310 in CRSwNP, which stratifies patients with tissue eosinophils.

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP), which currently affects approximately 4% of the global population, remains a clinical challenge.[1] The symptoms including nasal congestion, nasal discharge, facial pain or pressure, reduction or loss of smell, and sleep disturbance substantially impair patients' quality of life (QoL) and impose a heavy economic burden.[2] The identification of subtypes reveals that severe eosinophilic CRSwNP (ECRSwNP), which can be identified based on tissue or blood eosinophil counts, is highly correlated with both asthma comorbidity and severe symptom scores. When a cut-off value of 27% tissue eosinophils was used, the recurrence rate of ECRSwNP was found to be over 90%, indicating that it is the most refractory subtype of CRSwNP.[3–6]

The cornerstone of managing severe ECRSwNP mainly consists of treatment with intranasal corticosteroids (INCS); if INCS is insufficient, short courses of systemic corticosteroids (SCS) may be recommended. Patients who have failed medical management may be eligible for endoscopic sinus surgery (ESS).[1] However, even in such a medical and surgical management context, a high proportion of patients with severe ECRSwNP show a strong tendency for recurrence and subsequent revision surgery. In addition, Zhang et al. demonstrated that CRSwNP with asthma was essentially a systemic disease that inevitably recurs in the long run regardless of any kind of ESS strategies.[7]

Biologics targeting type 2 cytokines or their receptors, such as anti-immunoglobulin E (IgE), anti-IL-4Rα, anti-IL-5, and anti-IL-5Rα are developed as novel treatment strategies to fulfill the unmet medical needs of CRSwNP. Results from meta-analysis indicated that Dupilumab (anti-IL-4Rα) presents the most efficacy in uncontrolled CRSwNP. Dupilumab was the first biological agent approved by the FDA and PMDA for the treatment of CRSwNP.[8,9] However, clinical trials assessing the efficacy of monoclonal antibodies for those with severe ECRSwNP are lacking. In addition, the effect of monoclonal antibodies on eosinophils in polyp tissue has yet to be determined.

CM310 is a humanised antibody targeting IL-4Rα and efficiently blocks the interaction of cytokines IL-4 and IL-13 with their co-receptor subunit IL-4Rα. As an investigational monoclonal antibody, the safety and efficacy of CM310 have been demonstrated in healthy volunteers and type 2-related atopic dermatitis (AD) (phase 1b/2a, NCT04893941; phase 2b, NCT04805411, in submission). The epitope of CM310 to IL-4Rα is different with Dupilumab, reflected by different cross-species reactivity between CM310 and Dupilumab. CM310 has the capacity to interact with IL-4Rα in humans, cynomolgus monkeys, and rats, while Dupilumab only binds human IL-4Rα. which may represent differentiated mechanisms in inhibiting the signaling of IL-4Rα, and result in distinct clinical outcomes. Herein, this study aims to evaluate the efficacy and safety of the addition of CM310 therapy to INCS specifically in patients with severe ECRSwNP.

Methods

Study design and participants

This randomised, double-blind, placebo-controlled clinical trial was carried out at 19 hospitals in China between April 6, 2021, and March 18, 2022. This study is registered with ClinicalTrials.gov, NCT04805398. The trial chronologically consisted of a screening/run-in period (4 weeks), a randomised treatment period (16 weeks) and a safety follow-up period (8 weeks). The trial protocol was developed by the sponsor and investigators and approved by the institutional review board of each hospital (see Supplementary Data: Study Protocol). All patients provided written informed consent for study participation. The trial was conducted in full accordance with Good Clinical Practice guidelines and the Declaration of Helsinki or the laws and regulations of the local in China. The ethics committee at each study site approved the trial conduct and related documentation.

To participate in this study, patients with CRSwNP were required to be aged 18–70 years, to have received SCS treatment within 2 years prior to the run-in period, or have contraindicated or intolerant to SCS treatment or have undergone nasal polyp surgery 6 months before the run-in period, to have an endoscopic nasal polyp score (NPS) of at least 5 points (at least 2 points for each nostril), and to have moderate or severe nasal congestion (0 = no symptoms, 1 = mild, 2 = moderate, and 3 = severe) with a weekly average nasal congestion score (NCS) of 2 or 3 points and any other symptoms such as loss of smell or rhinorrhea. Additionally, stable and continuous usage of INCS was demanded for at least 4 weeks before screening, the patients were treated with mometasone furoate nasal spray (MFNS) as background therapy throughout the study. Meanwhile, the enrolled patients' eosinophil levels must meet one of the following conditions which are regarded as CRSwNP with high recurrence risk: 1) the percentage of peripheral blood eosinophils ≥6.9% (without asthma) or ≥3.7% (with asthma)[5]; 2) the tissue eosinophil absolute count ≥55/HPF or eosinophil percentage ≥27% through nasal polyp biopsy.[4] These criteria resulted in a study population with severe eosinophilic inflammation. The method of nasal polyp biopsy is described in Supplementary Methods.

Patients were excluded if they: 1) used IL-4Rα antagonist within 10 weeks or 5 half-lives (whichever is longer), or biological therapy/systemic immunosuppressants within 8 weeks or 5 half-lives (whichever is longer) or anti-IgE monoclonal antibody within 130 days prior to randomization; 2) experienced nasal polyp surgery during the 6 months prior to screening/run-in period; 3) received intermediate-acting and short-acting SCS within 4 weeks

or long-acting SCS therapy within 6 weeks before the screening. Other key inclusion and exclusion criteria are presented in Supplementary Methods.

Randomisation and masking

After enrollment, eligible patients were randomised in a 1:1 ratio to receive CM310 or matching placebo at 300 mg every two weeks. Interactive Web Response System (IWRS) was used in this study. Randomisation statisticians generate patient and drug randomization lists by SAS with a permuted block size of 8, which the system engineer subsequently imported into the IWRS system. CM310 and placebo were placed in prefilled syringes that were indistinguishable in appearance. Participants and investigators were blinded to the trial assignment.

Procedures

During the 4-week screening/run-in period, all patients received daily use of MFNS 100 μg in each nostril (total daily dose of 200 μg) and continued use throughout the clinical trial. In the randomised treatment period, patients were subcutaneously injected with CM310 300 mg or placebo, each treatment kit of 2 mL (CM310/placebo), every 2 weeks for 16 weeks.

