Journal of the Neurological Sciences 464 (2024) 123147

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Tricaprilin (CER-0001) for the preventive treatment of migraine: A phase 2 randomised, double-blind, placebo-controlled pilot study

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ARTICLE INFO

Keywords:
Migraine
Tricaprilin
Ketones
Efficacy
Safety

ABSTRACT

Background: Increasing evidence indicates a metabolic etiology for migraines, with ketosis potentially rectifying metabolic and clinical features. We conducted a pilot study to evaluate CER-0001, a ketogenic agent, for migraine prevention without dietary changes.
Methods: This was a 2-part, double-blind, randomised, placebo-controlled study conducted in Australia. Adults with at least a 1-year history of migraine and ≥ 1 prior preventive treatment failure were randomised to either oral CER-0001 (up to 30 g twice a day) or placebo for 12 weeks. The primary endpoint was Month 3 change in Migraine Headache Days from baseline.
Results: Part 1 results are presented. 81 participants were randomised and dosed (n = 40 CER-0001, n = 41 placebo), and 61 participants had evaluable efficacy data. No statistically significant difference was observed in the primary endpoint (LSMean difference 0.92 days; $p = 0.586$). During Month 2, a mean improvement of −2.8 days was observed for CER-0001 ($p = 0.056$). Withdrawal rates were 45.0% and 53.7% (CER-0001; placebo). The proportion of participants reporting at least one treatment-emergent adverse event was similar between arms (90.0% CER-0001, 82.9% placebo), mostly gastrointestinal (85.0% CER-0001, 70.7% placebo).
Conclusion: Results suggest positive directional promise over 2–3 months for CER-0001. A new formulation will be used for larger, fully powered phase 2/3 studies.
Trial registration: This study is registered at ClinicalTrials.gov (NCT04437199).

1. Introduction

Migraines are prevalent, disabling, and costly neurological disorders for which the available preventive treatments are not effective for all patients. The primary pathogenic mechanisms for migraine are not definitively elucidated, and to date, migraine research has been primarily focused on vasculature and neurotransmission; however, evidence points to brain energy metabolism abnormalities as being involved. [1]. Migraine is postulated as a response to cerebral energy deficiency or oxidative stress levels; the attack helps restore brain energy homeostasis and reduces harmful oxidative stress levels [2]. Ketosis has been proposed to restore brain electrical activity and metabolism and counteract neuroinflammation in migraine, although the precise mechanism by which it does this is unclear [3,4]. The efficacy of ketogenic diets (KDs) for preventing migraines has been shown in observational and case studies [5–9]. A randomised, controlled, double-blind, crossover trial comparing KD to very low-calorie non-KD in overweight/obese participants with migraine, showed that those on the KD experienced 3.73 fewer migraine days per month and a 3.02 decrease in migraine attacks per month compared to the non-KD group. [10].

Medium-chain triglycerides (MCTs) are a simple and safe method to induce elevated ketone bodies in plasma within any special diet. They have been safely used for years in parenteral nutrition, baby formulas, medical foods, drug products, energy supplements and other food products, orally and intravenously [11]. Tricaprilin (CER-0001), an eight-carbon MCT, has demonstrated efficacy in two Phase 2 Alzheimer's disease studies, where it is thought to supply neurons with an alternative source of energy to glucose [12,13]. This trial aimed to assess

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https://doi.org/10.1016/j.jns.2024.123147
Received 27 May 2024; Accepted 20 July 2024
Available online 22 July 2024

the efficacy of CER-0001 in preventing migraine in a 3-month trial with twice-daily administration.

2. Materials and methods

2.1. Study design

This was a randomised, double-blind, placebo-controlled, parallel-group, multi-centre, 3-month study conducted between December 2020 to February 2022 across 10 Australian sites to assess CER-0001 (formulated as AC-SD-03 or matching placebo in 240mls water) for the prevention of migraine in participants with frequent episodic and chronic migraine with and without aura. Originally, this study had two parts: Part 1, a pilot for sample size estimation, and Part 2, a fully powered proof of concept trial. Due to formulation issues, Part 2 will be a separate study, and only Part 1 results are presented.

