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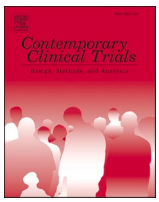

Design of a phase 3, randomized, double-blind, placebo-controlled, 48-week study to evaluate the efficacy and safety of cendakimab in adult and adolescent patients with eosinophilic esophagitis

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ABSTRACT

Background: Eosinophilic esophagitis (EoE) is a chronic, immune-mediated inflammatory condition that interferes with normal food ingestion, negatively impacting quality of life (QoL). Treatment options include proton pump inhibitors, corticosteroids, biologics, or dietary elimination; however, ~1/3 of patients remain insufficiently controlled. The pathogenesis of EoE involves interleukin-13 (IL-13); therefore, targeted IL-13 inhibition may be beneficial. In a phase 2 study, cendakimab, a recombinant, humanized anti–IL-13 monoclonal antibody, significantly reduced mean esophageal eosinophil counts and improved other inflammatory parameters in patients with EoE. These findings prompted further investigation of the efficacy and safety of cendakimab in adults and adolescents with EoE in a phase 3 registrational study (NCT04753697), the design of which is presented here.

Methods: This multicenter, multinational, randomized, double-blind, placebo-controlled, 48-week, treat-through study plans to enroll 399 adults and adolescents. Randomized patients (1:1:1) will receive subcutaneous administration of 1) cendakimab 360 mg once weekly (QW) for 48 weeks, 2) cendakimab 360 mg QW for 24 weeks followed by cendakimab 360 mg every other week (with matching placebo on alternative weeks to maintain the blind) for 24 weeks, or 3) placebo QW for 48 weeks. Co-primary endpoints are mean change from baseline in dysphagia days and proportion of patients with eosinophil histologic response, defined as peak esophageal eosinophil count ≤6 per high-power field, at 24 weeks. Secondary and exploratory endpoints will address endoscopic and histologic features, QoL, safety, and pharmacokinetic assessments.

Conclusion: This phase 3 pivotal study will determine whether cendakimab provides an effective, safe, targeted treatment for patients with EoE.

1. Introduction

Eosinophilic esophagitis (EoE) is a chronic, progressive, type 2 inflammatory disease characterized by esophageal inflammation with infiltration of eosinophils and symptoms of esophageal dysfunction [1–3]. In the United States, peak EoE prevalence in 2019 among females was between ages 40 and 44 years (44.5 per 100,000) and among males was between ages 35 and 39 years (95.9 per 100,000) [4], and a consistent rise in both incidence and prevalence rates of EoE across North America and Europe has been observed among children and adults [5]. EoE is the primary cause of esophageal food impaction, and dysphagia is one of the most common symptoms in adolescents and adults with EoE, although chest pain, gastroesophageal reflux disease–like symptoms, upper abdominal pain, and feeding dysfunction are

Abbreviations: DD, dysphagia day; EGD, esophagogastroduodenoscopy; EoEHSS, EoE histology scoring system; eos/hpf, eosinophils per high-power field; EREFS, EoE Endoscopic Reference Score; mDSD, modified Daily Symptom Diary; OLE, open-label extension.

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also reported across all ages [6–11]. The standard of care for patients with EoE includes first-line treatment with proton pump inhibitors (PPIs), swallowed topical corticosteroids, and/or dietary elimination; however, according to real-world data, one-third of patients with EoE are not in histologic and clinical remission under PPIs, topical steroids, or elimination diets [12–14]. The approval of the first biologic and two topical corticosteroid formulations (an orodispersible tablet available outside of the US and an oral suspension approved in the US) have expanded available treatment options [15–21].

The detailed mechanisms underlying EoE pathogenesis remain unclear; however, the infiltrating cell profile and overexpression of cytokines, particularly interleukin (IL)-13 and IL-5, are indicative of a type 2, cell-mediated inflammatory disease [3], involving innate and adaptive immune cells that produce IL-4, IL-5, and IL-13 [1,22]. The chronic inflammation in EoE is believed to be influenced by cytokine signaling as evidenced by the overexpression of IL-13 previously identified in the esophageal mucosa of patients with EoE [3,22]. IL-13 modulates cellular and molecular pathways involved in eosinophil recruitment [23], esophageal barrier function [24], and tissue remodeling and fibrosis [25]. In animal models, induced overexpression of IL-13 has been shown to cause changes in EoE disease status, esophageal function, and other related consequences [25,26]. These data suggest that a biologic agent targeting IL-13 may help control inflammation and fibrosis in patients with EoE.

Cendakimab (CC-93538 or BMS-986355, formerly RPC4046) is a recombinant, humanized, high-affinity, neutralizing immunoglobulin G1 kappa monoclonal antibody selective for IL-13. Binding of cendakimab to IL-13 prevents its interaction with IL-13 receptor alpha 1 (IL-13Rα1) and 2 (IL-13Rα2) [27]. In a phase 2, multicenter, randomized, double-blind, placebo-controlled study (NCT02098473) in 99 adults with clinically and histologically active EoE, subcutaneous (SC) administration of cendakimab 180 mg and 360 mg once weekly for 16 weeks significantly reduced the mean esophageal eosinophil count (primary endpoint) compared with placebo in the overall population, as well as in steroid-refractory patients, with no unexpected safety signals, supporting its continued clinical development [28]. In addition, improvement was demonstrated on validated, objective measures of endoscopic and histologic disease activity (EoE Endoscopic Reference Score [EREFS] and EoE histology scoring system [EoEHSS], respectively) [29,30]. Continued efficacy and safety were also observed in an optional 52-week, open-label extension (OLE) of the study following the 16-week double-blind treatment period (NCT04991935) [31].

