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Anti-IL-4Rα monoclonal antibody (CM310) in patients with chronic rhinosinusitis with nasal polyps (CROWNS-2): Rationale and design of a multicenter, randomized, double-blind, placebo-controlled, parallel-group study

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ABSTRACT

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) is a heterogeneous disease that affects a large proportion of the global population. The treatment of CRSwNP, especially eosinophilic CRSwNP (ECRSwNP), has always been of great obstacle. Our previous phase 2 trial showed that CM310, a monoclonal antibody that targets interleukin-4 receptor alpha, was both safe and effective in reducing the size of nasal polyps, improving symptom scores, and increasing the quality of life for those with severe ECRSwNP.

Objective: This phase 3 trial aims to evaluate the efficacy, safety, pharmacokinetic, pharmacodynamic, and immunogenicity of CM310 in participants with CRSwNP.

Result: The CROWNS-2 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial. The study consisted of a screening/run-in period (up to 4 weeks), a treatment period (24-week double-blind treatment period plus 28-week maintenance period), and a safety follow-up period (8 weeks). The study planned to enroll 180 participants with CRSwNP (at least 60% of ECRSwNP) to receive CM310 300 mg/placebo every 2 weeks (Q2W) subcutaneously for a total of 12 doses in double-blind treatment period and 300 mg CM310 Q2W subcutaneously for a total of 14 doses in maintenance period. Enrolled participants continued to use mometasone furoate nasal spray throughout the study. The primary endpoints are a change from baseline in nasal polyp score and nasal congestion score at week 24 between CM310 and placebo in both ECRSwNP and CRSwNP.

Conclusion: The CROWNS-2 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical study to evaluate the efficacy and safety of CM310 in patients with CRSwNP.

Trial registration: NCT05436275.

Keywords: Chronic rhinosinusitis with nasal polyps; interleukin-4 receptor alpha; placebo-controlled; randomized

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1. Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a heterogeneous disease that affects a large proportion of the global population. The prevalence of CRSwNP reported in China was 1.1% [1].

Precious study showed that CRSwNP can be classified into 5 phenotypes: eosinophil-dominant, neutrophil-dominant, lymphocyte-dominant, plasma cell-dominant, and mixed CRSwNP [2]. The recurrence rate of CRSwNP is as high as 55.3% [3]. The treatment of CRSwNP especially eosinophilic CRSwNP (ECRSwNP) has always been a challenge. Although oral corticosteroids (OCS) can attenuate nasal inflammation in CRSwNP, their side effects and poor maintenance of efficacy cannot be ignored [4]. Shao et al. [5] found that 43.8% of patients develop uncontrolled status at 9 weeks after OCS therapy. Zhang et al. [6] found that even after radical endoscopic sinus surgery combined with Draf 3, the recurrence rate after 5-year follow-up was 96%.

Recently, biological agents such as dupilumab, omalizumab, and mepolizumab have played important roles as add-on therapies in the treatment of CRSwNP [7-9]. Three network meta-analyses compared the efficacy of anti-interleukin (IL)-4 receptor alpha (IL-4Rα), anti-IL-5, anti-IL-5R, anti-immunoglobulin E (IgE),

anti-IL-33, and anti-siglec-8 monoclonal antibodies in the treatment of CRSwNP and found that the efficacy of anti-IL-4Rα monoclonal antibody was obviously superior [10-12]. CM310 is a recombinant humanized monoclonal antibody injection against IL-4Rα developed by KeyMed Biosciences (Chengdu) Co., Ltd (Chengdu, Sichuan, China). CM310 can specifically bind to IL-4Rα and suppress the signaling of IL-4 and IL-13, thereby inhibiting T helper 2 (Th2) cytokine-mediated inflammatory response. Previous phase 2 study has shown that CM310 can significantly reduce the size of nasal polyps, improve patients' symptom scores and quality of life (QoL), and have good safety [13].

To better explore the efficacy, safety, pharmacokinetic (PK), pharmacodynamic (PD), and immunogenicity of CM310 in patients with CRSwNP, we designed a phase 3 study.