The study followed International Headache Society (IHS) Guidelines for migraine drug trials [4]. This 19-week study comprised four periods (Fig. 1): (1) an up to 2 weeks screening period to assess eligibility, (2) a 4-week baseline measurement period prior where a sentinel dose of 12.5 g of AC-SD-03 containing 5 g of CER-0001 was administered, and baseline data (i.e., migraine headache days [MHDs]) was established for comparison of endpoints during the study, (3) a 12-week treatment period with a 3- to 6-week up-titration period from 5 g CER-0001 or placebo (AC-SD-03P containing safflower oil) twice a day (BID) to a target dose of 20 g BID or highest tolerated dose for those participants that met safety and baseline eligibility criteria and KD literature and (4) a 1-week safety follow-up period. The initial target dose of 30 g BID with a 2–4-week titration period was amended to a lower target dose of 20 g and a prolonged titration period of up to 6 weeks to enhance tolerability. Following this amendment, participants who had already titrated and tolerated a 30 g BID dose continued as scheduled.

2.2. Eligibility criteria

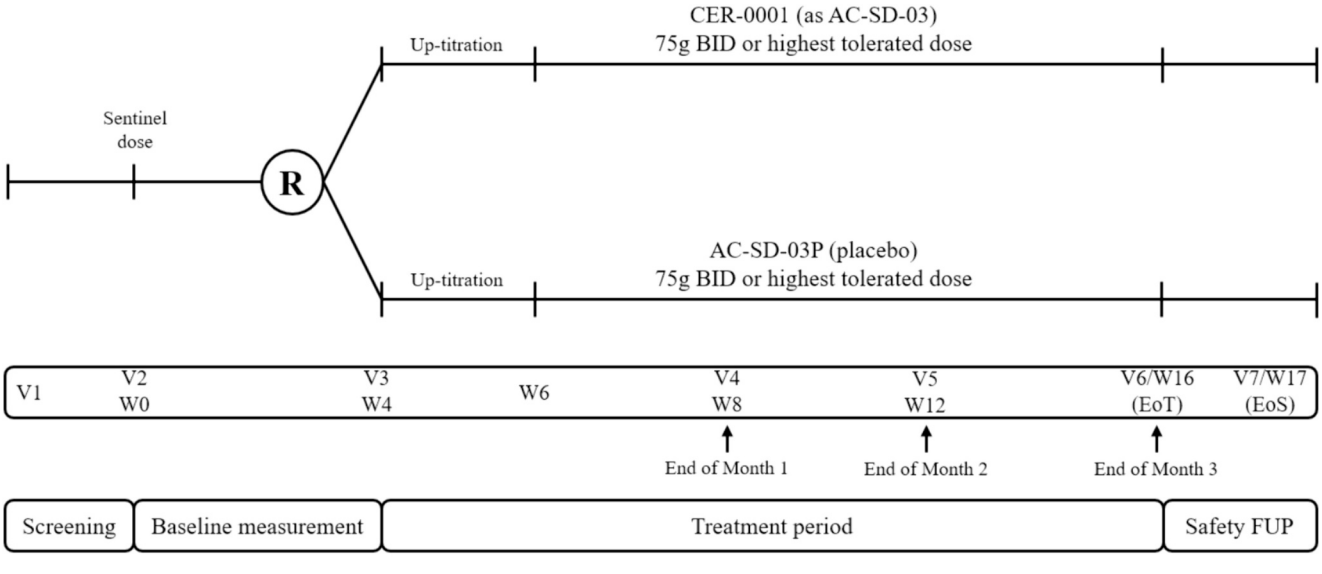
Adults between 18 and 70 years of age with a history of frequent (episodic or chronic) migraine with or without aura for at least one year, according to the International Classification of Headache Disorders – 3rd edition (ICHD 3-beta), with an onset age of under 50 years were included. Participants had to have between 4 and 24 MHDs per month and no therapeutic response to 1 to 4 categories of prophylactic treatments (Table 1) and had to be able to tolerate 12.5 g of AC-SD-03 containing 5 g of CER-0001 per sentinel dose challenge.

