Evaluating the efficacy and safety of pozelimab in patients with CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy disease: an open-label phase 2 and 3 study

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Summary

Background CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy (CHAPLE) is an ultra-rare genetic disorder characterised by intestinal lymphatic damage, lymphangiectasia, and protein-losing enteropathy caused by overactivation of the complement system. We assessed the efficacy and safety of pozelimab, an antibody blocking complement component 5.

Methods This open-label, single-arm, historically controlled, multicentre phase 2 and 3 study evaluated ten patients with CHAPLE disease. This study was conducted at three hospitals in Thailand, Türkiye, and the USA. Patients aged 1 year or older with a clinical diagnosis of CHAPLE disease and a *CD55* loss-of-function variant identified by genetic analysis and confirmed by flow cytometry or western blot of CD55 from peripheral blood cells were eligible for this study. Patients received a single intravenous loading dose of pozelimab 30 mg per kg of bodyweight, followed by a once-per-week subcutaneous dose over the treatment period based on bodyweight at a concentration of 200 mg/mL as either a single injection (<40 kg bodyweight) or two injections (≥40 kg bodyweight). The primary endpoint was proportion of patients with serum albumin normalisation with an improvement in active clinical outcomes and no worsening in inactive clinical outcomes (frequency of problematic abdominal pain, bowel movement frequency, facial oedema severity, and peripheral oedema severity) at week 24 compared with baseline, assessed in the full analysis set. This study is registered with ClinicalTrials.gov (NCT04209634) and is active but not recruiting.

Findings 11 patients were recruited between Jan 27, 2020, and May 12, 2021, ten of which were enrolled in the study and included in the analysis populations. The efficacy data corresponded to all patients completing the week 48 assessment and having at least 52 weeks of treatment exposure, and the safety data included an additional 90 days of follow-up and corresponded to all patients having at least 72 weeks of treatment. Patients were predominantly paediatric (with a median age of 8·5 years), and originated from Türkiye, Syria, Thailand, and Bolivia. Patients had markedly low weight-for-age and stature-for-age at baseline, and mean albumin at baseline was 2·2 g/dL, which was considerably less than the local laboratory reference range. After pozelimab treatment, all ten patients had serum albumin normalisation and improvement with no worsening in clinical outcomes. There was a complete inhibition of the total complement activity. Nine patients had adverse events; two were severe events, and one patient had an adverse event considered related to pozelimab.

Interpretation Pozelimab inhibits complement overactivation and resolves the clinical and laboratory manifestations of CHAPLE disease. Pozelimab is the only currently approved therapeutic drug for patients with this life-threatening, ultra-rare condition. In patients with protein-losing enteropathy where known causes have been excluded, testing for a CD55 deficiency should be contemplated. A diagnosis of CHAPLE disease should lead to early consideration of treatment with pozelimab.

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Introduction

CD55 deficiency with hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy (CHAPLE) disease is an ultra-rare autosomal recessive disorder caused by loss-of-function variants of the *CD55* gene. Heterozygous people are unaffected.[1] Loss of CD55 (also known as decay-accelerating factor), a cell surface regulator of complement components 3 and 5,[2] leads to the overactivation of the terminal complement system.[1,3] The intestinal lymphatics are damaged by complement

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See **Online** for appendix 1

Research in context

Evidence before this study

CD55 deficiency with the hyperactivation of complement, angiopathic thrombosis, and protein-losing enteropathy (CHAPLE) disease is a life-threatening, ultra-rare autosomal recessive disorder caused by loss-of-function variants of the *CD55* gene. CHAPLE disease is apparent in infancy and early childhood and is associated with severe morbidity and mortality. Patients present with hypoalbuminemia and oedema, severe and debilitating gastrointestinal symptoms, and chronic malabsorption. CHAPLE disease can progress to gastrointestinal obstruction and perforation as well as thromboembolic events, which can be fatal.

Before the study, we collected data under an investigator-initiated project that studied the natural history of CHAPLE disease in a worldwide cohort, the Transcriptome and Metabolic Analyses of CHAPLE Disease (CHAPLEOMIC) study (ClinicalTrials.gov number NCT03950804). Relevant information was derived from both published literature and unpublished data collected under a scientific study protocol. Given the ultra-rare nature of CHAPLE disease, this was considered the optimal approach to obtain up-to-date information on the epidemiology, natural history, and treatment responsiveness of CHAPLE disease to various interventions. This information was used to inform the design of the current study.

Given the causes of CHAPLE disease, anti-complement therapy has been proposed as a treatment. The off-label use of eculizumab, a humanised monoclonal anti-complement component 5 antibody, improved the clinical and laboratory features of CHAPLE disease. Eculizumab requires intravenous infusion every 2 weeks. Therefore, a rigorous study of a subcutaneously administered anti-complement component 5 therapy in CHAPLE disease is warranted.

Added value of this study

Pozelimab is a subcutaneously administered, investigational monoclonal antibody directed against the terminal complement protein component 5. We conducted an open-label, historically controlled study to assess the efficacy and safety of pozelimab in patients with CHAPLE disease. After pozelimab treatment, we observed complement inhibition and improvement in overall health. Patients had a complete and sustained resolution in the signs and symptoms of CHAPLE disease. Furthermore, patients had rapid catch-up growth as well as substantial improvements in disease morbidity, including reduced hospitalisations and use of corticosteroids. Serum albumin concentrations normalised and the need for albumin transfusions was eliminated.

Implications of all the available evidence

This study shows that single-agent, targeted therapy with pozelimab inhibits complement overactivation and reverses the manifestations of CHAPLE disease. Pozelimab treatment addresses an unmet medical need for patients with CHAPLE disease, a life-threatening, ultra-rare condition. Subcutaneous administration potentially allows greater access to treatment for this severe illness in low-resource settings. Notably, pozelimab was recently approved by the US Food and Drug Administration as the first treatment for adult and paediatric patients aged 1 year or older with CHAPLE disease based on the findings presented in this report.

deposition, causing lymphangiectasia, gastrointestinal dysfunction, and protein-losing enteropathy.[1,3] To date, fewer than 100 patients with CHAPLE disease have been identified.[1,3–8]

CHAPLE disease is associated with severe morbidity and mortality.[1] Clinical and laboratory features of CHAPLE disease are often apparent in infancy and early childhood, and include hypoalbuminemia and oedema; hypogammaglobulinemia leading to infections; and gastrointestinal symptoms such as abdominal pain, loss of appetite, vomiting, and diarrhoea. Because of protein loss and malnutrition, patients present with micronutrient deficiency, anaemia, and retardation of growth and maturation.[1,6] CHAPLE disease can progress to gastrointestinal obstruction and perforation as well as mesenteric, portal, and cardiopulmonary thromboembolic events, which can be fatal.[6,8]

