Within-Trial Interviews to Contextualize the Patient Experience and Supplement Clinical Outcomes Assessments in a Pivotal Trial of a Newly Described, Fatal, and Ultra-Rare Pediatric Disease

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Background

- CD55 deficiency with hyper-activation of complement, angiopathic thrombosis, and protein-losing enteropathy (CHAPLE) disease is an ultra-rare (<100 patients worldwide), potentially fatal condition caused by mutations in the *CD55* gene.[1]
- Loss of CD55 causes primary intestinal lymphangiectasia and protein-losing enteropathy, which can result in severe abdominal pain, chronic/recurrent diarrhea, vomiting, and edema that can require frequent hospitalizations and medical interventions.[1]
- Pozelimab is a fully human monoclonal immunoglobulin G4P antibody directed against the terminal complement protein C5, a key protein for activation of the terminal pathway of the complement system. It was approved by the US Food and Drug Administration as a subcutaneously administered treatment for CHAPLE disease in August 2023.[2]
- The most common adverse events for pozelimab are upper respiratory tract infections, fractures, hives, and alopecia.[2]

Objective

- Within-trial interviews and clinical outcome assessment (COA) questionnaires were used to evaluate the signs and symptoms of CHAPLE disease from the perspective of the patient before and during treatment with pozelimab.
- Here, we report on the treatment benefit of pozelimab on the signs and symptoms of CHAPLE disease, using a novel mixed-methods approach combining within-trial interviews and COA data, to contextualize patients' experience of the medication's effects.

Methods

Trial design

- NCT04209634 is an ongoing, open-label, single-arm, multicenter, phase 2/3 study evaluating the efficacy and safety of pozelimab in pediatric and adult patients with CHAPLE disease.[3]
- Six potential signs and symptoms identified through published literature and discussions with treating clinicians were selected for the COA measurement strategy, as key features of the disease experience expected to improve with treatment.[4] These were abdominal pain, facial edema/swelling, peripheral edema/swelling, nausea, diarrhea, and vomiting.

Within-trial interviews

- Two 60-minute interviews were conducted at screening and Week 24 with all trial participants and/or their caregivers.
  - For patients aged ≥8 years the primary respondent was the patient, with input from the caregiver as appropriate.
  - For patients aged <8 years or who had cognitive impairments the caregiver was the primary or sole respondent, although the patient was invited to contribute.
  - Screening interviews were conducted before pozelimab initiation to confirm core signs and symptoms and to document each patient's most bothersome sign or symptom (MBS). Week 24 interviews were conducted to understand the impact of treatment with pozelimab on the patient's experience of disease.
- Interviews were conducted by a trained interviewer in person or via telephone, and were recorded, transcribed, anonymized, and translated into US English by an independent company.

Clinical outcome assessments

- Several COAs were administered in-trial to assess potential core signs and symptoms.
- Core signs and symptoms included abdominal pain, diarrhea, facial edema/swelling, peripheral edema/swelling, nausea and vomiting.
- The primary respondent of COAs was the patient (if the patient was aged ≥12 years) or the caregiver (if the patient was aged <12 years).
- Global assessments of symptom/disease severity and change were completed by patients or caregivers and clinicians:
  - Global impression of severity (GIS) assesses overall sign and symptom severity from absent (0) to very severe (4)
  - Global impression of change (GIC) assesses disease severity from much worse (–3) to no change (0) to much better (3).

Analysis

- Interview data from patients and caregivers at screening and Week 24 were coded for each patient, with specific attention to any changes in signs and symptoms, using qualitative data analytic methods and following a pre-specified qualitative data analysis plan.
- Interview data were pooled across participants, and were analyzed for concept frequency and concept descriptions.
- Information from Week 24 interviews about signs and symptoms, as well as scores on the GIS and GIC (reported by the patient/caregiver and their clinician), were presented for each patient to understand the response to pozelimab and whether it was meaningful to patients.
- Change on the COAs to Week 24 was evaluated at the patient level to assess whether the sign or symptom improved did not change or worsened by Week 24.

Results

Patient characteristics

- Ten patients were enrolled in Türkiye (n=7), Thailand (n=2), and the USA (n=1). The mean (standard deviation) age was 9.3 (4.9) years (range 3–19 years) and six patients were female.
- One patient completed both interviews independently, and the remaining interviews were conducted either as dyads (n=5 at screening and n=6 at Week 24) or caregiver only (n=4 at screening and n=3 at Week 24); COAs were completed by caregivers for most patients (n=8).
- All 10 patients met the composite primary endpoint of albumin normalization and improvement (or no worsening) in clinical signs and symptoms at Week 24.