Participants were excluded if they had: any active gastrointestinal (GI) condition not well controlled by medication; use of barbiturates or opioids for acute migraine treatment; use of calcitonin gene-related peptide (CGRP) agents in the last three months prior to screening visit, botox injections, transcutaneous electrical nerve stimulation (TENS), cranial nerve blocks, trigger-point injections, acupuncture specifically for migraine, infusion therapy; current use or within three months of baseline visit of Axona® or other MCT-containing products, as well as a KD, low-carb diet, or intermittent fasting; and active suicidal thoughts within six months preceding the screening visit, assessed with the Columbia-Suicide Severity Rating Scale (C-SSRS).

The study protocol, amendments, informed consent form, Investigator Brochure, and relevant documents were submitted to an Independent Ethics Committee or Institutional Review Board for approval before study initiation. This study was conducted in accordance with the International Council for Harmonization Good Clinical Practice regulations/guidelines and the ethical principles set forth in the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines. Participants provided written informed consent before any study-specific tests or procedures were performed.

Table 1
Prophylactic treatment categories.

Category 1	Topiramate
Category 2	Other antiepileptics (e.g., divalproex sodium, sodium valproate, gabapentin)
Category 3	Beta-blockers
Category 4	Tricyclic antidepressants
Category 5	Other antidepressants (e.g., serotonin-norepinephrine reuptake inhibitors, selective serotonin-reuptake inhibitors
Category 6	Calcium channel blockers (e.g., verapamil, amlodipine, cinnarizine, lomerizine) or calcium antagonists (e.g., flunarizine)
Category 7	Angiotensin receptor blockers (e.g., candesartan) or angiotensin-converting enzyme (ACE) inhibitors (e.g., lisinopril)
Category 8	Onabotulinum toxin
Category 9	CGRP inhibitors (e.g., erenumab, fremanezumab, galcanezumab)
Category 10	Other (specify)



BID, twice a day; D, day; EoS, end of study; EoT, end of treatment; FUP, follow-up; R, randomisation; V, visit; W, week.

Fig. 1. Study Schema.

2.3. Outcomes

The primary endpoint was change from baseline in the number of MHDs during Month 3. Secondary endpoints included change from baseline in the number of MHDs during Month 1 and 2 and overall from Months 1 to 3; change from baseline in the duration of MHDs during Month 1 to 3 of treatment; proportion of participants with a 50% reduction from baseline in the number of MHDs in treatment Months 1 to 3; change from baseline in monthly acute migraine medicine and time to first usage of acute migraine medication; and change from baseline on the Headache Impact Test score (HIT-6) at the end of Months 1 to 3.

An MHD was defined as any calendar day on which an actual or probable migraine headache occurred. A migraine headache was defined as a headache, with or without aura, lasting for >30 min with (a) 2 or more of the following characteristics: unilateral location, throbbing/pulsatile quality, moderate to severe pain intensity, exacerbated with exercise/physical activity or causing avoidance of routine physical activity; and (b) 1 or more of the following associated symptoms: nausea and/or vomiting, photophobia and phonophobia. A probable migraine was defined as a headache with or without aura, lasting for >30 min, missing one of the features of a migraine (i.e. meets ≥2 (a) criteria and 0 (b) criteria, or meets 1 (a) and 1 (b) criterion).

2.4. Assessments

Safety assessments included vital signs, laboratory measurements, C-SSRS, and adverse events (AEs) which were coded using the Medical Dictionary for Regulatory Activities (MedDRA® Version 24.1). Participants were assessed for AEs and suicidal risk throughout the study; vital signs and laboratory tests were at screening and weeks 8, 12 and 16.