Patients with CHAPLE disease receive supportive interventions such as albumin infusions, immunoglobulin (Ig) replacement therapy, immunosuppressive medications, bowel resection surgery, and vitamin or micronutrient supplements, but these are not curative and do not result in lasting improvement.[6] Given the causes of CHAPLE disease, anti-complement therapy has been proposed as a treatment.[6] In a series of observational case studies, the off-label use of eculizumab, a humanised monoclonal anti-complement component 5 antibody,[5] showed consistent results across multiple cohorts of patients with CHAPLE disease (21 patients in total).[3,4,6,9–10] These studies collectively showed a reduction in complement activation, increased albumin and total protein concentrations, the restoration of metabolic and immune function, and an improvement in signs and symptoms and overall quality of life. These findings were not collected in accordance with the US Food and Drug Administration's (FDA) patient-focused drug development guidance,[11] but held promise for future interventional trials evaluating complement inhibitor therapies in CHAPLE disease. Eculizumab necessitates an intravenous infusion every 2 weeks, posing challenges in regions with little or no access to specialised medical facilities. Furthermore, this treatment is not available in many countries. Thus, a comprehensive investigation of a more accessible treatment approach is warranted.

Pozelimab is a subcutaneously administered, fully human Ig G4P (IgG4 with a proline substitution to promote light chain stabilisation) antibody directed against complement component 5. A previous study showed that pozelimab inhibits complement component 5 cleavage and membrane attack complex formation.[12] In this study, we conducted an open-label, historically controlled study to assess the efficacy and safety of pozelimab in patients with CHAPLE disease.

Methods

Study design

This ongoing, open-label, single-arm, historically controlled, multicentre phase 2 and 3 study evaluated the efficacy and safety of pozelimab in paediatric and adult patients with CHAPLE disease. This study comprised a screening period (≤4 weeks, or ≤10 weeks for patients with specific circumstances as defined in the protocol; appendix 1), a 144-week treatment period, and a 20-week follow-up period (appendix 2 p 29). At baseline (day 1), patients received a single intravenous loading dose of pozelimab 30 mg per kg of bodyweight, followed by a once-per-week subcutaneous dose over the treatment period based on bodyweight at a concentration of 200 mg/mL as either a single injection (<40 kg bodyweight) or two injections (≥40 kg bodyweight; appendix 2 p 8).

The study was initiated on Jan 27, 2020. The efficacy data (full analysis set) presented in this report correspond to all patients completing the week 48 assessment and having at least 52 weeks of treatment exposure (with a data cutoff date of May 24, 2022). The safety data (safety analysis set) in this report include an additional 90 days of follow-up and correspond to all patients having at least 72 weeks of treatment exposure (with a data cutoff date of Nov 2, 2022). Additional study information, including amendment history, is described in the protocol.

This study was conducted at three hospitals in Thailand, Türkiye, and the USA. The study protocol was approved by the local institutional review boards or ethics committees, or both, before study initiation. All patients or legally authorised representatives provided written informed consent before study enrolment.

This study was conducted in accordance with the principles of the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, and was consistent with the Good Clinical Practices of the International Conference on Harmonisation and applicable regulatory requirements. Monitoring and site supervision were performed with oversight by the sponsor (Regeneron Pharmaceuticals). Protocol deviations are described in appendix 2 (p 6).

Participants

Patients aged 1 year or older with a clinical diagnosis of CHAPLE disease and a *CD55* loss-of-function variant identified by genetic analysis and confirmed by flow cytometry or western blot of CD55 from peripheral blood cells were eligible for this study. Qualifying disease was defined as hypoalbuminemia (≤3·2 g/dL albumin) during screening and at least one of the following signs or symptoms attributable to CHAPLE disease within the previous 6 months: diarrhoea, vomiting, abdominal pain, peripheral or facial oedema, infection with concomitant hypogammaglobulinemia, or a new thromboembolic event. The exclusion criteria included a history of meningococcal infection, concomitant disease causing hypoproteinemia or secondary intestinal lymphangiectasia, or a history of hereditary complement deficiency other than a CD55 deficiency. Full inclusion and exclusion criteria are described in the protocol. The sex of each patient was established at screening, defined by the investigators.

Procedures and outcomes

The primary efficacy endpoint was the proportion of patients with active disease at baseline who had both the following at week 24: firstly, the normalisation of serum albumin, defined as serum albumin of 3·5 g/dL or more for 70% or more of all measurements taken between weeks 12 and 24, and no single albumin measurement of less than 2·5 g/dL or a requirement for an albumin infusion between weeks 12 and 24; and secondly, an improvement in four prespecified clinical outcomes (frequency of problematic abdominal pain, bowel movement frequency, facial oedema severity, and peripheral oedema severity) that were evaluable for improvement at baseline, with no worsening of the outcome (if not evaluable for improvement at baseline) at week 24. Serum albumin was analysed at a local laboratory. Additional information on collection and evaluation of the clinical outcomes is presented in appendix 2 (p 6).

See Online for appendix 2

The secondary efficacy endpoints included the measurement of total complement activity over time, the frequency of albumin infusions, weight-for-age and stature-for-age, the number of days in hospital over time (emergency and planned admissions), use and dose frequency of concomitant medications including corticosteroids, improvement in stool consistency (appendix 2 p 6), concentrations of total pozelimab in serum, and the following laboratory measurements: total albumin, protein, and immunoglobulin concentrations over time; α-1 antitrypsin concentrations in blood and stool at weeks 12 and 24; vitamin B12, iron, and iron-binding capacity over time; and plasma lipids (triglycerides and cholesterol) over time. Additional secondary endpoints included an improvement in the patient's most bothersome sign or symptom at week 24, of which details on the qualitative interviews conducted with patients or caregivers at screening and week 24 are in appendix 2 (p 6); changes in limitations in food and drink, as assessed by the PedsQL gastrointestinal symptom scales;[13–15] and changes in health-related quality of life as measured by the PedsQL generic core

	Pozelimab (N=10)
Age, years	8·5 (6·0–11·0)
Sex	
Male	4
Female	6
Country of origin	
Türkiye	5
Syria	2
Thailand	2
Bolivia	1
Race	
White	7
Asian	2
Other	1
Weight-for-age CDC percentile	13·0 (2·5–31·7)
Stature-for-age CDC percentile	6·9 (0·1–18·8)
Age at symptom onset, years	2·2 (0·6–3·5)
Duration of symptoms at baseline, years	6·0 (3·2–8·3)
Patients with a history of albumin transfusions	10
Patients with previous thromboembolic events	1
Albumin, g/dL*	2·2 (0·5)
Patients evaluable at baseline for each clinical outcome	
Frequency of problematic abdominal pain	7
Bowel movements per day	1
Physician-assessed facial oedema	4
Physician-assessed peripheral oedema	5
Physician-assessed facial oedema score†	2·0 (2·0–3·0)
Physician-assessed peripheral oedema score†	2·5 (2·0–3·0)
IgG, g/L‡	2·2 (0·9)
Faecal or serum α-1-antitrypsin ratio§	3·1 (1·4)
Most bothersome sign or symptom	
Abdominal pain	9
Facial oedema	1

Data are median (IQR), n, or mean (SD). The full analysis set of patients is presented. CDC=Centers for Disease Control and Prevention. Ig=immunoglobulin. *Typical normal reference range for local clinical laboratory: 3·5–5·5 g/dL. †The oedema scoring system uses a Likert scale, which spans from 1 to 5, where a rating of 1 indicates no oedema and a rating of 5 indicates very severe oedema. ‡The lower limit of normal for IgG varied by age and sex, with the lowest lower limit of normal of 4·13 g/L in male patients aged 1–3 years and the highest lower limit of normal of 8·04 g/L in female patients aged 16–17 years. §Central clinical laboratory normal reference range: a ratio of 0·28 or less.