Visits were planned once during the run-in period (V1), every 2 weeks during the randomised treatment period from week 0–16 (V2 to V10), and at week 20 and week 24 during the follow-up period (V11 and V12). Endoscopy for NPS, assessment of NCS and total symptom score (TSS, including nasal congestion, sense of smell, postnasal drip, and runny nose), University of Pennsylvania Smell Identification Test (UPSIT), 22-item Sino-Nasal Outcome Test (SNOT-22), as well as safety evaluation were done at week 4 of run-in period, week 0 (baseline), week 4, week 8, week 12, week 16 (end of treatment, EOT), week 20 and week 24 (end of study, EOS). Sinus CT scans were performed at baseline and EOT. Laboratory tests for pharmacodynamic (PD) biomarkers were conducted at weeks 0, 2, 6, 10, 14, 16, 20, and 24 and for immunogenicity at weeks 0, 4, 6, 10, 14, 16, 20, and 24. The study flow chart is listed in Supplementary Fig. S1.

Outcomes

The coprimary efficacy endpoints were changes from baseline in NPS and NCS at week 16 during the treatment period. NPS is the sum of the left and right nostril scores ranging from 0 to 8 (0–4 for each nostril), which is based on polyp size as evaluated by means of nasal endoscopy, with higher points indicating larger nasal polyp and more severe nasal obstruction of the nasal cavity, which was centrally assessed at Beijing TongRen Hospital. NCS ranging from 0 to 3 points is recorded by patients as daily symptom assessment of nasal congestion severity; the higher the score, the worse the nasal congestion.

Following secondary efficacy endpoints were included: 1) time to the first NPS response of ≥1 point; 2) change from baseline in the Lund-Mackay score at week 16; 3) change from baseline in sinus volume occupied by disease at week 16; 4) change from baseline in NPS at week 8; 5) frequency of rescue therapy; 6) change from baseline in UPSIT at week 16; 7) change from baseline in SNOT-22 at week 16; 8) change from baseline in TSS at week 16; 9) change from baseline of coprimary endpoints in patients with nasal polyps surgery or asthma at week 16.

The safety endpoints included adverse events, vital signs, physical examinations, electrocardiogram (ECG) and clinical laboratory tests. PD response and immunogenicity of CM310 were also assessed. Serum biomarkers including thymus- and activation-regulated chemokine (TARC), IgE and eosinophil count, as well as the infiltration situation of eosinophil in nasal polyps, were detected to reflect PD response. To examine the possible immunogenicity of CM310, the production of anti-drug antibodies (ADAs) and neutralizing antibodies (Nabs) were measured. A post-hoc analysis is conducted to screen the potential predictor of CM310 efficacy in CRSwNP after trial unmasking. The detailed information was shown in Supplementary Methods.

Statistical analysis

The sample size was calculated based on the results of the phase 2 study of Dupilumab in CRSwNP: The expected treatment effect in change from baseline in NCS of CM310 was −0.7, and its standard deviation was 0.8. Additionally, the Type I error was set to be 0.05, and the power (1-β) was 80%, 22 participants were required in each group; meanwhile, 22 participants in each group would provide 85% power for change from baseline in NPS with an expected treatment effect of −1.6 and a standard deviation of 1.7. Therefore, 22 participants in each group (a total of 44 participants) would meet the statistical requirements for the two primary efficacy endpoints. If a dropout rate of 20% is considered, a total of 56 patients should be enrolled in the study.

Different analysis populations were used to assess the efficacy, safety, PD, and immunogenicity of CM310. Full Analysis Set (FAS) included all randomised patients who had used the study drug at least once, obeying to intend-to-treated (ITT) principle. Per-protocol Set (PPS) includes all patients in the FAS except for those who are excluded because of major efficacy-related protocol violations. FAS was used as the primary efficacy analysis population, and PPS as the auxiliary analysis. Safety Set (SS) included all patients who received any study drug, Pharmacodynamic Set (PDS) and ADA Analysis Set (ADAS) included all patients, who received any study drug and had at least one corresponding qualified result. SS, PDS, and ADAS were analysed as treated.

The primary analysis for change from baseline in the NPS or the monthly average of NCS at week 16 was implemented by the mixed model for repeated measures (MMRM), which included the change value from

baseline to week 16 as the response variables, baseline value as a covariate, and treatment, visit, treatment-by-visit interaction, and baseline-by-visit interaction as fixed effects. Additional statistical methods used are described in Supplementary Data (Supplementary Methods and Statistical Analysis Plan). SAS version 9.4 was used for statistical analysis.

Role of the funding source

KeyMed Biosciences funded the trial, provided the trial treatments, and collaborated with the investigators on the design of the trial and the collection, analysis, interpretation of the data, and manuscript preparation. CW and LZ had full access to the data. All authors approved the final version of the manuscript and had final responsibility for the decision to submit for publication.

Results

Patients

Between April 6, 2021, and March 18, 2022, 109 patients were screened in this trial, and 56 patients with severe ECRSwNP were randomly assigned to the CM310 group (n = 28) or placebo group (n = 28) (Fig. 1). 27 patients per group completed 16 weeks of treatment. Early withdrawal from CM310 group was due to severe non-compliance to the protocol (n = 1), and from placebo group was due to adverse events (n = 1).

Demographics and baseline characteristics were balanced between the CM310 and placebo groups, and consistent with the purpose of CRSwNP enrollment (Table 1). The mean (SD) of baseline efficacy endpoints for all enrolled patients were: NPS (5.9 [0.8]), NCS (2.6 [0.5]), Lund-Mackay CT score (18.4 [3.9]), and percentage of the volume occupied by disease in the whole nasal cavity (76% [22%]). Additionally, the symptoms of CRSwNP greatly impaired these patients' sense of smell and QoL in accordance with UPSIT score (13.0 [6.3]), SNOT-22 score (58.5 [25.1]), and TSS (7.5 [1.2]). Furthermore, more than half (57% [32/56]) of the patients had received SCS therapy previously, 63% (35/56) had undergone nasal polyp surgery (all participants who had received surgery had at least the complete removal of nasal polyps under endoscopy), and 66% (37/56) had concomitant asthma.