Efficacy was assessed using an electronic diary to capture headache/migraine data, acute headache medication use, and a patient-reported outcome to measure headache related disability, HIT-6. Participants were prompted daily via a mobile app or phone provision to complete fields, including whether they had a headache lasting at least 30 min and questions to determine if it was a migraine (start and end time, severity, features, and symptoms). If they reported a headache, they were prompted to report any acute medication taken (name, dose, and frequency).

2.5. Statistical analysis

The full analysis set (FAS) and safety analysis set (SAF) included all randomised participants who received at least one dose of CER-0001 or placebo, analysed according to the intended treatment arm and the treatment received, respectively. The evaluable for efficacy set (EES) was a subset of the FAS with at least 14 of the 28 completed diary entries in any post-baseline month, and the intended titration evaluable for efficacy set (EEITS) was conducted as a per-protocol sensitivity analysis set per the protocol amendment which included only those participants who received the slower titration and achieved a maximum dose no higher than 40 g BID. No formal statistical analyses of AEs were undertaken.

The effect of CER-0001 on the change in the number of MHDs per month was estimated from a mixed-effects repeated measures model fitting the change from baseline as the response variable, treatment (CER-0001 or placebo), time (Month 1 to 3) and treatment by time interaction term as fixed effects, and as well as the continuous fixed covariate of baseline number of MHDs. For each month, participants needed a minimum of 14 diary entries to be considered evaluable. In cases where an evaluable participant had fewer than 28 days of headache diary data during a month, normalisation was applied to pro-rata the available data to estimate the 28-day total. For each treatment month, participants' mean migraine duration and the mean change from baseline in mean migraine duration were calculated. Participants who experienced no migraines were assigned a mean duration of 0 for that month. The mean headache duration and the change from baseline in the mean duration of migraine over time, by treatment, were analysed using the same methods as described for the primary endpoint. All other secondary endpoints were summarised using appropriate descriptive statistics.

A post hoc analysis was conducted to explore the difference in the trend during Month 3 between the EES and the EEITS populations. The impact of participants who had <4 or > 24 MHD during the baseline measure period (i.e., did not meet the inclusion criterion of 4 to 24 MHD at baseline) was explored. The primary efficacy analysis was repeated on the EES and EEITS, excluding these entry criterion violators using a rule-based approach. A per protocol analysis was performed as part of the post-hoc analysis, evaluating the impact of participants who did not meet the inclusion criteria of 4–24 MHDs during the baseline period, given that they had little room for improvement or conversely detriment (floor and ceiling effects).

3. Results

A total of 83 participants were randomised in a 1:1 ratio to CER-0001 ($n = 41$) or placebo ($n = 42$).; two participants withdrew prior to dosing (one per arm). Forty-one participants (50.6%) completed the study treatment, 22 (55.0%) in the CER-0001 group and 19 (46.3%) in the placebo group (Fig. 2). Eighteen participants (45.0%) receiving CER-0001 withdrew from the study (most common reasons for discontinuation were AEs (30.0%) followed by "other reasons" such as withdrawal of consent or refusal due to personal reasons [12.5%]), whilst 22 participants (53.7%) receiving placebo withdrew also mainly due to AEs (36.6%) followed by non-compliance with IMP (7.3%) and "other reasons" (7.3%). Out of the intended treatment duration of 84 days, the mean (standard deviation [SD]) for the actual exposure was 49.7 (28.6), CER-0001 arm, and 46.2 (29.1), placebo arm. On average, dose intensity (measuring the percentage of the intended dose received from the end of the titration period to day 84) was low in both treatment arms (56.3% CER-0001, 63.4% placebo).