Table 1: **Baseline demographics and clinical characteristics**

scales.[13,16–21] The secondary endpoint of the assessment of abdominal ascites (by measurement of abdominal circumference) from baseline to week 24 is not presented, because it is designed to be assessed only in participants with clinical abdominal ascites at baseline; because only one patient met this criterion, the data were not presented.

The incidence and severity of treatment-emergent adverse events and other safety variables (including anti-drug antibodies) over time were also evaluated as secondary endpoints. The following adverse events of special interest were assessed: moderate or severe infusion reactions, confirmed *Neisseria* infection, and thrombotic or embolic events. Markers of erythropoiesis and platelets were reported in the haematology panel. Exploratory endpoints included total sC5b-9 complement assay (appendix 2 pp 6–7); Clinician Global Impression of Change and Severity; Patient or Caregiver Global Impression of Change and Severity; change in the experience of nausea, vomiting, and diarrhoea, as assessed by the PedsQL GI Symptoms Scales' subscales; and caregiver wellbeing and family burden, as assessed by the PedsQL Family Impact Module. Number of days in hospital due to signs and symptoms of CHAPLE disease and a comparison in the change in pretreatment and post-treatment albumin concentrations were also evaluated post-hoc.

Statistical analysis

Sample size and power considerations for this study of an ultra-rare disease are presented in appendix 2 (p 7). Efficacy analyses were performed in the full analysis set, and safety analyses were performed in the safety analysis set. The full analysis set and safety analysis set comprised all enrolled patients who received any study drug. Additional analysis sets are described in appendix 2 (p 7). The proportion of patients reaching a normal albumin range and having an improvement in the prespecified evaluable clinical outcomes, and the Clopper Pearson 90% CIs, were reported. Summary statistics were calculated to evaluate the change from baseline in total complement activity; albumin, protein, and immunoglobulin concentrations; α-1 antitrypsin concentrations; and micronutrients including vitamin B12 and iron. Other clinical laboratory values (markers of erythropoiesis, platelets, and plasma lipid concentrations) were summarised descriptively including median time to reach the normal range estimated using a Kaplan-Meier estimation with 95% CIs. Frequency of albumin infusions, number of days in hospital, and number of bowel movements per day were summarised using counts by day or periods of time. Patient or Caregiver Global Impression of Change and Patient or Caregiver Global Impression of Severity scores were reported overall and stratified by respondent type. Safety events were described descriptively, and treatment-emergent adverse events were recorded using the Medical Dictionary for Regulatory Activities version 25.0. Statistical analyses were performed using SAS version 9.4 or higher according to the statistical analysis plan (appendix 3). The post-hoc piecewise model for

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estimating change in albumin concentrations is presented in appendix 2 (p 7). This study is registered with ClinicalTrials.gov (number NCT04209634).

Role of the funding source

The principal investigators (AO, VC, and MJL) and the sponsor (Regeneron Pharmaceuticals) designed the trial protocol and selected the participating sites. Additional study contributors are listed in appendix 2 (p 5). The sponsor participated in the collection, analysis, and interpretation of the data and checked information provided in the manuscript.

Results

11 patients were recruited between Jan 27, 2020, and May 12, 2021, ten of whom were enrolled in the study and included in the analysis populations (appendix 2 p 30). Baseline demographics and clinical characteristics are presented in table 1. Patients were predominantly paediatric with a median age of 8·5 years (IQR 6·0–11·0). Most patients originated from Türkiye (five patients), with the other patients originating from Syria (two patients), Thailand (two patients), and Bolivia (one patient). Three patients (including a pair of siblings) were born to non-consanguineous parents and seven patients were born to consanguineous parents. All ten patients had received a vaccination for *Neisseria meningitidis* and took antibiotics to prevent meningococcal infections while on pozelimab. Five patients had a history of iron deficiency and received iron supplementation before and during the study. No patients were receiving Ig replacement therapy at baseline.

All ten patients had active disease at baseline. Most patients had mild-to-moderate facial and peripheral oedema, with median scores of 2·0 (IQR 2·0–3·0) and 2·5 (2·0–3·0), respectively (with 1 indicating no oedema and 5 indicating very severe oedema). The median score for the frequency of problematic abdominal pain was 56·3 (20·8–83·3) and the median number of daily bowel movements was 1·6 (1·0–2·9). During the qualitative interviews, 31 different signs and symptoms of CHAPLE disease were reported, and the core signs and symptoms of CHAPLE disease (of which ≥90% of patients had at least one sign or symptom) were abdominal pain (ten patients), diarrhoea (ten patients), facial oedema (ten patients), peripheral oedema (ten patients), vomiting (ten patients), and nausea (nine patients). The most bothersome sign or symptom of CHAPLE disease was abdominal pain for nine patients and facial oedema for one patient (table 1). Patient histories revealed that abdominal pain was frequent and substantial, with some needing parenteral analgesics for pain relief. The clinical histories of four patients included in this study have been previously reported: patients 1 and 2;[8] patient 6;[1] and patient 9.[6] Only patient 9 had previous exposure to eculizumab. After the discontinuation of eculizumab on day –125, this patient re-developed active disease. Additional patient characteristics are presented in appendix 2 (p 9).