Primary endpoints

The improvement of NPS at week 16 in CM310 was significantly greater than that in placebo (LS mean difference [95% CI], –2.1 [–2.9, –1.4], $p < 0.0001$) (Fig. 2A, Table 2). Meanwhile, CM310 significantly improved nasal congestion scores compared with placebo (LS mean difference [95% CI], –0.9 [–1.4, –0.5], $p < 0.0001$) (Fig. 2B, Table 2).

Secondary endpoints

Patients in CM310 obtained full benefit in all secondary efficacy endpoints than those in placebo. The median (95% CI) of time to first NPS response was 30 (29, 32) days in CM310 group and 170 (58, not reached) days in placebo group respectively ($p < 0.0001$). Additional analysis of NPS or NCS improvement of ≥1- and ≥2-points in NPS or NCS was performed. Both the proportions of patients in CM310 group achieving ≥1- and ≥2-points reduction in NPS at week 16 were significantly higher (both 79% [22/28]) than those in placebo group (14% [4/28] and 7% [2/28]) (see Supplementary Fig. S2A). An improvement of ≥1- and ≥2-points in NCS at week 16 was observed (CM310 vs placebo): 61% (17/28) vs 25% (7/28), and 21% (6/28) vs 7% (2/28), respectively (see Supplementary Fig. S2B).

Lund-Mackay CT score in CM310 obviously decreased at week 16 (LS mean difference [95% CI] vs placebo, –7.6 [–9.4, –5.8], $p < 0.0001$) (Fig. 3A, Table 2). Moreover, results from sinus inflammation volume showed that LS mean change in the percentage of whole nasal cavity occupied by disease was –39% [95% CI –46%, –32%] with CM310 and –2% [95% CI –8%, 5%] with placebo (LS mean difference [95% CI], –37% [–47%, –28%]; $p < 0.0001$) (Fig. 3B, Table 2). The LS mean differences in percentages of frontal sinus, ethmoid sinus, maxillary sinus and sphenoid sinus occupied by disease at week 16 between CM310 and placebo were –42% (95% CI –57%, –27%; $p < 0.0001$), –45% (95% CI –57%, –33%; $p < 0.0001$), –29% (95% CI –41%, –16%; $p < 0.0001$), and –40% (95% CI –55%, –26%; $p < 0.0001$), respectively.

The amelioration of the overall nasal symptoms reflected by the decreased TSS was also observed in CM310 (LS mean difference [95% CI], –2.6 [–3.5, –1.6], $p < 0.0001$) (Fig. 3C, Table 2). Improvement of ≥1- and ≥2-point in TSS at week 16 (CM310 vs placebo) were 82% (23/28) vs 39% (11/28), and 75% (21/28) vs 18% (5/28), respectively (see Supplementary Fig. S3A). Smell test of UPSIT demonstrated that CM310 remarkably recovered patient's sense of smell when compared with placebo (LS mean difference [95% CI], 10.4 [6.8, 14.0], $p < 0.0001$) (Fig. 3D, Table 2). The improvement in the SNOT-22 score in the CM310 group was more obvious than that of placebo (LS mean difference [95% CI], –19.1 [–29.8, –8.5], $p = 0.00070$) (Fig. 3E, Table 2), and the proportion of patients exceeding the minimally clinically important difference (MCID) of 8.9 were 68% (19/28) vs 43% (12/28) (CM310 vs placebo) (see Supplementary Fig. S3B). In addition, no rescue therapies occurred during the study. Overall, the administration of CM310 was able to relieve CRS and improve patients' QoL.

Biomarker analyses demonstrated that CM310 administration significantly reduced the serum concentration of type 2-related biomarkers TARC and total IgE compared with placebo (Table 3). Serum total IgE of CM310 group showed a slow and continuous decrease until the end of study (Fig. 4A, Table 3). In addition, no difference in blood eosinophil count change was observed between CM310 and placebo groups (Fig. 4B, Table 3). Furthermore, we observed that eosinophils in