Here, we describe the design of a phase 3 registrational study to evaluate the efficacy and safety of cendakimab versus placebo (NCT04753697) in adults and adolescents with EoE.

2. Methods

2.1. Study objectives

The primary objectives of this study are to evaluate the efficacy of cendakimab administered SC once weekly versus placebo in reducing dysphagia symptoms and esophageal eosinophil counts following up to 24 weeks of treatment (induction phase). Key secondary objectives are to assess improvements in endoscopic and histologic features of EoE with cendakimab versus placebo at 24 weeks and to measure the persistence of effect of cendakimab (administered once weekly or once every other week from week 24 to week 48 [maintenance phase]) in reducing dysphagia symptoms and esophageal eosinophil counts and improving endoscopic and histologic features of EoE. Further secondary objectives include an evaluation of time-to-event and frequency of EoE flare events and corresponding use of rescue therapy, an evaluation of safety and tolerability of cendakimab including characterization of the immunogenicity profile, and an assessment of trough concentrations of cendakimab in patients with EoE. Select exploratory objectives in both the induction and maintenance phases include the proportion of patients with an eosinophil histologic and clinical response, changes in the Eosinophilic Esophagitis Activity Index and the Pediatric Eosinophilic Esophagitis Symptom Severity score, analysis of additional EoE symptoms (e.g., solid food avoidance, pain) as reported in the modified Daily Symptom Diary (mDSD), and an exploration of the clinical profile of cendakimab as a function of EoE biomarker expression in response to treatment.

2.2. Study design

This is a phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled treat-through study that includes a screening period of up to 4 weeks for symptom scoring (with up to 8 weeks allowed for esophagogastroduodenoscopy [EGD]). After this screening period, eligible patients will enter a 24-week induction phase, followed by a 24-week maintenance phase. Patients completing week 48 may transition to an optional OLE. Safety follow-up visits will take place 8 and 16 weeks after the final dose for those who do not enter the OLE or who discontinue the study prematurely (Fig. 1). The protocol was approved by the institutional review board/independent ethics committee of each site prior to the start of the study, and all personnel follow Good Clinical Practice, as described in International Council for Harmonisation Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study was designed in accordance with the US Food and Drug Administration guidance for developing drugs for EoE treatment, including the primary evaluation of efficacy at week 24, and incorporated global health authority feedback [32]. At the time of study design and protocol development, no approved treatments were available in the United States (US) for patients with EoE, and while the budesonide orodispersible tablet was approved in the European Union, the study population planned for enrollment targeted around 70 % steroid refractory or intolerant patients. Therefore, a placebo-controlled design was chosen to provide a robust assessment of the efficacy and safety of cendakimab. Patients are permitted to continue a stable dose of a PPI at study entry if use provides a benefit to the patient but does not result in a complete response. Further, the design of this study allows for the use of concomitant rescue therapy (standard-of-care pharmacotherapy, dietary elimination, and/or esophageal dilation) for a severe EoE flare (defined as any worsening of EoE symptoms, including a high-intensity episode resulting in an emergency department visit or hospitalization with the need for endoscopic intervention such as food impaction removal and/or the need for rescue therapy, or a worsening of EoE symptoms resulting in the need for rescue therapy only, without endoscopic intervention) ensuring patients have access to the available standard of care (if needed) while participating in the study.

After completion of 24 weeks (induction phase), eligible patients will continue participation until week 48 under placebo-controlled conditions (maintenance phase). Patients who complete week 48 will be eligible to enroll in the separate, optional OLE study. Patients who do not qualify for entry into the maintenance phase, including those with a severe EoE flare requiring endoscopic intervention and/or concomitant rescue therapy in the initial 24 weeks and those with significant worsening (i.e., development of severe rings or strictures requiring dilation) on endoscopic assessment from baseline to week 24, will be eligible to enroll in the OLE study following completion of week 24. Patients who experience a severe EoE flare requiring endoscopic intervention and/or concomitant rescue therapy in the maintenance phase will be eligible for enrollment in the OLE study after completing week 48. Patients who are permanently discontinued from the study drug are encouraged to remain in the phase in which the discontinuation occurs in order to complete all efficacy and safety assessments.