Participant demographics and baseline characteristics are listed in Table 2. Age, height and BMI were well-balanced between treatment groups, mean (SD) age was 45.8 (11.8) years, mostwhite (90.1%), and female (80.2%). A slight imbalance was observed between arms with respect to sex: the CER-0001 arm had more males (25.0%) than the placebo arm (14.6%), which explains the imbalance in weight between both arms (means 80.1 and 74.9, for active and placebo, respectively). Most participants had family history of migraine ($n = 49$, 60.5%), and all met the ICHD-3 criteria for migraine, reporting at least five attacks, with headaches lasting 4 to 72 h. Acute headache migraine medication was used by 87.7% ($n = 71$) during baseline, ibuprofen being the most frequently used ($n = 19$, 23.5%), followed by paracetamol (17, 21.0%) and sumatriptan (12, 14.8%). The number of participants on prophylactic medication at baseline was 18 (45.0%) for CER-0001 and 15 (36.6%) for the placebo arm. It was also noted that the CER-0001 arm had more participants with chronic migraine at baseline than the placebo arm, based on the baseline number of MHDs.

Protocol deviations were most often due to treatment compliance (<75.0% intended doses consumed for reasons other than safety) in 14 (17.3%) of the 24 important deviations reported. No deviation affected the safety of participants. Notably, 8 deviations were due to participants not meeting the baseline criteria of 4–24 MHDs during the baseline period, including 5 deviations in participants in the EES.

3.1. Efficacy

In the EES overall ($n = 62$), the unadjusted mean number of MHD at baseline was 12.4 (SD 6.37) and 10.3 days (SD 5.91) for CER-0001 and placebo respectively, whilst for the per-protocol EEITS overall ($n = 24$), it was 11.9 (SD 6.02) and 8.4 days (SD3.58) for CER-0001 and placebo. In both populations, on average, participants in the CER-0001 arm had