	Pozelimab (N=10)
Patients meeting the primary endpoint: normalisation of serum albumin and improvement in clinical symptoms that were evaluable for improvement at baseline	10/10
Clopper Pearson 90% CI	74·1–100·0%
Normalisation of serum albumin between week 12 and 24	10/10
70% of serum albumin measurements ≥3·5 g/dL between week 12 and week 24	10/10
No single albumin measurement of <2·5 g/dL between week 12 and week 24	10/10
No requirement for albumin transfusion between week 12 and week 24	10/10
Improvement and no worsening in clinical symptoms at week 24	10/10
Improvement and no worsening in the frequency of problematic abdominal pain at week 24*	10/10
Improvement†	7/7
No worsening‡	3/3
Improvement and no worsening in the number of bowel movements per day at week 24§	10/10
Improvement†	1/1
No worsening‡	9/9
Improvement and no worsening in facial oedema by physician assessment at week 24¶	10/10
Improvement†	4/4
No worsening‡	6/6
Improvement and no worsening in peripheral oedema by physician assessment at week 24¶	10/10
Improvement†	5/5
No worsening‡	5/5

Data are n/N, unless otherwise stated. The full analysis set of patients is presented. *Patient or caregiver assessed using the stomach pain and hurt subscale of the PedsQL gastrointestinal symptom scales. Evaluable was defined as 70 points or less at baseline; improvement was defined as an increase of 25 points or more; worsening was defined as a decrease of 25 points or more. †In patients that were able to be evaluated for improvement at baseline. ‡In patients that were not able to be evaluated for improvement at baseline. §Patient or caregiver assessed using an electronic diary. Evaluable was defined as having three or more bowel movements per day at baseline; improvement was defined as a reduction of 50% or more over a 1-week average; worsening was defined as an increase of 30% or more over a 1-week average. ¶Physician-assessed score. Evaluable was defined as 3 points or more (out of 5) at baseline; improvement was defined as a reduction of 2 points or more (out of 5); worsening was defined as an increase of 2 points or more (out of 5).

Table 2: **Primary efficacy endpoint**

Loss-of-function mutations in the *CD55* gene for each patient are presented in appendix 2 (p 9). Eight patients had homozygous mutations and two patients (siblings) had compound heterozygous mutations. Two pairs of patients shared identical mutations, one of which was the sibling pair. Three patients had novel *CD55* variants, with one previously described as a variant of uncertain significance.[22] The other variants have been previously reported.[1,3,6,8] All patients had deficient CD55 cell surface protein expression.

Complete inhibition of the ex vivo total complement activity biomarker of the classical complement pathway[23] was observed in patients given pozelimab (appendix 2 p 31). Furthermore, mean sC5b-9 concentrations in plasma, a biomarker of terminal complement pathway activation,[24] sharply decreased after treatment and reached a plateau after week 2 with continued dosing (appendix 2 p 31). All ten patients reported persistent hypoalbuminemia (appendix 2 pp 10–11) and had a history of albumin transfusions, with abnormal albumin values at baseline (table 1). After pozelimab treatment, all ten patients had a normalisation of serum albumin between weeks 12 and 24 (table 2). Albumin concentrations rapidly improved after pozelimab treatment and were sustained at a normal range, with all measurements after 4 weeks more than 3·5 g/dL (figure 1A).

After pozelimab treatment, the need for albumin transfusions was eliminated (figure 1B). Five of ten patients received an albumin transfusion in the 48 weeks before treatment, with a pretreatment mean number of albumin transfusions of 6·0 across all ten patients (with 60 transfusions in total). The mean number of albumin transfusions across all ten patients decreased to 0·1 (one transfusion) by week 24 (appendix 2 p 12). Only one patient received an albumin transfusion during the study, which occurred on day 1 due to low albumin (1·1 g/dL) at baseline. A post-hoc analysis of pretreatment and post-treatment albumin concentrations showed no change in albumin concentrations during the pretreatment period, with a sharp increase during weeks 0 to 12 post-treatment and sustained normalisation during weeks 12 to 48 (appendix 2 p 13).

Over the short 48-week treatment period, most patients had notable catch-up growth (figure 2; appendix 2 pp 14–15). Weight-for-age and stature-for-age percentiles increased substantially, with a mean change from baseline in growth percentiles of 15·5 and 11·2, respectively. Corresponding increases in BMI were small because of parallel increases in height and weight.

Before treatment, patients had substantial morbidity. Patient histories indicated persistent signs and symptoms with various life-threatening episodes that affected patients' daily functioning and activities. All ten patients had a history of abdominal imaging, endoscopies, or

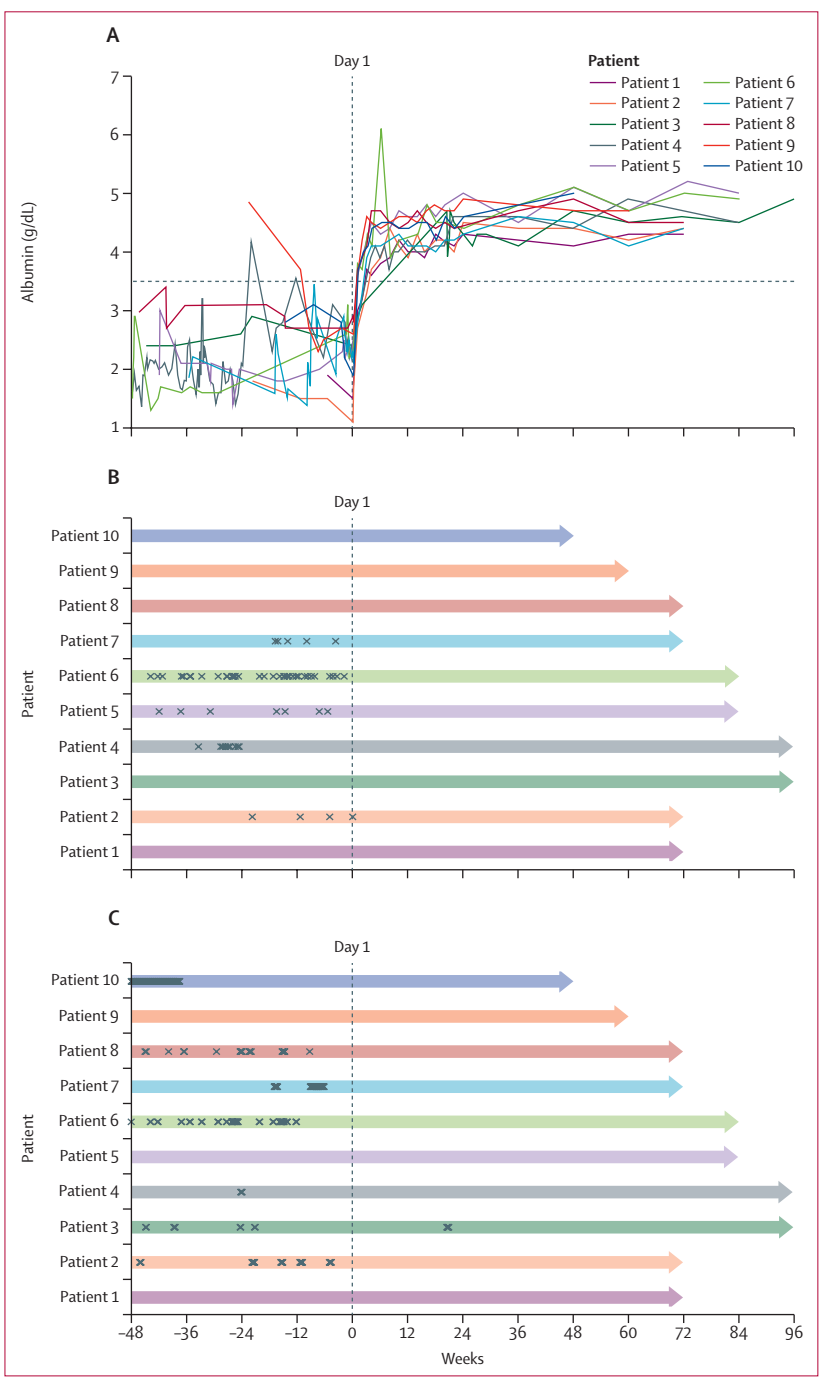

Figure 1: **Serum albumin, albumin transfusions, and hospitalisations over time**