2.3. Patient population

Patients aged 12 to 75 years with histologic evidence of EoE and at

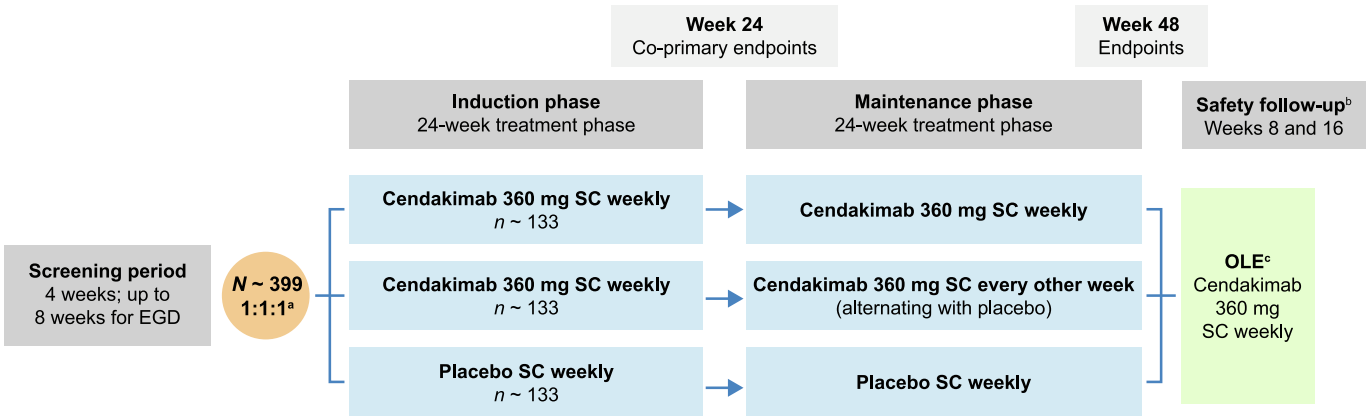

Fig. 1. Study design. EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; OLE, open-label extension; SC, subcutaneous.
[a]Treatment is assigned at baseline and is stratified by steroid responder status; [b]Patients who do not participate in the OLE study or who discontinue the study prematurely will complete 2 safety follow-up visits, at week 8 and 16, after the final dose of cendakimab or placebo; [c]Patients with a severe EoE flare requiring endoscopy and/or concomitant rescue therapy during the induction phase will be eligible for entry into the OLE study at week 24.

least 4 dysphagia days (DDs), as assessed with the patient-reported mDSD over the previous 2 consecutive weeks prior to day 1, are eligible. The study includes both patients who are classified as steroid inadequate responders/intolerant (patients with an inadequate response or intolerance to corticosteroid therapy; approximately 70 % of the study population) and as steroid responders/naive (patients who were naive to steroid treatment or had an adequate response to previous steroid therapy). All patients are required to provide signed, written

Table 1
Key eligibility criteria.

Inclusion criteria
- Males or females aged ≥12 and ≤ 75 years
- Body weight ≥ 40 kg
- Histologic evidence of EoE (peak count of ≥15 eos/hpf at any 2 levels [proximal, mid, and/or distal] of the esophagus) as confirmed by a centrally read assessment of EGD biopsies
- Patient-reported history of ≥4 DDs, as assessed with the mDSD instrument, within the 2 consecutive weeks prior to the end of screening
- Lack of complete response to an adequate trial of a PPI (8 weeks); patients on a PPI must have been on a stable dose for ≥4 weeks prior to first screening visit and agree to continue the same dose throughout the study
- Patients currently receiving inhaled corticosteroids, leukotriene receptor antagonists, or mast cell stabilizers for indications other than EoE, or medium-potency topical corticosteroids for dermatologic conditions, must maintain stable doses for ≥4 weeks prior to the first screening visit and throughout the study
- Patients must agree to maintain a stable diet (including any food elimination diet for the treatment of food allergy or EoE) and not introduce any changes in their diet from the first screening visit to the end of the study
- Females of childbearing potential must have 2 negative pregnancy tests as verified by the investigator prior to starting study therapy and agree to practice a highly effective method of contraception until 5 months after the last dose
- Patients must be either (1) naive or have had an adequate response to corticosteroid therapy (classified as steroid responders/naive) or (2) have had an inadequate response to corticosteroid therapy and are not considered to be a candidate for continued corticosteroid therapy, or are intolerant to corticosteroid therapy (classified as steroid inadequate responders/intolerant; ~70 % of the study population)

Exclusion criteria
- Clinical or endoscopic evidence of other diseases that may affect the histologic, endoscopic, and clinical symptom evaluation
- Other GI disorders (e.g., active *Helicobacter pylori* infection, esophageal varices, gastritis, colitis, celiac disease, Mendelian disorder associated with EoE, liver function impairment, or known hereditary fructose intolerance)
- Evidence of a severe endoscopic structural abnormality in the esophagus
- Esophageal dilation for symptom relief within 8 weeks prior to first screening visit or during the screening period or if esophageal dilation is anticipated within 48 weeks of dosing during the study
- Evidence of immunosuppression or of having received systemic immunosuppressive or immunomodulating drugs within 5 drug half-lives prior to the first screening visit (exceptions are if corticosteroids are used as rescue therapy for an EoE flare or AE treatment)
- Treatment with a high-potency topical corticosteroid for dermatologic use or a systemic corticosteroid within 8 weeks of the first screening visit
- Treatment with a swallowed topical corticosteroid, leukotriene receptor antagonist, or mast cell stabilizer for EoE within 4 weeks of the first screening visit
- Treatment with oral or sublingual immunotherapy within 6 months of the first screening visit (any use will be prohibited during the study); subcutaneous immunotherapy may be allowed if on stable doses for at least 3 months prior to the first screening visit and during the study
- Actively successful dietary modification adherence (e.g., food elimination diet) resulting in a complete response to EoE
- Prior treatment with cendakimab during a phase 1 or 2 clinical study
- Receipt of a live attenuated vaccine within 4 weeks of the first screening visit
- Any disease that would affect the conduct of the protocol or interpretation of the study results or would put a patient at risk by participating in the study (severe uncontrolled asthma, infection causing eosinophilia, hypereosinophilic syndrome, or cardiovascular condition or a neurologic disorder or psychiatric illness that compromises the patient's ability to accurately document symptoms of EoE)
- Active or ongoing infections, including parasitic/helminthic, hepatitis, tuberculosis, or HIV
- SARS-CoV-2 infection within 4 weeks of the first screening visit
- Females who are pregnant or lactating
- History of idiopathic anaphylaxis or a major immunologic reaction to immunoglobulin G–containing agent
- History of cancer or lymphoproliferative disease, other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or adequately treated cervical carcinoma in situ, within 5 years of screening