2. Methods

2.1. Study design

The CROWNS-2 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial to evaluate the efficacy and safety of CM310 in participants with CRSwNP. The study plans to enroll 180 participants with CRSwNP, of which at least 60% are characterized as ECRSwNP. ECRSwNP needs to meet either of the following criteria: (1) percentage of peripheral blood eosinophil ≥6.9% (participants without asthma) or ≥3.7% (participants with asthma) at screening/run-in period; (2) the count of eosinophil in nasal polyp ≥55/high power field (HPF) or percentage ≥27% during screening/run-in period. Those who do not meet the above criteria will be referred to as the non-ECRSwNP. The study will be composed of 3 periods: a screening/run-in period of up to 4 weeks, a 52-week treatment period (24 weeks of double-blind treatment period + 28 weeks of maintenance period), and a safety follow-up period of 8 weeks. Eligible participants will be assigned to subcutaneous CM310 300 mg/placebo every 2 weeks (Q2W) at double-blind treatment period, then receive CM310 300 mg, Q2W at maintenance period. During the study period, all participants will continue to use mometasone furoate nasal spray (MFNS), 200 μg/time, once daily. The graphical study design is shown in Figure 1.

2.2. Participants

2.2.1. Inclusion criteria Participants must meet all of the following inclusion criteria to be eligible for participation in this study:

[1] Able to understand the purpose of the study and voluntarily sign the informed consent form (ICF);
[2] Should be 18~75 years of age (both inclusive), male or female;
[3] Bilateral CRSwNP meeting the diagnostic criteria of Chinese Guidelines for the Diagnosis and Treatment of Chronic Sinusitis (2018);
[4] Participants who have received systemic corticosteroids (SCS) treatment such as OCS within 2 years before screening but still have bilateral CRSwNP, have contraindications or intolerance to SCS treatment, and/or have received surgical treatment for nasal polyps within 6 months before screening;
[5] Have been on intranasal corticosteroids at a stable dose for ≥4 weeks prior to screening;
[6] Concurrent presence of the following symptoms for ≥4 weeks prior to the screening/run-in period: (i) nasal congestion; (ii) any other symptom such as decrease/loss of smell or rhinorrhea (anterior/posterior);
[7] At screening/run-in and baseline, a total bilateral nasal polyp score (NPS) ≥5 and at least NPS ≥ 2 in each nasal cavity (based on central reading);
[8] Moderate to severe nasal congestion (nasal congestion score [NCS] of 2 or 3) at screening/run-in visit; average weekly NCS score ≥ 2 points at baseline;
[9] Compliance of ≥80% with MFNS administration during the run-in period;
[10] The participants agree to use a highly effective method of birth control throughout the study (from signing the ICF until 3 months after the last dose of investigational medicinal product [IMP]).

2.2.2. Exclusion criteria Participants are not enrolled if they meet any of the following criteria:

[1] Treatment with anti-IL-4Rα monoclonal antibody, anti-thymic stromal lymphopoietin monoclonal antibody, anti-IgE monoclonal antibody, other monoclonal antibodies, or other biologic agents within 10 weeks or 5 half-lives (whichever is longer) prior to baseline;
[2] Previous participation in any clinical trial with CM310;
[3] Systemic immunosuppressants (including but not limited to methotrexate, cyclosporine, mycophenolate mofetil, tacrolimus, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine, and cyclophosphamide) for the treatment of inflammatory diseases or autoimmune diseases (such as rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus

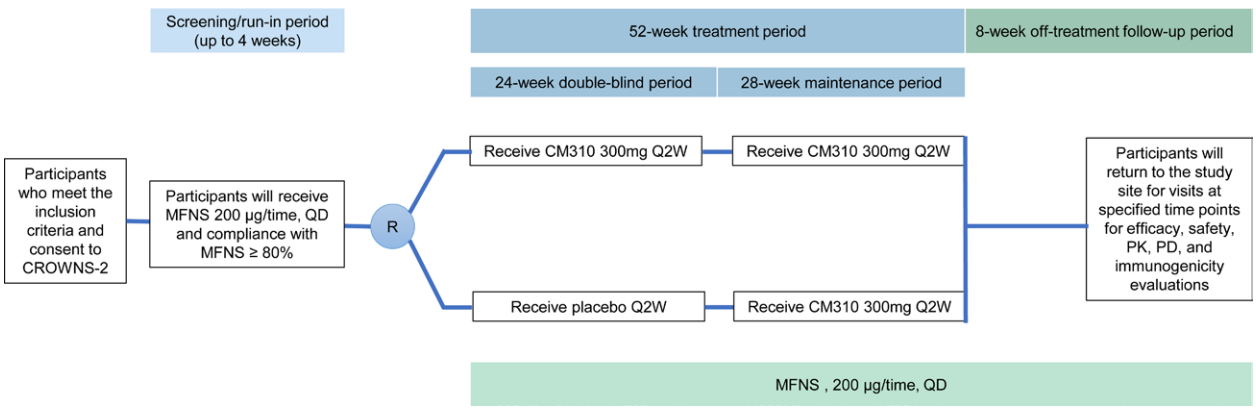

Figure 1. Graphical study design. MFNS, mometasone furoate aqueous nasal spray; PD, pharmacodynamics; PK, pharmacokinetics; R, randomisation; Q2W, every two weeks; QD, once daily.

erythematosus, and multiple sclerosis) within 8 weeks or 5 half-lives (whichever is longer) prior to baseline;
[4] Initiation of leukotriene receptor antagonist treatment within 4 weeks prior to baseline (those who have received a stable dose of leukotriene receptor antagonist treatment for at least 4 weeks prior to randomization can be enrolled);
[5] Initiation of allergen-specific immunotherapy (desensitization therapy) within 3 months prior to baseline or planned initiation of such therapy within the study period;
[6] Participants who have received medium- or short-acting SCS (including oral, intravenous, or intramuscular glucocorticoids), traditional Chinese medicine (including systemic and local traditional Chinese medicine preparations) for chronic rhinosinusitis within 4 weeks prior to screening, long-acting SCS (such as triamcinolone acetonide injection) within 6 weeks prior to screening, or plan to receive the above drugs during the study;
[7] Infections requiring treatment with systemic antibacterial, antiviral, antifungal, antiparasitic, or antiprotozoal agents within 7 days prior to baseline;
[8] Participants with concomitant asthma and initiation of inhaled glucocorticoid treatment within 4 weeks prior to screening (stable dose of inhaled glucocorticoid treatment for at least 4 weeks prior to screening and assessed as appropriate to maintain the dose in double-blind period; dose of inhaled glucocorticoid is ≤1000 μg fluticasone propionate or equivalent dose of other inhaled glucocorticoid; participant's condition is stable as assessed by the investigator);
[9] Participants with forced expiratory volume in 1 second (FEV_1) ≤50% of predicted normal during screening/run-in period;
[10] Nasal surgery (including nasal polypectomy) within 6 months prior to screening; or participants who have had surgery that alters nasal structure and precludes assessment of NPS;
[11] Antrochoanal polyp;
[12] More severe septal deviation obliterating at least one nostril;
[13] Persistent rhinitis medicamentosa;
[14] Allergic granulomatous vasculitis (Churg–Strauss syndrome), granulomatosis with polyangiitis (Wegener granulomatosis), Young syndrome, Kartagener syndrome or other ciliary dyskinesia syndromes, and cystic fibrosis;
[15] Acute rhinosinusitis, nasal infection or upper respiratory tract infection at screening or within 2 weeks prior to screening;
[16] Symptomatic or computed tomography (CT) scan suggestive of allergic fungal rhinosinusitis;
[17] Malignant tumor or benign tumor of the nasal cavity;
[18] Participants who have received prior treatment with anti-IL-4Rα monoclonal antibody drugs (eg, dupilumab) with poor response (eg, treatment failure or participants who are intolerant to the treatment);
[19] Hypersensitivity to MFNS or anti-IL-4Rα monoclonal antibodies or CM310 components;
[20] Concomitant with other poorly controlled serious diseases or recurrent chronic diseases, including but not limited to active infection, cardiovascular and cerebrovascular diseases, pulmonary tuberculosis or other pathogen infection, diabetes, autoimmune diseases, human immunodeficiency virus infection, treponema pallidum infection, active hepatitis B, hepatitis C, or parasitic diseases;
[21] Participants with malignancy within 5 years prior to screening (except for completely cured cervical carcinoma in situ and nonmetastatic squamous cell or basal cell carcinoma of the skin);
[22] Participants with severe hepatic or renal impairment, such as aspartate aminotransferase or alanine aminotransferase > 2 times of the upper limit of normal (ULN), total bilirubin >1.5 times the ULN, or serum creatinine >1.2 times of the ULN;
[23] Vaccination with a live-attenuated vaccine within 12 weeks prior to randomization or planned vaccination during the study;
[24] Known or suspected immunosuppression, including but not limited to a history of invasive opportunistic infections (eg, tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis), even if the infection has resolved; or unusually frequent, recurrent or long-term infections (as judged by the investigator);
[25] Pregnant or breast-feeding women, or women who plan to become pregnant or breast-feeding during the study;
[26] Heavy alcohol consumption (ie, more than 14 units of alcohol per week [1 unit = 360 ml of beer or 45 ml of spirits with 40% alcohol content or 150 ml of wine]) or history of drug abuse within 3 months prior to screening;
[27] Participants of other medical or nonmedical conditions that, in the opinion of the investigator, would make participation in the study unsuitable.