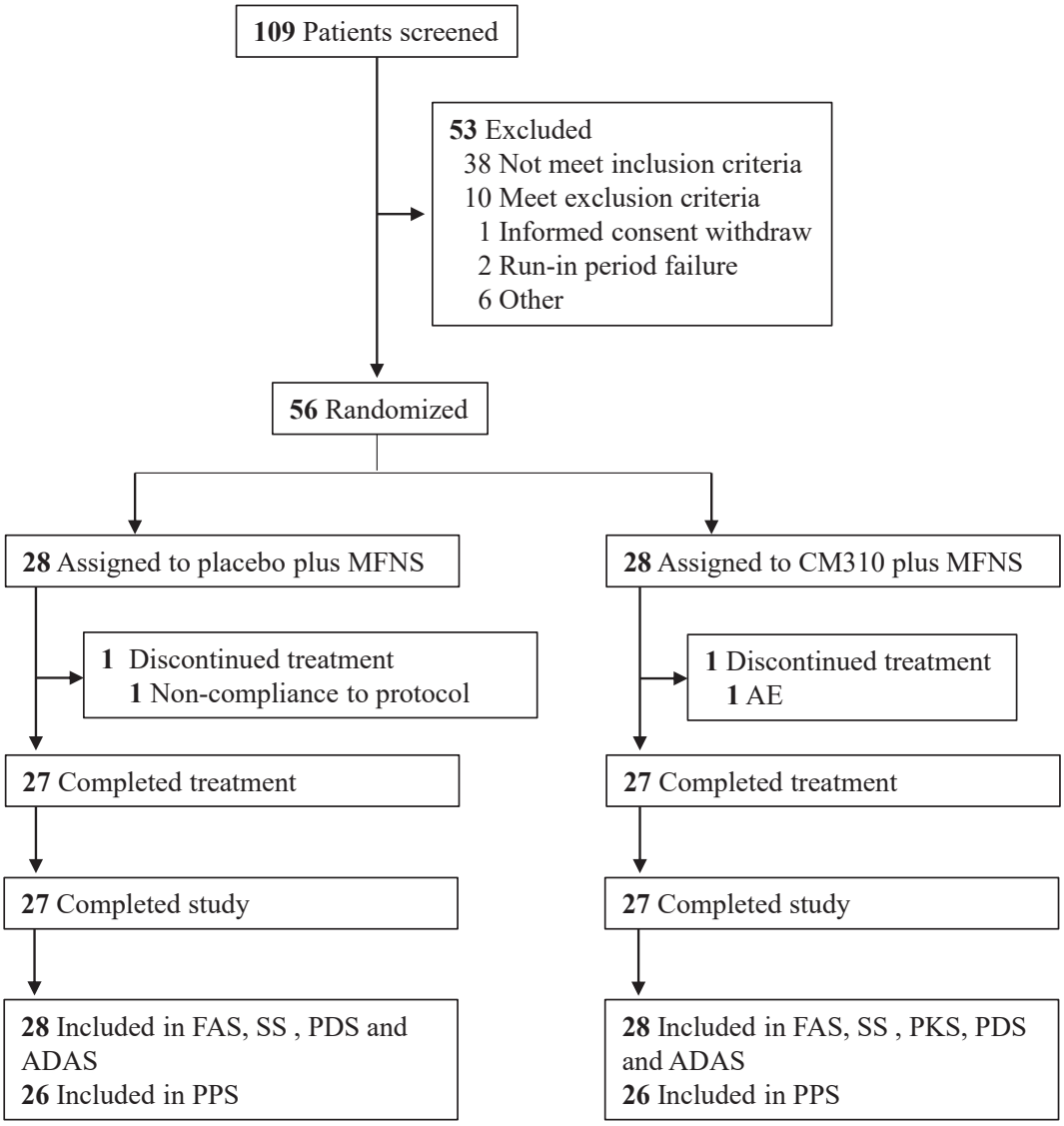

Fig. 1: **Trial profile**. All patients randomly assigned to the treatment were included in the analysis of the prespecified primary and secondary endpoints at week 16. MFNS, Mometasone furoate nasal spray; FAS, Full analysis sets.

nasal polyp tissue in CM310 decreased significantly at week 16 compared with placebo (p = 0.049, Fig. 4C, Table 3).

No clinically deleterious changes in vital signs, physical examinations, electrocardiograms, and clinical laboratory tests were detected with CM310 administration. The occurrence of adverse events was similar between the two groups (75% [21/28] vs 79% [22/28], CM310 vs placebo) (Table 4). The most common AE, defined as those that occurred in at least 5% of the patients and at a higher incidence among patients who received CM310 than that in placebo, were upper respiratory tract infection (18% [5/28] in CM310 group vs 14% [4/28] in placebo group), blood cholesterol increased (7% [2/28] in only CM310 group), and tinnitus (7% [2/28] in only CM310 group). None of them were considered drug-related. Only injection site reactions (both 4% [1/28] in CM310 and placebo group) were considered drug-related. All severe adverse events (11% [3/28]) occurred in placebo group, of them one died for an unknown reason while accompanied with asthma exacerbation during hospitalisation. No serious adverse events occurred in CM310 group. The immunogenicity assessment of CM310 showed that the positive incidences of ADA and Nab after treatment were both 4% (1/28). However, the production of ADA and Nab at this level had no obvious effect on the exposure of patients given CM310.

	CM310 (n = 28)	Placebo (n = 28)	Total (n = 56)
Age, years	48.8 (12.2)	46.4 (12.5)	47.6 (12.3)
Sex, n (%)			
Female	10 (36)	14 (50)	24 (43)
Male	18 (64)	14 (50)	32 (57)
Race, Han, n (%)	27 (96)	26 (93)	53 (95)
BMI (kg/m^2)[a]	24.4 (2.9)	24.6 (4.6)	24.5 (3.8)
History of smoking, yes, n (%)	7 (25)	6 (21)	13 (23)
History of drinking, yes, n (%)	12 (43)	3 (11)	15 (27)
Drug abuse within 3 months before screening, yes, n (%)	0 (0)	0 (0)	0 (0)
Duration of CRSwNP, years	8.9 (9.3)	8.9 (7.6)	8.9 (8.4)
Baseline blood eosinophils, 10^9 cells/L	0.4 (0.3)	0.5 (0.4)	0.5 (0.3)
Baseline blood eosinophils, n (%)			
$<0.15*10^9$/L	4 (14)	2 (7)	6 (11)
$\geq 0.15*10^9$/L	24 (86)	26 (93)	50 (89)
$\leq 0.30*10^9$/L	9 (32)	9 (32)	18 (32)
$\geq 0.30*10^9$/L	19 (68)	19 (68)	38 (68)
History of nasal polyposis surgery, yes, n (%)	16 (57)	19 (68)	35 (63)
Comorbid asthma, yes, n (%)	18 (64)	19 (68)	37 (66)
NPS[b]	5.8 (0.8)	6.1 (0.7)	5.9 (0.8)
NCS (scale 0–3)[c]	2.5 (0.4)	2.6 (0.5)	2.6 (0.5)
Lund-Mackay CT total score, (scale 0–24)[d]	18.0 (3.6)	18.7 (4.2)	18.4 (3.9)
Percentage of sinus inflammation volume occupied by diseases, %			
Whole nasal cavity	70 (23)	82 (21)	76 (22)
Frontal sinus	77 (33)	88 (28)	83 (30)
Ethmoid sinus	83 (21)	93 (13)	88 (18)
Sphenoid sinus	64 (35)	75 (31)	69 (33)
Maxillary sinus	67 (25)	80 (23)	73 (25)
Baseline TSS (scale 0–9)[f]	7.3 (1.1)	7.6 (1.4)	7.5 (1.2)
Baseline SNOT-22 (scale 0–110)[g]	53.3 (24.0)	63.8 (25.5)	58.5 (25.1)
Baseline UPSIT (scale 0–40)[h]	12.5 (5.9)	13.5 (6.7)	13.0 (6.3)
Serum TARC, pg/mL	256.2 (106.2)	274.3 (154.1)	265.3 (130.2)
Total serum IgE, ng/mL	491.4 (771.4)	566.6 (1063.7)	529.0 (917.6)

For continuous variables, mean and standard deviation are displayed, and for categorical variables, number and percentage are displayed. [a]BMI, Determined as weight in kilograms divided by height in meters squared. [b]Higher scores mean worse outcomes. [c]Higher scores indicate more severe symptom. [d]Higher scores mean more opacification. [e]Higher scores mean poorer outcomes. [f]Higher scores suggest worse outcomes. [g]Higher scores indicate worse outcomes, and the minimum clinically important difference is 8.90 points. [h]Higher scores of 35–40 denote normal sense of smell. BMI, Body mass index; CRSwNP, Chronic rhinosinusitis with nasal polyps; CT, Computed tomography; IgE, Immunoglobulin E; NCS, Nasal congestion score; NPS, Nasal polyp score; SNOT-22, 22-item Sino-nasal Outcome Test score; TARC, Thymus- and activator-regulated chemokine; TSS, Total symptom score; UPSIT, University of pennsylvania smell identification test score.