AE, adverse event; DD, dysphagia day; EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field; GI, gastrointestinal; mDSD, modified Daily Symptom Diary; PPI, proton pump inhibitor.

informed consent prior to the performance of any study-related procedures. Inclusion and exclusion criteria are shown in Table 1.

2.4. Randomization and masking

Eligible patients are randomized 1:1:1 to receive double-blind SC treatment with 1) cendakimab 360 mg once weekly for 48 weeks, 2) cendakimab 360 mg once weekly for 24 weeks followed by cendakimab 360 mg once every other week (along with matching placebo on the alternating weeks to maintain blinding) for 24 weeks, or 3) placebo once weekly for 48 weeks. Treatment assignment for the entire study occurs at baseline and is stratified by steroid responder status to ensure equal balance in the treatment arms. Randomization is carried out through an interactive web response system.

2.5. Procedures and assessments

During the screening period, the mDSD is completed daily after the last meal of the day for at least the last 3 consecutive weeks prior to day 1 to assess dysphagia symptoms. The mDSD is a modified version of the Daily Symptom Diary (DSD) that has been psychometrically validated to assess symptoms of dysphagia (*manuscript under review*), and the DSD was previously completed by patients in the phase 2 trial [28]. The mDSD includes questions that cover an assessment of solid food

Table 2
Cendakimab for EoE: induction phase (week 24) efficacy and safety endpoints.

Study endpoints at week 24				
Endpoint[a]	Name	Description	Time frame	Statistical method
Primary	Change in DD clinical response	Mean change in DD evaluated with the mDSD (over the prior 14-day period)	Baseline to week 24	ANCOVA model
Primary	Eosinophil histologic response (≤6 eos/hpf)	Proportion of patients with eosinophilic histologic response (peak esophageal count ≤6 eos/hpf)	At week 24	CMH test
Key Secondary	Eosinophil histologic response (<15 eos/hpf)	Proportion of patients with eosinophilic histologic response (peak esophageal count <15 eos/hpf)	At week 24	CMH test
Key Secondary	EREFS	Mean change in endoscopic features of EoE	Baseline to week 24	ANCOVA model
Key Secondary	EoEHSS grade score	Mean change in the mean adjusted histology grade score	Baseline to week 24	ANCOVA model
Key Secondary	EoEHSS stage score	Mean change in the mean adjusted histology stage score	Baseline to week 24	ANCOVA model
Key Secondary	mDSD composite score	Mean change in the mDSD composite score	Baseline to week 24	ANCOVA model
Secondary	DD clinical responder definition	Proportion of patients with a ≥ 50 % decrease in DDs from baseline	At week 24	CMH test
Secondary	Kinetics and onset of clinical response: DDs	Mean change in DDs over time	Baseline through week 24	ANCOVA model
Secondary	Kinetics and onset of clinical response: mDSD	Mean change in mDSD composite score over time	Baseline through week 24	ANCOVA model
Secondary	Time to event: EoE flare	Time to EoE flare	Through week 24	Kaplan-Meier estimates and stratified log-rank test
Secondary	Time to event: rescue therapy	Time to use of rescue therapy	Through week 24	Kaplan-Meier estimates and stratified log-rank test
Secondary	Proportion of patients with event: EoE flare	Proportion of patients with an EoE flare	Through week 24	Descriptive
Secondary	Proportion of patients with event: rescue therapy	Proportion of patients with use of rescue therapy	Through week 24	Descriptive
Secondary	Assessment of immunogenicity	Presence of anti-drug antibodies to cendakimab	Through week 24	Descriptive
Secondary	Pharmacokinetics	Measurement of trough concentrations of cendakimab	Through week 24	Descriptive
Secondary	Incidence of adverse events	Proportion of patients with adverse events	Through week 24	Descriptive
Exploratory	Clinical and eosinophil histologic response composite	Proportion of patients who achieve eosinophilic histologic response defined as peak esophageal count <15 eos/hpf at week 24 and dysphagia symptom response defined as the proportion of patients with ≥50 % decrease in DDs from baseline at week 24	Week 24	Descriptive
Exploratory	Clinical and histologic response composite	Proportion of patients who achieve eosinophilic histologic response defined as peak esophageal count ≤6 eos/hpf at week 24 and dysphagia symptom response defined as the proportion of patients with ≥50 % decrease in DDs from baseline at week 24	Week 24	CMH test
Exploratory	EEsAI	The mean change in dysphagia clinical symptom frequency and severity as assessed by the EEsAI total score from baseline to week 24 and proportion of patients that meet various response thresholds (including but not limited to EEsAI score ≤ 20) at week 24	Week 24	Descriptive
Exploratory	PEESS	The mean change in adolescent patient's EoE symptoms using the PEESS total metric score from baseline to week 24 (adolescent patients only)	Week 24	Descriptive
Exploratory	Additional EoE symptoms	Additional EoE symptoms reported on the mDSD evaluated by the distribution of patient responses regarding solid food avoidance, percentage of days solid food avoidance was due to EoE symptoms, percentage of days pain was associated with swallowing food, and the mean change in pain rating through week 24	Through week 24	Descriptive