(A) A plot of serum albumin concentration as a function of time before and after treatment. Each coloured line represents an individual patient. The horizontal line at 3·5 g/dL is the minimum value of the normal range as per the standards of the local clinical laboratory. (B) A plot of albumin transfusions (denoted using an X symbol) as a function of time before and after treatment. Pre-study albumin transfusions were collected from medical history and previous or concomitant medications, and on-study albumin transfusions were captured as adverse events. (C) A plot of the post-hoc analysis of hospitalisations due to either one or more sign or symptom of CHAPLE disease or complications of CHAPLE disease (denoted using an X symbol) as a function of time before and after treatment. Pre-study hospitalisations were based on historical medical records of hospitalisations, due to one or more sign or symptom consistent with CHAPLE disease. On-study hospitalisations were defined as admission to a hospital or emergency room for longer than 24 h due to one or more sign or symptom consistent with CHAPLE disease. In (B) and (C), each bar represents an individual patient, and the length of the bar represents the time to the last scheduled visit before the cutoff date. Data in all panels are plotted from 48 weeks before baseline up to the data cutoff date of May 24, 2022. Treatment was initiated at study day 1. The full analysis set of patients is presented.

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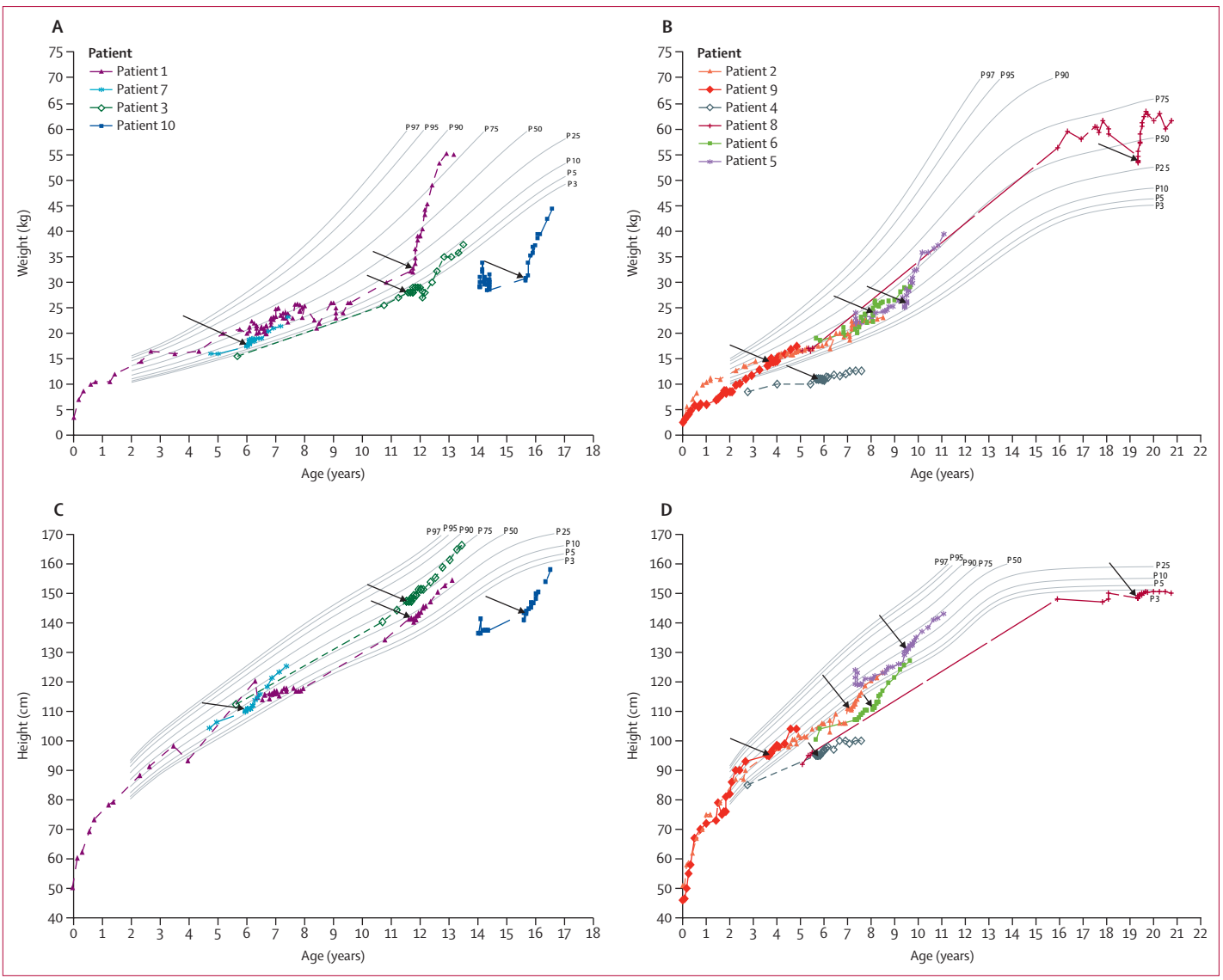

Figure 2: **Bodyweight-for-age and stature-for-age based on the Centers for Disease Control and Prevention growth charts**
(A) The weight-for-age plot for male patients (four patients). (B) The weight-for-age plot for female patients (six patients). (C) The stature-for-age plot for male patients (four patients). (D) The stature-for-age plot for female patients (six patients). Each line and corresponding coloured symbol represents a patient. Arrows indicate the first administration of pozelimab. The grey lines indicate Centers for Disease Control and Prevention growth percentiles. Percentiles are sourced from the Centers for Disease Control and Prevention growth charts. The full analysis set of patients is presented.

surgeries, or a combination, with two patients having multiple bowel resections. Additionally, all ten patients had multiple admissions to hospital since disease onset, with some requiring admission to the intensive care unit. In a post-hoc analysis accounting only for admissions to hosiptal due to one or more sign or symptom consistent with CHAPLE disease, seven patients were hospitalised for a mean of 19·6 days across all ten patients (196 days in hospital in total) in the 48 weeks before treatment. Similarly, in the prespecified analysis of all-cause hospitalisations, nine patients were hospitalised for a mean number of 26·8 days across all ten patients (268 hospitalisation days in total) in the 48 weeks before treatment.