Table 1: **Demographics and clinical characteristics.**

Exploratory analyses

Subgroup analyses demonstrated that in patients with a baseline blood eosinophil count of ≥150 cells per microliter, CM310 resulted in improvements in both NPS and NCS (see Supplementary Figs. S4 and S5). In addition, the magnitude of improvements in NPS was similar among different subgroups according to baseline tissue eosinophil count and IgE level, but better in subgroups with Lund-Mackay CT score of ≥19, or with nasal polyp surgery, or with asthma (see Supplementary Fig. S4). The improvement in NCS was similar between different subgroups according to tissue eosinophil count, IgE level, Lund-Mackay CT score, surgery, and asthma status (see Supplementary Fig. S5).

A post-hoc analysis was conducted to explore the variations in the number and activation of baseline tissue eosinophils between the groups of patients who exhibited a positive response to CM310 and those who did not. The classification of the two groups was based on the change from baseline in NPS (patients with improvement of NPS ≥ 1-point at week 16 were defined as responders, otherwise as non-responders). The detailed methods are shown in Supplementary Methods. Baseline characteristics and eosinophil-related markers' expression are shown in Supplementary Tables S1–S3. Results of post-hoc analysis indicated that non-responders presented fewer eosinophil cationic protein-positive cells than responders (see Supplementary Table S3 and Supplementary Fig. S6).

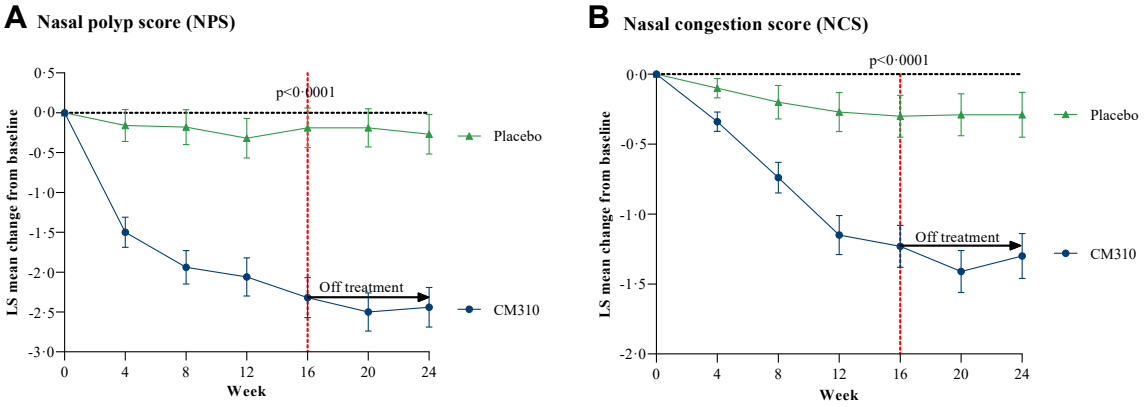

Fig. 2: **Change from baseline over time in NPS (A) and NCS (B) based on MMRM**. The p value represents the comparison between CM310 and placebo at week 16. Error bars indicated SE. LS, Least squares; NPS, Nasal polyp score; NCS, Nasal congestion score.

Discussion

As the most important subtype of uncontrolled CRSwNP, patients with ECRSwNP generally have severe symptom distress, especially anosmia, poor QoL, and the comorbidity of asthma. When the eosinophil status reaches a cut-off value, patients are at a fairly high risk of recurrence after ESS.[6,7] In the present study, in adult patients with severe ECRSwNP uncontrolled with the standard of care, CM310 provided rapid and significant improvements regarding all aspects of the disease, involving polyp size, sinus opacification, the severity of symptoms, and QoL. In comparison, in patients in the placebo groups who received daily MFNS alone, no meaningful improvements were noted in NCS, NPS, Lund-Mackay CT score, and sense of smell. CM310 administration significantly reduced type 2 related biomarkers, such as circulating total IgE and TARC compared with placebo, which further supports a common set of underlying type 2 inflammatory mechanisms in CRSwNP, suggesting CM310's great potential in the treatment of allergic diseases including AD, allergic rhinitis and asthma. Notably, with pre-and post-treatment nasal polyp biopsies, we provided evidence for the first time that CM310 showed significantly stronger