ANCOVA, analysis of covariance; CMH, Cochran-Mantel-Haenszel; DD, dysphagia day; EEsAI, Eosinophilic Esophagitis Activity Index; EoE, eosinophilic esophagitis; EoEHSS, EoE histology scoring system; eos/hpf, eosinophils per high-power field; EREFS, EoE Endoscopic Reference Score; mDSD, modified Daily Symptom Diary; PEESS, Pediatric Eosinophilic Esophagitis Symptom Severity Module.

[a] Select exploratory endpoints included only.

consumption that day, experience with trouble swallowing, food going down slowly, food getting stuck in the throat or chest, any action taken by the patient to obtain relief, and any pain associated with swallowing. A DD is defined as any "yes" response to mDSD questions assessing dysphagia (trouble swallowing, food going down slowly, and food getting stuck in the throat or chest). The assessment of the number of DDs over a 14-day period using the mDSD captures the symptoms of dysphagia most important to patients with EoE and is a clinically meaningful and easily interpretable endpoint (according to a content validation patient-reported outcome study [*manuscript under review*]). The EGD cannot be performed during the last 2 weeks of the screening period, as this could interfere with the baseline mDSD evaluation of dysphagia symptoms. Health-related quality of life will be measured using the 12-Item Short Form Health Survey [33] and the 10-Item Short Form Health Survey for Children [34] at day 1, week 24, and week 48. Other baseline assessments are carried out on day 1, prior to randomization.

Post-baseline visits are scheduled every 2 weeks for the first month, then every 4 weeks thereafter through 48 weeks of treatment. Key efficacy endpoints during the treatment phase are summarized in Table 2 (induction phase) and Table 3 (maintenance phase). Histologic assessments are made by analysis of EGD biopsy results at a centralized reading facility by readers blinded to treatment assignment. Histologic findings are evaluated through enumeration of esophageal eosinophil count (peak esophageal eosinophil count) by analysis of hematoxylin- and eosin-stained esophageal biopsies and based on the validated EoEHSS [30]. Esophageal mucosal appearance is assessed with the modified EREFS [29], a validated metric assessing the presence and severity of inflammation and remodeling EoE signs including edema, rings, exudates, furrows, and strictures in the esophagus, scored according to their esophageal level (proximal, mid, and distal). The total maximum score of 24 is composed of a maximum potential score of 8 at each esophageal level.

Patients with a worsening of EoE symptoms are required to complete an EoE flare assessment visit, which requires an EGD for investigator determination of whether rescue therapy is clinically indicated. Safety and tolerability will be evaluated at screening and at each study visit throughout the 48-week treatment period and at the safety follow-up, if applicable. This includes assessment of the incidence, severity, and relationship of adverse events (AEs) to study treatment; the proportion of patients with and the nature of serious AEs; the presence of clinical laboratory abnormalities, changes in vital signs, and physical examination findings; and the presence of anti-drug antibodies (ADAs). Patients who discontinue from the study prior to completing the induction phase at week 24 or who complete the induction phase but do not enter the maintenance phase (from 24-week onward) or enroll in the OLE study will return for an interim and final safety follow-up visit at 8 and 16 weeks, respectively, after the last dose. In the maintenance phase, those who discontinue prior to completing week 48 or who complete week 48 but do not enroll in the OLE study will also return for an interim and final safety follow-up visit at 8 and 16 weeks, respectively, after the last dose.

Serum samples to assess titers of cendakimab ADAs will be obtained pre-dose at baseline and at weeks 4, 8, 24, 28, 36, and 48. ADA levels (including neutralizing antibodies for ADA-positive samples) will be monitored to assess the impact of immunogenicity on the safety, pharmacokinetics, and efficacy of cendakimab. Pharmacokinetic analyses will include measurement of serum trough concentrations of cendakimab during treatment. Several exploratory endpoints, including exposure-response and population pharmacokinetics, will also be assessed.

2.6. Statistical methods

For patients who discontinue treatment without the use of rescue therapy or prohibited medications that may impact efficacy before 24

Table 3
Cendakimab for EoE: maintenance phase (week 48) efficacy and safety endpoints.