Results

Pre-treatment signs and symptoms

- Before treatment initiation, a total of 25 signs/symptoms were reported during the screening interview. Nine patients (90%) reported experiencing all of the core signs/symptoms; one patient reported experiencing all core signs/symptoms except nausea. All other signs and symptoms were reported by ≤4 patients.
- Abdominal pain was reported as being the MBS for nine patients (90%); facial edema was the MBS for one patient (10%).
  - Abdominal pain was also the most important symptom patients wanted to see improved.

Signs and symptoms at Week 24

- All patients reported complete resolution of core signs and symptoms at Week 24 (**Figure 1**), and nine (90%) had improvement in all signs and symptoms.
- One patient (10%) reported an improvement in all signs and symptoms except for inability to gain weight, which did not change following treatment.
- No patients reported worsening of any signs and symptoms.
- Overall, interview results aligned with changes in scores on COAs and global assessments of CHAPLE disease activity by participants and their physicians (**Table 1**).
- Notably, disease severity was rated as absent by both interview respondents and clinicians at Week 24.

Figure 1. Selection of quotes from interview participants at Week 24

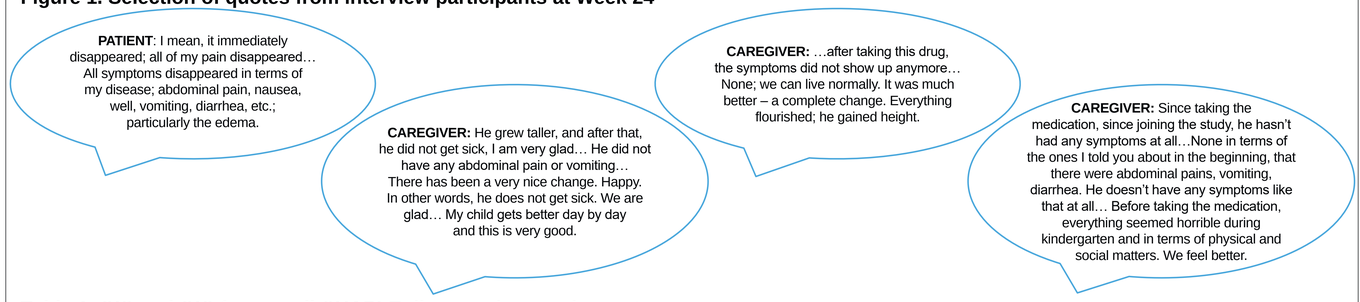

Table 1. GIS and GIC for overall CHAPLE disease signs and symptoms

		Screening (pre-treatment) global assessment of severity		Week 24 (post-treatment) global assessment of severity	
Participant #	Respondents	Patient/caregiver GIS score	Clinician GIS score	Patient/caregiver GIS score	Clinician GIS score
#1	Caregiver and clinician	3	1	0	0
#2	Caregiver and clinician	4	3	0	0
#3	Caregiver and clinician	1	1	0	0
#4	Caregiver and clinician	1	1	0	0
#5	Caregiver and clinician	2	2	0	0
#6	Caregiver and clinician	1	2	0	0
#7	Caregiver and clinician	1	2	0	0
#8	Patient and clinician	2	3	0	0
#9	Caregiver and clinician	1	2	0	0
#10	Patient and clinician	3	2	0	0

CHAPLE, CD55 deficiency with hyper-activation of complement, angiopathic thrombosis, and protein losing enteropathy; GIC, global impression of change; GIS, global impression of severity.
GIS range of scores is based on a five-point Likert scale (0, absent, no symptoms; 1, mild; 2, moderate; 3, severe; 4, very severe); higher scores indicate worse symptoms.
GIC scores are based on the following response options: –3, much worse; –2, moderately worse; –1, a little worse; 0, no change; 1, a little better; 2, moderately better; and 3, much better. Higher scores indicate more improvement.

Limitations

- There may be differences between patient-/caregiver-reported concepts and those in the COAs selected, as well as how the concepts were reported and measured (eg, different time-frames/recall periods).
- Caregivers provided data on the child's experience of signs and symptoms.
- This study had a small sample size (N=10) and was not a randomized controlled trial.

Conclusions

- Findings from within-trial interviews aligned with changes in COA scores and patient/caregiver clinical global assessments of CHAPLE disease activity.
- This mixed-methods approach contextualized the patient experience by providing comprehensive, complementary, and supplementary information beyond COAs.
- Overall, findings supported the efficacy of pozelimab on improving the signs and symptoms of CHAPLE disease, as well as the transformative impact on the lives of patients.
- Mixed-methods approaches may be supportive in demonstrating treatment efficacy, particularly in the context of rare and severe diseases.

References

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Competing interests

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