	CM310				Placebo				Difference for CM310 vs placebo, LS mean (95% CI)	p value
	Baseline, mean (SD)	Week 16, mean (SD)	Change from baseline, LS mean (95% CI)	p value	Baseline, mean (SD)	Week 16, mean (SD)	Change from baseline, LS mean (95% CI)	p value		
Primary endpoints										
NPS (scale 0–8)[a]	5.8 (0.8)	3.4 (1.9)	−2.3 (−2.8, −1.8)	<0.0001	6.1 (0.7)	5.9 (1.3)	−0.2 (−0.7, 0.3)	0.46	−2.1 (−2.9, −1.4)	<0.0001
NCS (scale 0–3)[b]	2.5 (0.4)	1.3 (0.7)	−1.2 (−1.5, −0.9)	<0.0001	2.6 (0.5)	2.3 (0.9)	−0.3 (−0.6, 0.0)	0.051	−0.9 (−1.4, −0.5)	<0.0001
Secondary endpoints										
Lund-Mackay CT score (scale 0–24)[c]	18.0 (3.6)	10.2 (3.7)	−7.9 (−9.2, −6.7)	<0.0001	18.7 (4.2)	18.3 (4.8)	−0.3 (−1.6, 0.9)	0.60	−7.6 (−9.4, −5.8)	<0.0001
Percentage of sinus inflammation volume occupied by disease[d], %										
Whole nasal cavity	70 (23)	34 (19)	−39 (−46, −32)	<0.0001	82 (21)	78 (20)	−2 (−8, 5)	0.60	−37 (−47, −28)	<0.0001
Frontal sinus	77 (33)	42 (40)	−38 (−48, −27)	<0.0001	88 (28)	91 (23)	5 (−6, 15)	0.38	−42 (−57, −27)	<0.0001
Ethmoid sinus	83 (21)	37 (28)	−48 (−56, −40)	<0.0001	93 (13)	89 (20)	−3 (−11, 6)	0.52	−45 (−57, −33)	<0.0001
Sphenoid sinus	64 (35)	17 (24)	−50 (−60, −39)	<0.0001	75 (31)	63 (37)	−9 (−19, 1)	0.083	−40 (−55, −26)	<0.0001
Maxillary sinus	67 (25)	39 (26)	−31 (−40, −22)	<0.0001	80 (23)	74 (24)	−2 (−11, 6)	0.60	−29 (−41, −16)	<0.0001
TSS (scale 0–9)[e]	7.3 (1.1)	4.1 (1.8)	−3.3 (−4.0, −2.6)	<0.0001	7.6 (1.4)	6.8 (2.0)	−0.7 (−1.4, −0.1)	0.034	−2.6 (−3.5, −1.6)	<0.0001
SNOT-22 (scale 0–110)[f]	53.3 (24.0)	28.5 (20.5)	−27.1 (−34.5, −19.7)	<0.0001	63.8 (25.5)	53.4 (26.8)	−8.0 (−15.5, −0.5)	0.038	−19.1 (−29.8, −8.5)	0.00070
Smell test UPSIT (scale 0–40)[g]	12.5 (5.9)	22.8 (8.1)	9.9 (7.4, 12.5)	<0.0001	13.5 (6.7)	12.7 (5.3)	−0.5 (−3.0, 2.1)	0.71	10.4 (6.8, 14.0)	<0.0001

NPS, Bilateral nasal polyp score; NCS, Nasal congestion score. [a]Higher scores mean worse outcomes. [b]Higher scores indicate severer symptom. [c]Higher scores mean more opacification. [d]Higher scores mean poorer outcomes. [e]Higher scores suggest worse outcomes. [f]Higher scores indicate worse outcomes, and the minimum clinically important difference of 8.90 points. [g]Higher scores of 35–40 denote normal sense of smell. UPSIT, University of Pennsylvania smell identification test; SNOT-22, 22-item sino-nasal outcome test.

Table 2: **Summary of changes from baseline at week 16 in coprimary, secondary endpoints.**

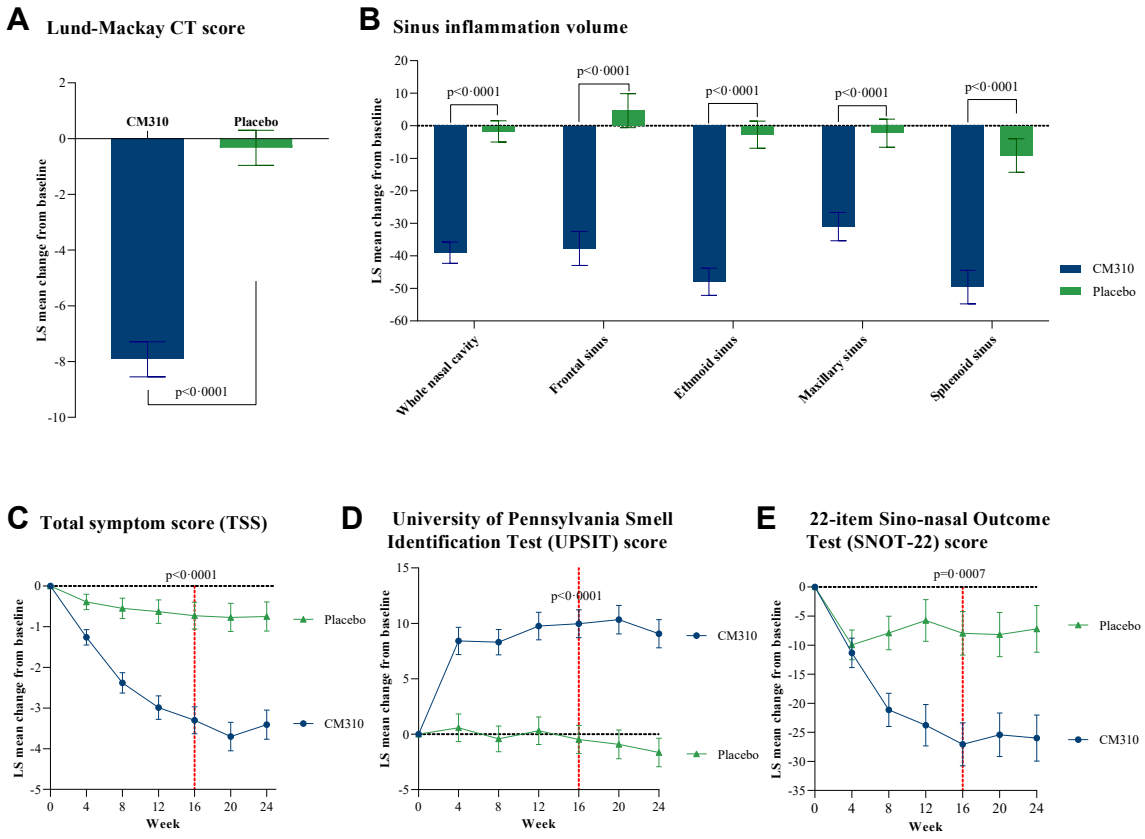

***Fig. 3*: Change from baseline over time in Lund-Mackay CT (A), sinus inflammation volume (B), TSS (C), UPSIT (D), and SNOT-22 score (E) based on MMRM/ANCOVA**. The p value represents the comparison between CM310 and placebo at week 16. Error bars indicate SE. MMRM was applied in monthly average TSS, SNOT-22 and UPSIT. Analysis of covariance (ANCOVA) model was used for change from baseline in LMK, and sinus volume occupied by disease, which included change from baseline at week 16 as the response variable, the baseline value as covariate, and treatment as the independent variable.