Study endpoints at week 48				
Endpoint[a]	Name	Description	Time frame	Statistical method
Secondary	Change in DD clinical response	Mean change in DDs over the prior 14-day period preceding each visit on the mDSD	Baseline to week 48	ANCOVA model
Secondary	Eosinophil histologic response (≤6 eos/hpf)	Proportion of patients with eosinophilic histologic response defined as a peak esophageal count ≤6 eos/hpf	At week 48	CMH test
Secondary	Eosinophil histologic response (<15 eos/hpf)	Proportion of patients with eosinophilic histologic response defined as a peak esophageal count <15 eos/hpf	At week 48	CMH test
Secondary	Mean change in EREFS	Mean change in EoE endoscopic features	Baseline to week 48	ANCOVA model
Secondary	EoEHSS grade score	Mean change in the mean adjusted histology grade score	Baseline to week 48	ANCOVA model
Secondary	EoEHSS stage score	Mean change in the mean adjusted histology stage score	Baseline to week 48	ANCOVA model
Secondary	mDSD composite score	Mean change in mDSD composite score	Baseline to week 48	ANCOVA model
Secondary	Eosinophil histologic response (≤6 eos/hpf)	Proportion of patients with eosinophilic histologic response defined as a peak esophageal count ≤6 eos/hpf at week 48 among patients with a peak esophageal count ≤6 eos/hpf at week 24	At week 48	Descriptive
Secondary	Time to event: EoE flare	Time to EoE flare	Through week 48	Kaplan-Meier estimates and stratified log-rank test
Secondary	Time to event: rescue therapy	Time to use of rescue therapy	Through week 48	Kaplan-Meier estimates and stratified log-rank test
Secondary	Proportion of patients with event: EoE flare	Proportion of patients with an EoE flare	Through week 48	Descriptive

(*continued on next page*)

Table 3 (*continued*)

Study endpoints at week 48				
Endpoint[a]	Name	Description	Time frame	Statistical method
Secondary	Proportion of patients with event: rescue therapy	Proportion of patients with use of rescue therapy	Through week 48	Descriptive
Secondary	Assessment of immunogenicity	Presence of anti-drug antibodies to cendakimab	Through week 48	Descriptive
Secondary	Pharmacokinetics	Measurement of trough concentrations of cendakimab	Through week 48	Descriptive
Secondary	Incidence of adverse events	Proportion of patients with adverse events	Through week 48	Descriptive
Exploratory	Clinical and eosinophil histologic response composite	Proportion of patients who achieve eosinophilic histologic response defined as peak esophageal count <15 eos/hpf at week 48 and dysphagia symptom response defined as the proportion of patients with ≥50 % decrease in DDs from baseline at week 48	Week 48	Descriptive
Exploratory	Clinical and eosinophil histologic response composite	Proportion of patients who achieve eosinophilic histologic response defined as peak esophageal count ≤6 eos/hpf at week 48 and dysphagia symptom response defined as the proportion of patients with ≥50 % decrease in DDs from baseline at week 48	Week 48	Descriptive
Exploratory	EEsAI	The mean change in dysphagia clinical symptom frequency and severity as assessed by the EEsAI total score from baseline to week 48 and proportion of patients that meet various response thresholds (including but not limited to EEsAI score ≤ 20) at week 48	Week 48	Descriptive
Exploratory	PEESS	The mean change in adolescent patient's EoE symptoms using the PEESS total metric score from baseline to week 48 (adolescent patients only)	Week 48	Descriptive
Exploratory	Additional EoE symptoms	Additional EoE symptoms reported on the mDSD evaluated by the distribution of patient responses regarding solid food avoidance, percentage of days solid food avoidance was due to EoE symptoms, percentage of days pain was associated with swallowing food, and the mean change in pain rating through week 48	Through week 48	Descriptive

ANCOVA, analysis of covariance; CMH, Cochran-Mantel-Haenszel; DD, dysphagia day; EEsAI, Eosinophilic Esophagitis Activity Index; EoE, eosinophilic esophagitis; EoEHSS, EoE histology scoring system; eos/hpf, eosinophils per high-power field; EREFS, EoE Endoscopic Reference Score; mDSD, modified Daily Symptom Diary; PEESS, Pediatric Eosinophilic Esophagitis Symptom Severity Module.

[a] Select exploratory endpoints included only.

weeks, a treatment policy strategy will be used, where all observed data will be included in the primary analysis according to the respective endpoint definition. In circumstances in which the efficacy assessment of cendakimab might be impacted (e.g., in patients who used concomitant rescue therapy or prohibited medication that may impact efficacy and remained in the study or in those who discontinued treatment and then used rescue therapy or prohibited medication that may impact efficacy), a composite variable estimand strategy will be used in which data will be set as nonresponders for histologic response and worst possible value for change in DDs.

A total sample size of 399 patients with a 20 % dropout rate at the end of the initial 24-week treatment phase (212 patients for the cendakimab group and 106 patients for the placebo group) is estimated to provide ≥90 % power to detect a difference of −2.79 from baseline in DDs at week 24 and to detect a 15 % reduction in eosinophil histologic response at week 24 between cendakimab and placebo. Calculations are based on a 2-sample *t*-test, assuming a pooled standard deviation of 4.76 (to account for 70 % of enrolled patients being classified as steroid inadequate responders/intolerant) for change in DDs from baseline, and the chi-square test to compare the difference in 2 independent proportions for the eosinophil histologic response, assuming that the true placebo response proportion is 0.05. The study was designed to ensure that both co-primary endpoints were met before proceeding down the stepwise hierarchy. In addition, the planned sample size also takes into consideration the inclusion of a sufficient number of patients for the cendakimab safety database. A hierarchical testing procedure will be employed to control the overall type I error rate at 0.05 for the following

study endpoints: the 2 co-primary and 5 key secondary endpoints for the induction phase at week 24, the 2 secondary endpoints (corresponding to the co-primary endpoints for the study) for both doses at week 48, and in the steroid inadequate responders/intolerant subgroup, the co-primary endpoints for the induction phase at week 24, and the 2 secondary endpoints (corresponding to the co-primary endpoints for the study) for both doses at week 48.