Seven patients received corticosteroids at any time before study enrolment. Pretreatment clinical data showed that the corticosteroid effect was partial, dose-dependent, heterogeneous, and not considered to be a lasting solution because of its low efficacy on overall disease manifestations (appendix 2 pp 32–33). Five patients initiated corticosteroid treatment in the 48 weeks before our study treatment, three of these patients for the first time; four of these patients were still receiving corticosteroids at baseline. One patient had their corticosteroid doses tapered and withdrawn in the 48 weeks before treatment.

After pozelimab treatment, patients had a reduced number of days in hospital due to one or more sign or symptom consistent with CHAPLE disease (figure 1C;

For the **Centers for Disease Control and Prevention growth charts** see: https://www.cdc.gov/growthcharts/percentile_data_files.htm

post-hoc analysis). The mean number of days in hospital across all ten patients decreased to 0·4 days (4 days in hospital in total) by week 24 after treatment, with no admissions to hospital after week 24. One patient was admitted to hospital during the study for vomiting and dehydration due to suspected food poisoning, neither of which were deemed by the investigator to be related to pozelimab treatment or the underlying condition. The prespecified analysis of all-cause admission to hospital also showed a reduced number of days in hospital after pozelimab treatment, with a mean number of hospitalisation days of 0·7 across all ten patients (7 hospitalisation days in total; appendix 2 p 16).

No patients took immunomodulators or anticoagulants after starting pozelimab, and no small bowel resection surgeries were performed. Seven patients who underwent standard-of-care abdominal CT or MRI imaging before and during the treatment period showed a resolution of small bowel wall thickening or enhancement and mesenteric lymphadenopathy (data not shown). Notably, all four patients who were on corticosteroids at baseline had been withdrawn from corticosteroids as of the time of data cutoff for this study (appendix 2 p 17). There was a decrease in the mean cumulative corticosteroid use, expressed in mg of hydrocortisone equivalents, across all ten patients from 898·7 mg (SD 1402·2) in the 24 weeks before baseline (weeks –24 to 0) to 589·2 mg (1016·9) in the 24 weeks after dosing (weeks 0 to 24), and a further decrease to 126·0 mg (398·5) in the subsequent 24 weeks (weeks 24 to 48). The relationship between albumin concentration, corticosteroid use, and albumin transfusions in several patients is shown in appendix 2 (pp 32–33).

Total protein and Ig concentrations rapidly improved with pozelimab treatment (appendix 2 pp 18, 34). Patients had rapid and sustained normalisation in other serum protein concentrations, including IgG, IgM, IgA, and total protein (appendix 2 p 18). We evaluated faecal to serum α-1-antitrypsin ratio as a measure of enteric protein loss. Nine patients evaluated at baseline had elevated ratios, with a mean value of 3·1 (SD 1·4), reflective of active disease. After pozelimab treatment, the ratios rapidly normalised, with mean values of 0·1 (0·0) by week 12 (in four patients with measurements taken at week 12) and 0·1 (0·0) by week 24 (in eight patients with measurements taken at week 24; appendix 2 p 35).

We observed clinically meaningful improvements in markers of erythropoiesis after pozelimab treatment, with increases in haemoglobin concentrations (appendix 2 p 19), erythrocyte mean corpuscular haemoglobin, and erythrocyte mean corpuscular volume; and a concomitant decrease from baseline in absolute reticulocytes along with haematological recovery (appendix 2 p 20). Concentrations of vitamin B12, haemoglobin, unsaturated iron binding capacity, and ferritin also increased markedly over time (appendix 2 p 19).

Elevated platelets are a distinct but consistent feature of CHAPLE disease (compared with other acquired or genetic protein-losing enteropathy). Additionally, high triglycerides are a feature of protein-losing enteropathy. For both triglycerides and platelets, there was a consistent trend towards a decrease (improvement) over time after pozelimab treatment (appendix 2 p 21).

At baseline, seven patients were evaluable for improvement in the frequency of problematic abdominal pain (appendix 2 p 36), one patient was evaluable for improvement in the number of bowel movements per day (appendix 2 p 37), four patients were evaluable for improvement in facial oedema severity (figure 3A), and five patients were evaluable for improvement in peripheral oedema severity (figure 3B). After 24 weeks of pozelimab treatment, all patients that were evaluable at baseline met the criteria for improvement in these four prespecified clinical outcomes, with no worsening in the other patients (table 2).

As assessed by qualitative interviews, all ten patients also had a complete resolution of the core signs and symptoms of CHAPLE disease at week 24, including those that were reported as most bothersome. Nine patients had an improvement in all disease-related signs and symptoms, and no patients reported worsening of any signs and symptoms.

Patient-reported or caregiver-reported outcomes were collected on stool consistency and quality of life. Patients or caregivers and clinicians also answered questions regarding their impression of disease severity and change, measured using Patient or Caregiver Global Impression of Change and Patient or Caregiver Global Impression of Severity scores. The median number of days with a loose or watery stool consistency was 2·0 (IQR 0·0–2·3) at baseline and 0 (0·0–2·0) by week 24. Furthermore, consistent with the complete resolution of the core signs and symptoms of disease described earlier, we observed sustained improvements from baseline in Patient or Caregiver Global Impression of Change and Patient or Caregiver Global Impression of Severity question scores from the perspective of the patient or caregiver and clinician (appendix 2 pp 22–25). Additionally, other patient-reported or caregiver-reported outcome measures showed substantial and sustained improvements in quality of life and alleviation of signs and symptoms of disease (appendix 2 pp 26, 38–40). Treatment also had a positive effect on caregiver wellbeing (appendix 2 p 27).

Nine patients had 47 treatment-emergent adverse events during the study, two of which were considered severe (COVID-19 and a traumatic fracture; appendix 2 p 28). One patient had six adverse events that were considered by the investigator to be related to pozelimab treatment, including three events of metabolic acidosis, one event of alopecia, one event of contact dermatitis, and one event of injection-site erythema; all events were mild. The most common adverse events were rhinitis,