Type 2-related biomarkers[a]	CM310				Placebo				Difference of change from baseline, mean (95%CI)	p value[b]
	Baseline, mean (SD)	Week 16, mean (SD)	Change from baseline, mean (SD)	p value	Baseline, mean (SD)	Week 16, mean (SD)	Change from baseline, mean (SD)	p value		
Serum TARC, pg/mL	256.2 (106.2)	141.2 (55.7)	−118.0 (104.4)	<0.0001	274.3 (154.1)	255.7 (206.6)	−17.3 (127.1)	0.49	−100.7 (−165.5, −35.9)	0.0030
Total serum IgE, ng/mL	491.4 (771.4)	239.1 (289.3)	−276.9 (522.1)	0.012	566.6 (1063.6)	533.2 (1025.7)	−41.7 (209.2)	0.32	−235.2 (−456.8, −13.7)	0.038
Blood eosinophil count, 10^9/L	0.4 (0.3)	0.4 (0.5)	0.0 (0.5)	1.00	0.5 (0.4)	0.5 (0.4)	−0.02 (0.2)	0.64	0.0 (−0.2, 0.2)	0.83
Blood eosinophil percentage, %	6.2 (2.8)	6.4 (6.4)	0.1 (5.7)	0.91	7.3 (4.3)	7.2 (5.2)	−0.04 (3.2)	0.95	0.2 (−2.4, 2.7)	0.90
Tissue eosinophil count,/HPF	227.5 (222.5)	30.7 (49.7)	−180.4 (196.6)	<0.0001	266.4 (215.6)	195.2 (184.0)	−67.7 (205.1)	0.10	−112.7 (−224.6, −0.8)	0.049
Tissue eosinophil percentage, %	47 (27)	19 (25)	−27 (34)	0.00035	55 (23)	48 (32)	−7 (33)	0.27	−20 (−39, −2)	0.035

HPF, Per high power field; IgE, Immunoglobulin E; TARC, Thymus and activator-regulated chemokine. [a]Change from baseline. [b]p value was calculated using two-sample t-test.

***Table 3*: Summary of changes from baseline at week 16 in pharmacodynamics and type 2 inflammation biomarkers.**

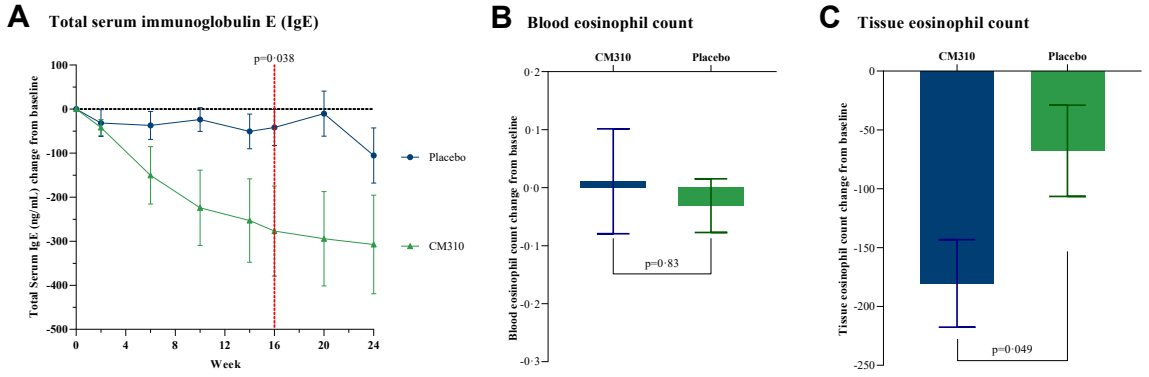

Fig. 4: **Change from baseline in total serum IgE, blood eosinophils, and tissue eosinophils**. A, Change from baseline over time in total serum IgE. B–C, Change from baseline in blood eosinophils and tissue eosinophils. IgE, Immunoglobulin E.

improvement of local eosinophilic inflammation than placebo. CM310 was generally well tolerated and had an acceptable safety profile for the treatment of patients with severe ECRSwNP. All TEAEs were mild or moderate in CM310 group and had resolved or were resolving at or before the last visit.

At present, several monoclonal antibody therapies targeting type 2/eosinophilic inflammatory factors are in different stages of clinical trials for the treatment of CRSwNP. It mainly includes IgE targeting Omalizumab (Novartis/Genentech), IL-5 targeting Reslizumab (Teva) and Mepolizumab (GlaxoSmithKline), IL-5Rα targeting Benralizumab (AstraZeneca) and IL-4Rα targeting Dupilumab (Regeneron/Sanofi), of which, Dupilumab possessed a better efficacy and safety profile compared to the other biologics in indirect treatment comparisons (see Supplementary Table S4).[10,11] For instance, Dupilumab demonstrated superiority over Omalizumab in improving NPS, QoL, and symptoms including the most bothersome anosmia and nasal congestion[8] Compared with Mepolizumab, Dupilumab achieved a LS mean difference of 2.4 points in improvement in NPS relative to placebo after 52 weeks of treatment, which was significantly better than the 0.73 points for Mepolizumab.[12]

Currently, in comparison with the initial fully human monoclonal antibody Dupilumab, CM310 represents the first humanised monoclonal antibody to exhibit both safety and efficacy in individuals with CRSwNP by blocking the IL-4Rα pathway to diminish type 2 inflammation. In addition, despite both CM310 and Dupilumab targets at IL-4Rα, distinct epitopes are selected. Our preclinical data have demonstrated CM310 binds to IL-4Rα at a location closer to the ligand binding site than Dupilumab. In the present study, CM310 demonstrated considerable efficacy profiles, with an improvement in NPS at week 16 (the last dosage of CM310, LS mean difference, –2.1) and week 24 (off-

	CM310 (n = 28)	Placebo (n = 28)
Any adverse event	21 (75%)	22 (79%)
Any serious adverse event	0	3 (11%)
Any adverse event leading to death	0	1 (4%)[c]
Any adverse event leading to permanent treatment discontinuation	0	0
Adverse event occurring in ≥5% of patients[b]		
Upper respiratory tract infection	5 (18%)	4 (14%)
Pneumonia	0	2 (7%)
Asthma	0	6 (21%)
Laryngeal pain	0	2 (7%)
Blood cholesterol increased	2 (7%)	0
Blood triglycerides increased	0	2 (7%)
Toothache	0	2 (7%)
Tinnitus	2 (7%)	0

Data are presented as n (%). [a]The adverse event data collected are from those that emerged from the first treatment or before but exacerbated after first administration. [b]According to Medical Dictionary for Regulatory Activities preferred terms. [c]The death (due to) was deemed not to be related to CM310 therapy.