2.3. Objectives

2.3.1. Primary objective To evaluate the efficacy of CM310 in participants with bilateral CRSwNP.

2.3.2. Secondary objectives

(1) To evaluate the safety of CM310 in participants with CRSwNP;
(2) To evaluate the PK profile of CM310 in participants with CRSwNP;
(3) To evaluate the PD effects of CM310 in participants with CRSwNP;
(4) To evaluate the immunogenicity of CM310 in participants with CRSwNP.

2.3.3. Exploratory objectives To explore the lung function improvement of CM310 in participants with CRSwNP and asthma.

2.4. Randomization and blinding

Patients were randomly assigned (1:1) to CM310 or placebo and allocated according to an Interactive Web Response System. Randomization statistician generated the patient randomization list by stratified block randomization method and SAS 9.4 (100 SAS Campus Drive Cary, NC, USA). The stratification factors included the status of comorbid asthma, sinonasal surgery history, and eosinophilic status.

CM310 and matching placebo were packaged in vials with identical appearance. Patients and investigators were masked to treatment assignment during the double-blind period. Allocation and treatment group information was concealed until database of double-blind period lock.

2.5. Intervention

The IMPs in this study include the CM310 and its placebo, which are provided by KeyMed Biosciences (Chengdu) Co., Ltd.

The strength of CM310 is 300 mg/2 ml. The placebo matching CM310 is prepared from the same formulation without the protein. Both CM310 and placebo are packaged in vials and are indistinguishable by the naked eye. Storage condition: 2~8°C, protected from light.

2.5.1. Double-blind treatment period Participants who meet the inclusion criteria will be assigned to subcutaneous CM310 300 mg or placebo Q2W for 24 weeks in a 1:1 ratio, depending on their group.

2.5.2. Maintenance period All participants will receive 300 mg CM310 Q2W for a total of 14 doses. In general, the interval between 2 adjacent doses should not be less than 11 days. In view of the uncontrollable factors such as COVID-19 pandemic, on the premise of ensuring the safety, rights, and interests of participants, it is acceptable to occasionally administer adjacent doses with an interval of 7 to 11 days (inclusive).

2.6. Sample collection

(1) Blood samples will be collected for analysis of routine blood tests, blood biochemical, PK, PD, immunogenicity, serum thymus activation-regulated chemokine (TARC), serum total IgE, serum eotaxin-3, and subsequent exploratory studies at visit (V) 2, V4, V6, V8, V10, V12, V14, V16, V18, V22, V28, and V29;
(2) Sample collection of nasal polyp biopsy: nasal polyp biopsy will be performed at the screening/run-in period, V14, and end of treatment. Nasal polyp biopsy samples will be collected by each study site and sent to the leading site for central reading, and some of them will be used for subsequent exploratory studies;
(3) Nasal secretions sample collection: nasal secretions sample collection will be performed at V2, V4, V6, V8, V10, V12, V14, V16, V18, V22, V25, V28, and V29. Nasal secretion samples will be used for subsequent potential exploratory studies;
(4) Nasal brushing sample collection: nasal brushing sample collection will be performed at V2, V4, V6, V8, V10, V12, V14, V16, V18, V22, V25, V28, and V29. Nasal brushing samples will be used for subsequent potential exploratory studies.