2.7. Study endpoints

The co-primary endpoints are the mean change in the number of DDs (evaluated over the prior 14-day period using the mDSD) experienced from baseline to week 24 and the proportion of patients with eosinophil histologic response, defined as a peak esophageal eosinophil count $\leq$6 per high-power field at week 24. A minimum of 11 measurable diary days in the 2-week period prior to day 1 and a minimum of 8 measurable diary days post-baseline (with at least 3 diary days in each week) are required to derive a DD score for the 14-day period. Select secondary and exploratory endpoints measured at week 24 and week 48 are listed in Tables 2 and 3, respectively.

All safety analyses will be conducted for patients who receive at least 1 dose of study drug, by treatment, for the initial 24-week induction phase and for the combined induction and maintenance phases.

2.8. Data monitoring

An external, independent data monitoring committee comprising physician experts with experience treating patients with EoE and a statistician, all of whom are not otherwise involved in the study conduct and for whom there is no identified conflict of interest, will review safety and selected efficacy data on a regular basis during the study for assessment of benefit-risk and determination of study continuation.

3. Discussion

Eosinophilic esophagitis is a chronic, progressive, inflammatory disease with a considerable impact on health-related quality of life [2]. Patients with EoE require long-term treatment to improve symptoms, reduce inflammation, and reduce associated fibrostenotic complications [35]. EoE can have a negative impact on quality of life, as most patients must make behavioral and dietary modifications to adapt to the needs that living with EoE places on their food intake [8,22]. The reduction in quality of life experienced by patients with EoE has been associated with the level of disease activity, suggesting that controlling the progression of the disease could further improve the quality of life for these patients [36]. Pharmacologic treatments with PPIs and swallowed topical corticosteroids, as well as dietary interventions, fail to provide meaningful benefit to many patients and are associated with AEs, disease relapse, and reduced adherence [12]. Left untreated, EoE can lead to stricture formation [37–42], highlighting the importance of effective treatment for these patients, not only to treat active symptoms, but also to prevent disease consequences [1].

There are strong preclinical data supporting the role of IL-13 in the pathophysiology of EoE, which provide the rationale to investigate methods to block its activity through the development of targeted therapy. A 16-fold increase in IL-13 messenger RNA was identified in the esophageal tissue of patients with EoE compared with that in healthy patients without gastrointestinal pathology, and significant overlap was found between IL-13–induced genes in esophageal squamous epithelial cells and the EoE transcriptome [43]. These findings suggested the involvement of IL-13 in EoE pathogenesis and helped prompt the development of cendakimab, a recombinant, humanized, monoclonal antibody against IL-13 that blocks interaction with both IL-13Rα1 and IL-13Rα2 [27].

Results of the randomized, double-blind, placebo-controlled phase 2 study of cendakimab in adult patients with EoE indicated that targeting IL-13 with cendakimab improved many of the key disease features of EoE. Weekly administration of cendakimab 360 mg SC for 16 weeks was well tolerated and led to a reduction in the mean esophageal eosinophil count. Improved endoscopic activity, histologic grade and stage, and other inflammatory parameters of EoE, with results independent of the patient's steroid response status, were also observed; symptoms (frequency and severity of dysphagia measured by the DSD composite score) were also numerically improved with cendakimab 360 mg SC once weekly versus placebo (the study was not powered to assess this outcome) [28]. Further, a post hoc analysis of data from this study revealed a statistically significant reduction in DDs overall, as well as in patients known to be steroid refractory [44]. These results suggest that steroid-refractory patients, a subset of the EoE population that may reflect greater disease severity, were equally likely to benefit from cendakimab treatment, providing a much needed potential treatment option for this difficult-to-manage group of patients. In addition, analysis of epithelial-mesenchymal transition biomarkers in esophageal biopsies showed a significant reduction in vimentin-positive cells and a significant increase in E-cadherin expression with cendakimab 360 mg versus placebo, indicating beneficial effects on inflammatory and remodeling pathways [45]. The long-term OLE of this phase 2 study demonstrated that 1) patients who received cendakimab for an additional 52 weeks maintained the endoscopic, histologic, and clinical improvements in disease activity that they achieved in the double-blind phase, 2) patients who switched from placebo experienced improvements with cendakimab after 12 weeks that were maintained throughout the remainder of the OLE, 3) patients achieved a numerical reduction in dysphagia symptoms measured using the DSD, and 4) cendakimab is generally well tolerated in patients with EoE [28,31]. These findings justified further study of cendakimab in a phase 3 trial.