Table 4: **Adverse events occurred during the study**[a].

treatment follow-up period, LS mean difference, –2.2) comparable to that of Dupilumab in LIBERTY NP SINUS–24 (LS mean difference, –2.06) and SINUS-52 (LS mean difference, –1.80) at week 24 (see Supplementary Table S4).[8] Furthermore, 79% (22/28) of patients on CM310 achieved at least 2-point improvement in NPS at week 16, while for patients on Dupilumab, this percentage was appropriately 46% (66/143 in SINUS-24 and 136/295 in SINUS-52). However, due to the ethnic diversity of patients enrolled and the un-unified eligibility criteria between our trial and those of LIBERTY NP SINUS-24 and SINUS-52, there may be variations in baseline characteristics that could affect treatment outcomes and overall efficiency rate. Therefore, it is necessary to conduct head-to-head comparisons between the trials.

This is the first study to investigate the efficacy of anti-IL-4Rα monoclonal antibody in CRSwNP in the Chinese population. Considering the prevalence difference of ECRSwNP in China (ranging from 20% to 60%) and Western countries (approximately 80%, for instance, in Benelux, Germany and the USA) and the anti-IL-4Rα monoclonal antibodies are supposed to target type 2 inflammation,[13,14] we selected patients with severe ECRSwNP who meet the criteria as outlined in previous studies with expectations for CM310 more tailored to patients.[3–5] As a result, a high proportion of patients with tissue eosinophilia (88% [49/56]) were enrolled. However, no current trial has included local tissue eosinophilia in the evaluation of the eosinophilic status of CRSwNP.[15,16] Results from the post-hoc analysis further indicated that CM310 was more likely to be effective for those with higher levels of nasal mucosal eosinophilic cationic protein-positive cells. Whether the high proportion of patients with tissue eosinophilia is responsible for the good efficacy of CM310 in this study will be further validated in the ongoing phase 3 of CM310 in CRSwNP, which stratifies patients with tissue eosinophils (NCT05436275).

CM310 showed significantly better improvement of tissue eosinophilic inflammation than the placebo. As compared with blood eosinophils, the degree of local eosinophilic infiltration is regarded to be more closely related to the prognosis and severity of the disease.[1,17–19] So far, no previous study has evaluated the effect of type 2-targeting biologics on local eosinophils, while this is the initial study to provide direct pathological evidence on the capacity of anti-IL-4Rα monoclonal antibodies in effectively reducing local type 2 inflammation. We propose that type 2 cytokines and chemokines responsible for attracting eosinophils to the nasal mucosa are produced by both immune and stromal cells, where IL-4Rα is widely distributed and thus can be effectively blocked by anti-IL-4Rα monoclonal antibodies.[20] It is worth mentioning that in placebo-treated patients who received MFNS alone, little reductions were noted in eosinophil infiltration in nasal polyp tissue over the entire study period, indicating that continuous background INCS therapy cannot effectively diminish the local eosinophilic inflammation.

In contrast to local eosinophils, no significant reduction in blood eosinophils was seen at the end of CM310 treatment. Concordant with our study, the finding of blood eosinophil levels remain unaltered following anti-IL-4Rα antibody administration has been evidenced in previous trials of patients with atopic dermatitis, asthma, or CRSwNP.[8,9,21,22] The maturation of eosinophil is stimulated by IL-5 rather than IL-4.[23] In accordance, it is logical to target the IL-5-IL-5R axis instead of the IL-4/IL-13-IL-4R signaling to regulate the number of blood eosinophils. Reduction in blood eosinophils following treatment with biologics targeting IL-5 such as Mepolizumab further supports this hypothesis.[12] Collectively, we suggest that attenuated tissue eosinophil infiltration, instead of a reduction in blood eosinophils, is the primary factor that contributes to suppressing local eosinophilic inflammation after CM310 therapy.

This trial has several clinical implications. The administration of CM310 resulted in inconsistent changes in blood and tissue eosinophil levels, indicating that blood eosinophil counts may not be a reliable parameter for predicting the response early in the treatment course or evaluating the effectiveness of the anti-4Rα monoclonal antibodies. Thereby, it emphasises the great significance of routinely monitoring the levels of local type 2 inflammatory markers throughout the treatment and the follow-up period to assess the severity of mucosal inflammation and to guide the usage of biological treatment. In addition, CM310 exhibited positive outcomes in patients with severe ECRSwNP, irrespective of their history of ESS, indicating its potential as a viable treatment alternative for those with contraindications for ESS.

Our studies had some limitations. The study duration was limited to 16 weeks, which hindered the evaluation of the long-term safety and efficacy of CM310. Further studies are warranted to confirm these findings and properly define the target population. We will assess the long-term efficacy and safety during or more than 24 weeks in the ongoing phase 3 clinical study of CM310 (NCT05436275) with a large sample size.

In conclusion, our data support the benefits of CM310 in patients with severe ECRSwNP as an effective approach to treating the entire spectrum of clinical manifestations.

Contributors

YZ, BY, SS, XS, YJ, LS, CZ, YY, LJ, JL, JY, JL, LW, YY, JC, FL, LS, YX, GT, SY, YZ, LW, SL, HY, WL, BC, CW, and LZ developed the initial research concept, contributed to protocol development, study procedures, and delivery of the study. WL wrote the first draft of the manuscript. YZ, BY, HY, WL, BC, and CW reviewed and revised the manuscript. CW and LZ have full access to the data and verified the data. All authors approved the final version of the manuscript and had final responsibility for the decision to submit for publication.

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

Declaration of interests
HY, WL, and BC are employees of Keymed Biosciences (Chengdu) Limited. All other authors declare no competing interests.

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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102076.

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