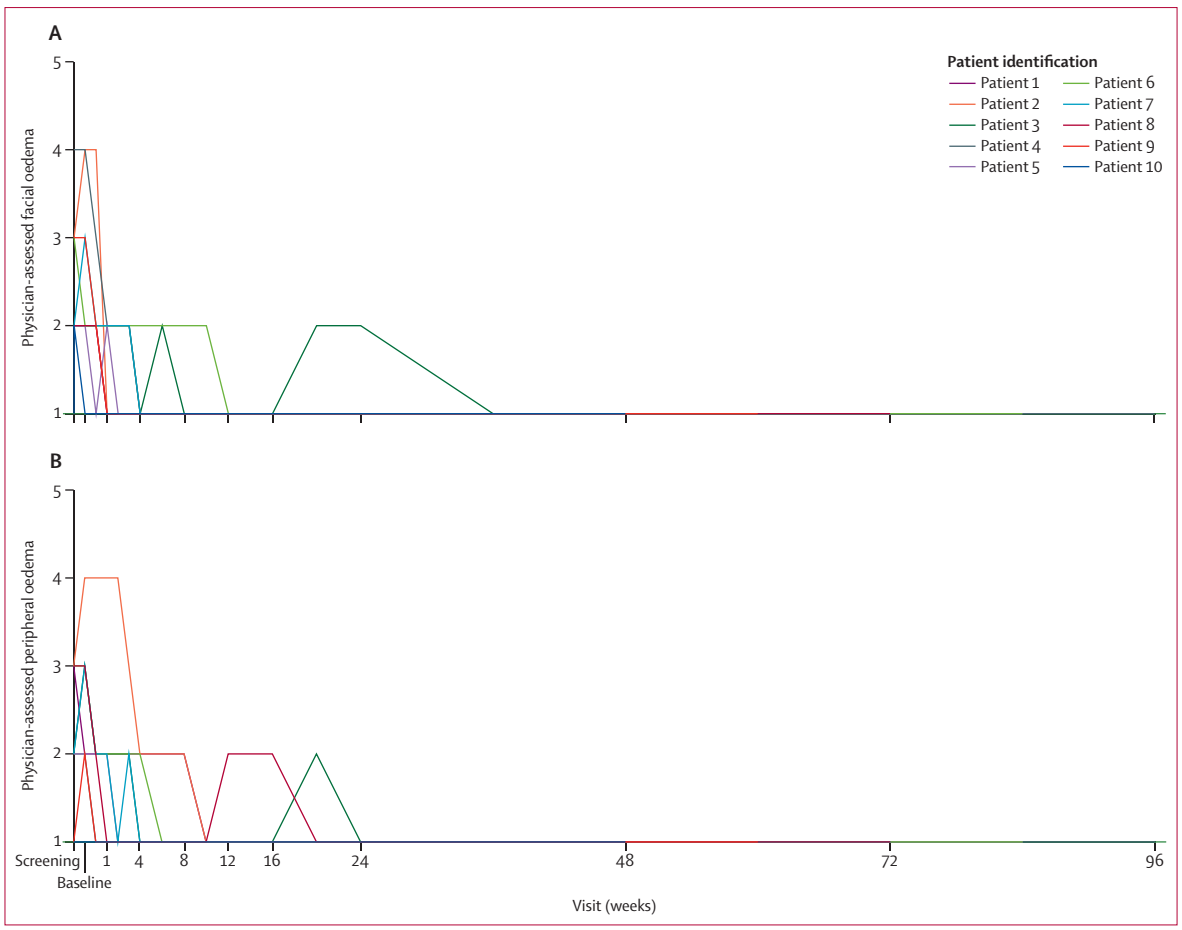

Figure 3: **Physician assessments of facial and peripheral oedema over time**
(A) Data for facial oedema. (B) Data for peripheral oedema. Data are plotted from baseline to the data cutoff date of May 24, 2022. Each line represents an individual patient. Severity was assessed using responses of: 1 meaning no oedema, 2 meaning mild oedema, 3 meaning moderate oedema, 4 meaning severe oedema, and 5 meaning very severe oedema. The full analysis set of patients is presented.

abdominal pain, vomiting, iron deficiency, upper limb fracture, urticaria, and pyrexia (table 3); each of these occurred in two patients, and none were considered related to pozelimab treatment. No adverse events were considered a worsening of CHAPLE disease.

Two patients had three serious adverse events. One patient had two treatment-emergent serious adverse events of vomiting and diarrhoea leading to admission to hospital, neither of which were considered related to pozelimab treatment. One patient had a treatment-emergent serious adverse event of traumatic limb fracture requiring internal fixation, which was not considered related to pozelimab treatment. There were no deaths and no adverse events that led to withdrawal from the study or permanent discontinuation of study drug.

There were no thrombotic or embolic events, consistent with decreased platelets after pozelimab treatment (appendix 2 p 21). No patients receiving pozelimab had an anti-drug antibody response. No moderate or severe infusion reactions or *Neisseria* infections were observed.

The median concentration–time profile of total pozelimab was characterised by a rapid rise in total pozelimab concentrations after the initial 30 mg/kg intravenous dose, with continued accumulation until reaching a steady state by approximately week 20 (appendix 2 p 41). The median steady state pozelimab trough concentration was approximately 426 mg/L (range 237–639 mg/L).

Discussion

We hypothesised that complement pathway overactivation in CHAPLE disease[25] might be ameliorated by pozelimab treatment, a monoclonal antibody directed against the terminal complement component 5. Patients with CHAPLE disease showed complement inhibition and a complete and sustained resolution in signs and symptoms of disease after pozelimab treatment. Patients had rapid catch-up growth and substantial improvements in disease morbidity, including a reduced number of days in hospital and use of concomitant therapies such as

	Pozelimab (N=10)
Number of patients with at least one treatment-emergent adverse event	9
Infections and infestations	6
Rhinitis	2
Acarodermatitis	1
COVID-19	1
Nasopharyngitis	1
Tonsillitis	1
Gastrointestinal disorders	5
Abdominal pain	2
Vomiting	2
Constipation	1
Gingival bleeding	1
Metabolism and nutrition disorders	5
Iron deficiency	2
Dehydration	1
Hypokalaemia	1
Metabolic acidosis	1
Vitamin B12 deficiency	1
Injury, poisoning, and procedural complications	4
Upper limb fracture	2
Contusion	1
Fall	1
Traumatic fracture	1
Skin and subcutaneous tissue disorders	4
Alopecia	1
Alopecia areata	1
Chronic spontaneous urticaria	1
Dermatitis contact	1
Urticaria	1
General disorders and administration site conditions	3
Pyrexia	2
Injection-site erythema	1
Investigations	2
Blood glucose increased	1
Blood uric acid increased	1
Hepatic enzyme increased	1
Blood and lymphatic system disorders	1
Anaemia folate deficiency	1
Cardiac disorders	1
Tachycardia	1
Immune system disorders	1
Immunisation reaction*	1
Nervous system disorders	1
Headache	1
Renal and urinary disorders	1
Haematuria	1
Proteinuria	1

The safety analysis set of patients is presented. *The verbatim term is fever secondary to the COVID-19 vaccine.