Until the approval of dupilumab in 2022 and budesonide oral suspension in 2024, no treatments had been approved in the US for the treatment of EoE [14,18,46]; instead, patients were often treated with off-label medications, dietary modifications, and, in many cases, endoscopic dilation [14]. PPIs are often used as an off-label treatment in a first-line setting for patients with EoE; however, PPIs only provide an overall eosinophil histologic response in 42 % of patients [14]. The standard of care for both PPI-naive and relapsing patients also includes topical corticosteroids (swallowed preparations as an add-on to PPIs or as a standalone), with overall response rates of 65 % [14]. However, most patients receiving this treatment option relapse within 1 to 4 months following discontinuation, requiring additional courses of therapy, and, in some cases, losing response, even if steroids are continued long term [47,48].

The current registrational phase 3 trial is enrolling a greater proportion of patients who are steroid inadequate responders or intolerant compared with the phase 2 study (approximately 47 %) based on the aforementioned results, as well as patients who are naive or have had an adequate response to steroid therapy, and is the first to prospectively evaluate treatment in the steroid-refractory patient population. A double-blind, placebo-controlled, treat-through design with use of concomitant rescue therapy has been chosen to enhance patient recruitment and retention to permit evaluation of the short- and long-term efficacy and safety findings associated with cendakimab treatment in patients with EoE. In addition, the increasing incidence and prevalence of EoE [5] seen in children and adults and the preliminary safety and efficacy data [28] support the inclusion of adolescents in this study. The multiple endpoints chosen in this study provide a broader view of the treatment impact by assessing the symptomatic, histologic, and endoscopic outcomes on patients with EoE. Unlike previous clinical studies that explored the use of biologics for patients with EoE for a 24-week period, this study has been designed to evaluate efficacy and safety beyond this time point using a scientifically rigorous placebo-controlled maintenance phase and to evaluate whether a less-frequent dosing regimen would provide a similar persistence of response during the maintenance phase.

Increasing evidence for the development of transmural inflammation and remodeling as consequences of EoE [1,38] further supports the notion that systemic treatments may provide additional value over topical treatments [1]. Cendakimab therefore represents a promising treatment option for EoE that warrants further exploration to confirm and extend the findings obtained from the positive phase 2 study. Results from this pivotal phase 3 trial will further substantiate the role of IL-13 in EoE if treatment with cendakimab proves successful.

4. Conclusion

The results of this phase 3 registrational study will confirm the efficacy and inform the benefit-risk profile of cendakimab, an anti–IL-13 monoclonal antibody, for the treatment of patients with EoE, addressing a critical need among patients with a chronic condition that interferes with food intake and negatively impacts quality of life.

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CRediT authorship contribution statement

Christina M. Charriez: Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Sandra Zhang:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Claudia H.M.C. de Oliveira:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Investigation. **Vrunda Patel:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Young S. Oh:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Investigation. **Ikuo Hirano:** Writing – review & editing, Supervision, Methodology, Investigation. **Alain Schoepfer:** Writing – review & editing, Methodology, Conceptualization. **Evan S. Dellon:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

Ikuo Hirano has served as a consultant for Adare, Allakos, Amgen, Arena, AstraZeneca, Celgene/Receptos/Bristol Myers Squibb, EsoCap, Gossamer Bio, Parexel/Calyx, Regeneron/Sanofi, and Shire/Takeda; and has received grant/research support from Adare, Allakos, Celgene/Receptos/Bristol Myers Squibb, Regeneron, and Shire/Takeda.

Christina M. Charriez, Sandra Zhang, Claudia H.M.C. de Oliveira, Vrunda Patel, and Young S. Oh are or were employees of Bristol Myers Squibb at the time of the study and are shareholders in the company.

Alain Schoepfer has served a consultant for Adare/Ellodi, AbbVie, AstraZeneca, Celgene/Receptos/Bristol Myers Squibb, Dr. Falk Pharma, Gossamer Bio, GSK, Janssen, MSD, Pfizer, Regeneron/Sanofi, Takeda, and Vifor; and has received grant/research support from Adare/Ellodi, Celgene/Receptos/BMS, GSK, and Regeneron/Sanofi.

Evan S. Dellon has served as a consultant for Abbott, AbbVie, Adare/Ellodi, Aimmune, Akesobio, Alfasigma, ALK, Allakos, Amgen, Apollo, Aqilion, Arena/Pfizer, Aslan, AstraZeneca, Avir, Biorasi, Bryn, Calypso, Celgene/Receptos/Bristol Myers Squibb, Celldex, Eli Lilly, EsoCap, Eupraxia, Dr. Falk Pharma, Ferring, GSK, Gossamer Bio, Holoclara, Invea, Knightpoint, Landos, LucidDx, Morphic, Nexstone Immunology/Uniquity, Nutricia, Parexel/Calyx, Phathom, Regeneron, Revolo, Robarts/Alimentiv, Salix, Sanofi, Shire/Takeda, Target RWE, and Upstream Bio; has received grant/research support from Adare/Ellodi, Allakos, Arena/Pfizer, AstraZeneca, Eupraxia, GSK, Meritage, Miraca, Nutricia, Celgene/Receptos/Bristol Myers Squibb, Regeneron, Revolov, and Shire/Takeda; and has received educational grants from Allakos, Aqilion, Holoclara, and Invea.

Data availability

No data was used for the research described in the article.

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