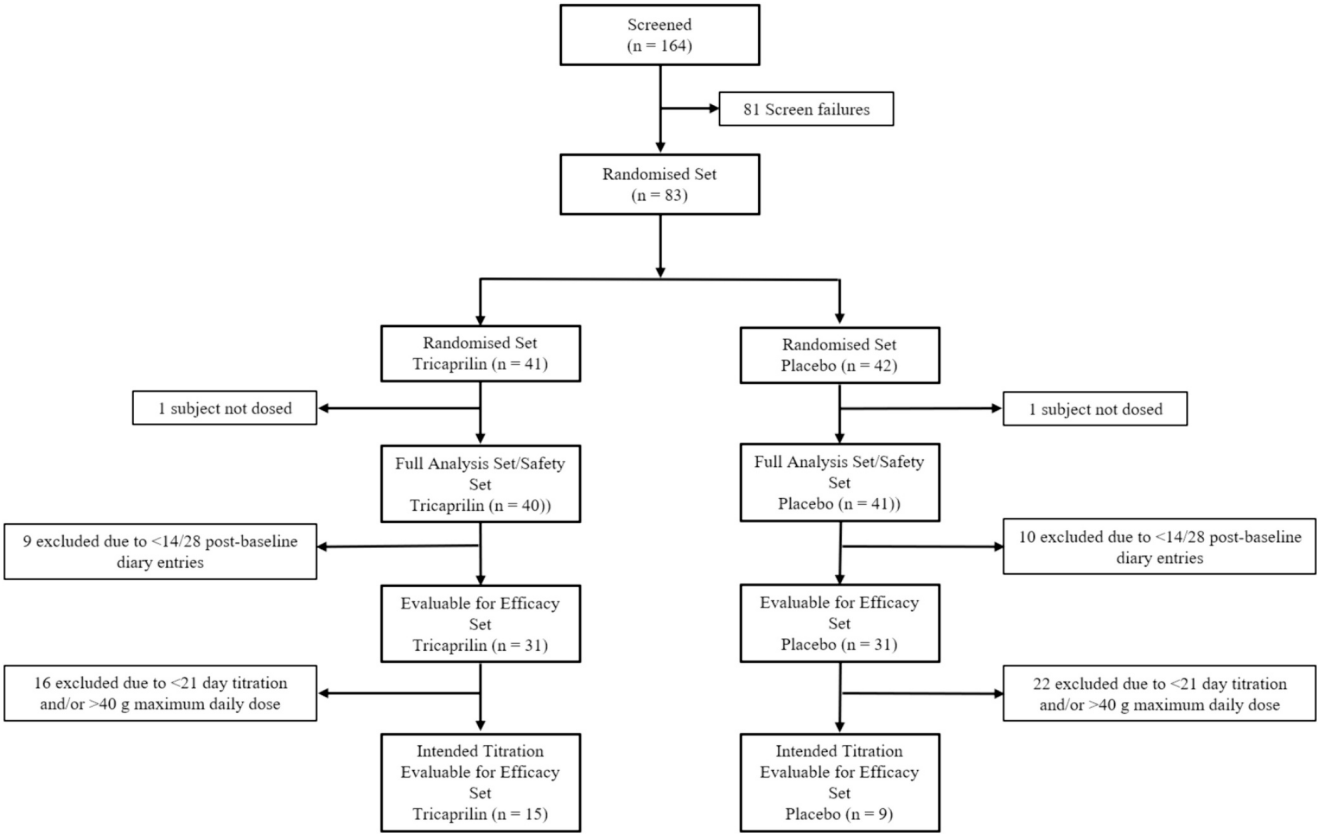


Fig. 2. Participant disposition.

Table 2
Demographics and baseline characteristics.

Parameter	CER-0001 (***n*** = 40)	Placebo (***n*** = 41)	Total (***n*** = 81)
Age, years			
Mean (SD)	44.8 (12.21)	46.9 (11.50)	45.8 (11.3)
Median	46.0	49.0	48.0
Minimum, Maximum	18, 70	22, 66	18, 70
Sex, n (%)			
Female	30 (75.0%)	35 (85.4%)	65 (80.2%)
Male	10 (25.0%)	6 (14.6%)	16 (19.8%)
Race, n (%)			
White	38 (95.0%)	37 (90.2%)	79 (90.1%)
Indian/Indian sub-continent	0 (0%)	1 (2.4%)	1 (1.2%)
Chinese	1 (2.5%)	0 (0%)	1 (1.2%)
Japanese	1 (2.5%)	0 (0%)	1 (1.2%)
Aboriginal Australian	0 (0%)	3 (7.3%)	3 (3.7%)
Other	0 (0%)	1 (2.4%)	1 (1.2%)
Weight (kg)			
Mean (SD)	80.086 (23.8935)	74.939 (15.9503)	77.481 (20.3033)
Median	77.950	73.900	75.00
Minimum, Maximum	50.50, 171.00	41.80, 113.00	41.80, 171.00
BMI (kg/m^2)			
Mean (SD)	27.37 (6.860)	26.80 (5.343)	27.08 (6.107)
Median	26.10	27.40	26.60
Minimum, Maximum	18.7, 51.1	17.9, 40.3	17.9, 51.1

more MHDs at baseline compared to the placebo arm.

During Month 3, the EES statistical analysis showed that participants in the CER-0001 arm experienced a mean reduction of 3.4 MHDs compared to a mean reduction of 4.3 MHD for the placebo arm, a mean difference of 0.92 MHD (*p*-value 0.586), whereas the per-protocol EEITS analysis showed a mean reduction of 4.7 MHD in the CER-0001 arm

Table 3
Summary of MHDs and change from baseline in MHDs over time – EEITS and EES.

	EEITS		EES	
	CER-0001	Placebo	CER-0001	Placebo
Month 1				
n	15	9	31	31
Unadjusted mean	−1.2	−1.0	−1.4	−1.7
Adjusted mean	−0.5	−1.8	−1.0	−2.0
Difference in adjusted means	1.24		1.03	
2-sided p-value	0.512		0.323	
95% CI	(−2.64, 5.13)		(−1.04, 3.10)	
Month 2				
n	10	8	22	23
Unadjusted mean	−5.3	−0.4	−5.4	−1.9
Adjusted mean	−4.5	−1.2	−5.0	−2.2
Difference in adjusted means	−3.27		−2.75	
2-sided p-value	0.132		0.056	
95% CI	(−7.62, 1.08)		(−5.57, 0.07)	
Month 3				
n	10	7	21	19
Unadjusted mean	−5.4	−3.3	−3.4	−4.6
Adjusted mean	−4.7	−3.2	−3.4	−4.3
Difference in adjusted means	−1.49		0.92	
2-sided p-value	0.539		0.586	
95% CI	(−6.60, 3.62)		(−2.46, 4.30)	