2.7. Outcomes

2.7.1. Primary outcomes

(1) Change from baseline in NPS in participants with ECRSwNP and CRSwNP at week 24;
(2) Change from baseline in NCS in participants with ECRSwNP and CRSwNP at week 24.

2.7.2. Secondary outcomes

2.7.2.1. Efficacy outcomes

[1] Change from baseline in NPS at each visit;
[2] Proportion of participants with ≥1 point improvement from baseline in NPS at each visit;
[3] Proportion of participants with ≥2 points improvement from baseline in NPS at each visit;
[4] Change from baseline in NCS, total symptom score (TSS), loss of smell, University of Pennsylvania Smell Identification Test score, Lund–Mackay CT score, 22-item Sinonasal Outcome Test, asthma control scale-6 (in participants with prior asthma), and visual analog scale score for the European QD-5L at each visit;
[5] Proportion of participants who received rescue therapy;
[6] The time to the first use of rescue therapy.

2.7.2.2. Safety outcomes Adverse events (AEs), abnormalities in laboratory tests, physical examination, vital signs, 12-lead electrocardiogram, etc.

2.7.2.3. PK and PD outcomes

(1) Plasma concentration of CM310;
(2) Extends and rates of change from baseline in serum human TARC concentration, plasma eotaxin-3 concentration, serum total IgE concentration, and nasal polyp biopsy eosinophil count at each visit.

2.7.2.4. Immunogenicity outcomes Incidence of treatment-emergent antidrug antibodies and neutralizing antibodies.

2.7.3. Exploratory outcomes Changes from baseline in FEV_1, forced vital capacity, and mean flow with the forced expiratory volume of 25%~75% vital capacity at each visit (only for participants with asthma).

2.8. Quality control and assurance

The sponsor and the investigator should establish their own quality assurance systems, fulfill their respective responsibilities, strictly follow the clinical study protocol, and adopt the corresponding standard operating procedures to ensure the implementation of quality control and quality assurance systems in clinical studies. Prior to the clinical trial, the sponsor should evaluate whether the study institution and the investigators have the appropriate qualifications and capabilities to properly conduct the study. Prior to the start of the clinical study, all personnel participating in the study must be trained on the study protocol through the kick-off meeting or the investigator meeting. During the study, the sponsor's monitors or its representatives should maintain regular communication with the study sites via telephone and in writing. To evaluate compliance with regulatory requirements, ensure the safety, welfare, and privacy of participants are protected, and ensure the protocol compliance, completeness, and accuracy of case report form (CRF) data entry, validation of CRF data and source documents, and monitor the occurrence of AEs, periodic on-site monitoring will be performed. Additionally, the sponsor or its representatives may conduct audits in the study sites. Regulatory authorities may inspect the study sites during or after the completion of the study.

2.9. Sample size

Based on the previous phase 2 study [13], we assumed the treatment effects of CM310 in ECRSwNP to be −1.62 (standard deviation [SD] =1.85) in the change from baseline in NPS at week 24 and −0.76 (SD = 1.16) in the change from baseline in NCS at week 24. With an allocation ratio of 1:1 and 2-tailed alpha 0.05, a sample size of 108 would provide a power of 99.46% and 92.12% to detect the difference between CM310 and placebo groups in the change from baseline in NPS and NCS at week 24, respectively. For participants with CRSwNP (at least 60% ECRSwNP), effects of CM310 were estimated to be −1.17 (SD = 1.85) in the change from baseline in NPS at week 24 and −0.55 (SD = 1.16) in the change from baseline

in NCS at week 24. A sample size of 180 (allocation ratio 1:1) would provide a power of 98.81% and 88.56% (2-tailed alpha = 0·05) to detect the difference between treatment groups in the change from baseline in NPS and NCS at week 24, respectively. The sample size calculations were completed using PASS 2022 (329 North 1000 East Kaysville, UT, USA).