Table 3: **Summary of treatment-emergent adverse events**

corticosteroids. Serum albumin concentrations normalised and the need for albumin transfusions was eliminated. Furthermore, we observed clinically meaningful improvements in other laboratory measures of disease, including serum proteins, faecal α-1-antitrypsin, markers of erythropoiesis, micronutrient status, and thrombocythemia. Notably, pozelimab was recently approved by the US FDA as the first treatment for adult and paediatric patients aged 1 years and older with CHAPLE disease on the basis of the findings presented in this report.[26]

Signs and symptoms of CHAPLE disease were promptly and reproducibly reversed with pozelimab treatment in all patients. All patients had improvement in or no worsening of the prespecified clinical outcomes (frequency of problematic abdominal pain, bowel movement frequency, facial oedema severity, and peripheral oedema severity) at week 24. Additionally, after 24 weeks of pozelimab treatment, all patients had a complete resolution of their core signs and symptoms of CHAPLE disease, including their most bothersome symptom, which had a substantial effect on how the participants felt and functioned.

Pozelimab was generally well tolerated in this study, with few treatment-related side-effects, none of which indicated worsening of CHAPLE disease. There were no deaths, no meningococcal infections, and no thrombotic or embolic events. The totality of efficacy and safety data showed an overall encouraging benefit–risk profile.

The design of this study surmounted multiple challenges and limitations in measuring the clinical effects of a therapeutic drug in an ultra-rare disorder identified in 2017.[1] The sample size is appropriate for a disease with a total worldwide prevalence of less than 100 patients. Given the rarity of CHAPLE disease in outbred populations, we identified patients from previously identified areas with high consanguinity.[6] Notably, albeit in a very small dataset, we did not observe a difference in response based on genotype, region, age, or disease duration. The rationale for an open-label, single-arm design was that the disease is too severe for patients to be allocated to placebo. Moreover, at the time of study design, eculizumab had not been rigorously studied to be suitable as an active comparator, with its effects described in case series and not yet in a clinical trial. Furthermore, because each patient served as their own control, we used a historical control period of at least 2 years before enrolment in the study, including the inspection of full records of clinical documentation, to ensure sufficient characterisation of the pretreatment clinical spectrum of disease. This method allowed us to choose objective endpoints for efficacy measurements, such as the number of days in hospital and frequency of albumin transfusions. Additionally, some of the outcome measures reported by patients, caregivers, and physicians used to capture clinical improvement in this study were implemented despite having not been previously used in studies on this disease. It was considered impractical to develop such

experience in the context of an ultra-rare disorder, because a validation study would exhaust the potential pool of study patients and potentially delay access to treatment. Therefore, to evaluate the clinical outcome assessment strategy and incorporate the patient perspective, we conducted semi-structured interviews at screening and week 24. The interviews elicited the core signs and symptoms of disease, as well as the most bothersome symptom, and assessment of pozelimab treatment on patients' signs or symptoms of disease and quality of life. The strategy was to pursue a totality of the data approach, with an emphasis on objective endpoints using pre-enrolment data as the controls supplemented by qualitative data obtained during the interviews to capture the patient experience.

The apparent disease mechanism is that the absence of functioning CD55 on gastrointestinal lymphatic endothelial cell membranes contributes to the constitutive production of membrane attack complexes, leading to a loss of membrane integrity and cellular dysfunction, lymphangiectasia, intestinal inflammation, and lymph-wasting gastrointestinal disease.[27,28] Furthermore, CD59, a membrane-bound inhibitor that functions downstream of CD55 in the complement activation cascade, is not expressed in lymphatic endothelial cells.[29] We hypothesised that the manifestations of CHAPLE disease, a genetic form of primary intestinal lymphangiectasia, might be because of a loss of function in CD55 and the absence of complement regulation by CD59 in gastrointestinal lymphatics. It appears that lymphatic endothelial cells are either not destroyed by the membrane attack complex or can be regenerated by repair processes, since protein-losing enteropathy rapidly and completely resolved upon complement component 5 inhibition. Considering the genetic cause of the disease, pharmacotherapy cannot cure it. Whether treatment throughout adulthood will be necessary is uncertain.

This study confirms and extends the currently available information on the natural history of CHAPLE disease.[1,3,4,6,8,9,25] Historical and baseline data show the clinical and laboratory manifestations of severe enteric protein loss in children, and the conduct of within-trial semi-structured interviews was used to confirm the appropriateness of the clinical outcome assessment strategy. For children with CHAPLE disease, pozelimab treatment has a clear, substantial, and sustained improvement in disease variables. Compared with the eculizumab case series,[6] our study presents more rigorous evidence for the safety and efficacy of pozelimab in CHAPLE disease. Notably, this is an interim report of an ongoing study. Additional 2-year and 3-year treatment data will provide further information on efficacy, effects on puberty, persistence of growth, and safety.

In conclusion, we show that single-agent targeted therapy with pozelimab inhibits complement over-activation and reverses the manifestations of CHAPLE disease. Pozelimab addresses an unmet medical need, and is the only currently approved therapeutic drug for patients with CHAPLE disease, a life-threatening, ultra-rare condition.

Contributors

AO, VC, JJJ, KAM, HBF, LP, OAH, GDY, and MJL conceived and designed the study. AO, VC, APS, BK, SB, EK-A, RE, IJF, HM, NS, KS, and MJL recruited patients and collected the data. JJJ, KAM, TB, and OAH conducted the data analysis. CFT (included in the Pozelimab CHAPLE Working Group) wrote the initial draft of the manuscript. TB and AO accessed and verified the data. All authors had full access to the data; contributed to data analysis and interpretation; and provided critical review, revision, and approval of the report. All authors accept responsibility to submit this report for publication.

Declaration of interests

AO is a consultant and steering committee member for Regeneron Pharmaceuticals; received sample analysis support for a previous collaborative study (https://doi.org/10·1038/s41590-020-00830-z) from Regeneron Pharmaceuticals; and has a pending patent on component 5 inhibitor treatment in CHAPLE disease. VC, NS, and KS received support to conduct the study and received provision of the investigational product from Regeneron Pharmaceuticals. JJJ, TB, and LP are Regeneron Pharmaceuticals employees and stockholders. KAM is a Regeneron Pharmaceuticals employee and stockholder and has both pending and issued patents with Regeneron Pharmaceuticals. HBF is a consultant and advisory board member for Regeneron Pharmaceuticals. IJF is an associate on a cooperative research and development agreement between Merck Pharmaceuticals and the National Institutes for Health. OAH and GDY are Regeneron Pharmaceuticals employees and stockholders and have a pending patent on complement component 5 inhibitor treatment in CHAPLE disease. MJL received support for a federally approved cooperative research and development agreement to support the clinical trial and has a pending patent on complement component 5 inhibitor treatment in CHAPLE disease. All other authors declare no competing interests.

Data sharing

Qualified researchers can request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, and statistical analysis plan) that support the methods and findings reported in this study. Individual anonymised participant data will be considered for sharing once the product and indication has been approved by major health authorities (eg, the US Food and Drug Administration, European Medicines Agency, and Pharmaceuticals and Medical Devices Agency), if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification. Requests should be submitted to https://vivli.org/.

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