Considering the sample size calculations based on both the ECRSwNP and the CRSwNP, this study plans to enroll a total of 180 participants, with 90 participants per group.

2.10. Statistical analysis

Efficacy endpoints will be analyzed based on the efficacy analysis set, including all randomized participants who received at least one dose of IMP and had at least one efficacy data collected. Safety analyses will be performed in the safety set, including all participants who received at least one dose of IMP. PD set and immunogenicity set include all participants who received at least one dose of IMP and have at least one valid postdose data.

Efficacy analyses will be performed separately in participants with ECRSwNP and CRSwNP. For participants without rescue therapy, prohibited concomitant medication affecting efficacy, and early termination of treatment due to lack of efficacy, missing continuous data were multiply imputed. For participants with rescue therapy, prohibited concomitant medication affecting efficacy, and early termination of treatment due to lack of efficacy, data collected afterward will be set to missing and imputed using the worst observation carried forward method, and a multiple imputation approach will be used to impute missing values for the other participants. Each of the imputed complete data will be analyzed by an analysis of covariance model with the baseline value of the corresponding endpoint, treatment, and randomization stratification factors as covariates. Statistical inference obtained from all imputed data will be combined using Rubin rule. The least squares mean and 95% confidence interval (95% CI) are displayed.

The 95% CI of the percentage of participants with improvement in NPS ≥ 1 or 2 will be calculated using the Clopper–Pearson method, and the difference between groups and the corresponding 95% CI will be calculated using the stratified Newcombe method and tested by stratified Cochran–Mantel–Haenszel method with adjustment for the randomization stratification factors. For participants without rescue therapy, prohibited concomitant medication affecting efficacy and early termination of treatment due to lack of efficacy, missing binary data is imputed as nonresponse.

AEs will be coded according to the Medical Dictionary for Regulatory Activities and treatment-emergent AEs were mainly analyzed by system organ class and preferred term.

SAS 9.4 (100 SAS Campus Drive Cary, NC 27513-2414, USA) will be used for statistical analyses.

2.11. Ethics

Ethical approval for this study (TREC2022-48) was provided by the Ethical Committee of Beijing TongRen Hospital, Beijing, China (Chairperson Prof Yan Liu) on June 9, 2022. This protocol is version 4.0, dated November 11, 2022 (sponsor protocol number CM310-102208). The first participant was enrolled on August 9, 2022. The study is expected to be completed in July 2024. The study is currently in the maintenance period.

3. Discussion

ECRSwNP has a high recurrence rate and inevitably needs repeated rescue surgeries. Lou et al. [3] found that a percentage of eosinophils exceeding 27% or a count exceeding 55/HPF in nasal polyp tissue can effectively predict the postoperative recurrence. ECRSwNP is difficult to control with conventional treatment. As add-on therapies, monoclonal antibodies such as dupilumab, omalizumab, and mepolizumab have been proven to be effective [7-9]. Among them, the anti-IL-4Rα monoclonal antibodies have proved to be effectively blocking the interaction between IL-4 and IL-13 with the coreceptor IL-4Rα, thereby inhibiting type 2 inflammation. As an anti-IL-4Rα monoclonal antibody, CM310 has been shown to significantly improve NPS, NCS, Lund–Mackay CT score, TSS, and QoL of severe ECRSwNP in phase 2 trial (CROWNS-1 study) [13].

The CROWNS-2 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical study to evaluate the efficacy and safety of CM310 in patients with CRSwNP. To better validate the efficacy and safety of CM310, we have expanded the sample size of patients in this study. In addition, this study also included non-ECRSwNP, and the efficacy of CM310 in patients with non-ECRSwNP will be presented in subgroup analysis.

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Conflicts of interest

The authors have no financial conflicts of interest.

Author contributions

CW and LZ provided input for the study design. SS, BY, MW, and DW prepared the manuscript. All authors have read and approved the final manuscript.

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