compared to a mean reduction of 3.2 MHD for the placebo arm, a mean difference of −1.49 MHD (p-value = 0.539) (Table 3). In all analysis sets, there was an improvement relative to placebo observed during Month 2, which was of a clinically relevant magnitude (EES: −2.75 MHDs, p = 0.056; EEITS -3.27 MHDs, p = 0.132) (Fig. 3).

The proportion of participants in the EES analysis with ≥ 50% reduction in the number of MHDs during Month 1 was 9.7% and 22.6% (p-value 0.960), 41.9% and 25.8% during Month 2 (p-value 0.142), and 25.8% and 22.6% during Month 3 (p-value 0.500) for CER-0001 and placebo, respectively (Fig. 4); whereas the per-protocol EEITS analysis showed that during Month 1, 20.0% of participants on the CER-0001 arm and 11.1% on the placebo arm reached a 50% reduction in MHDs (p-value 0.514), 46.7% and 22.2% during Month 2 (p-value 0.225), and 33.3% for both arms during Month 3 (p-value 0.675).

Due to the differing directional trends observed between the EES and EEITS at Month 3, investigations were performed to better understand the reasons for the differences. Outliers were observed in the EES analysis, which were participants who did not meet the entry criteria of 4–24 MHDs at baseline. To further explore whether these participants might explain the differing directional trends between the EES and EEITS, a post-hoc sensitivity analysis was performed excluding all participants who did not meet the baseline entry criteria of 4–24 MHDS at baseline. Excluding these participants revealed that the varying trend between EES and EEITS was mainly influenced by those with limited scope for improvement (floor effects) or, conversely those with little scope for deterioration (ceiling effects). Based on the post-hoc analysis of 4–24 MHD enrolees by the EES sub-group with chronic migraine at baseline, there was a significant − 9.0 MHD difference observed between the treatment and placebo group during Month 2 and a − 5.0 for Month 3, which contrasts with the current CGRP drugs where only a < 2 MHD difference was observed as per the drug label data (Figs. 4 and 5. Proportion (±SE) of Participants with 50% Reduction From Baseline in MHD Over Time - Evaluable for Efficacy Set). In all analysis sets, a clinically relevant improvement relative to placebo was observed during Month 2 (EES: −2.75 MHDs; EEITS -3.27 MHD; per protocol EES: −2.94). During Month 3, the per-protocol post hoc analysis demonstrated a mean difference of −0.08 days which aligns in the direction of the trend seen in the per-protocol EEITS (−1.49).

The average migraine duration for participants and highest reduction from baseline in MHDs on the CER-0001 arm showed a statistically significant reduction in Month 2. The acute migraine medication usage and HIT-6 score showed a similar trend with a clear reduction during Month 2 that was not sustained during Month 3. It is postulated that the poor GI tolerability, and resulting decreases in treatment compliance over time, may have contributed to the lack of sustained efficacy between Months 2 and 3. Other limitations were baseline headache frequency differences, caloric differences in active groups and ketosis only reached as study end.

3.2. Safety

Overall, 70 participants (86.4%) reported at least one treatment emergent adverse event (TEAE), with a total of 186 events reported, with similar prevalence between arms. The incidence of TEAEs considered “related to treatment” was high for both treatment arms (87.5% and 68.3% for CER-0001 and placebo, respectively). Similar proportions had any TEAE (36 [90.0%] for the CER-0001 arm and 34 [82.9%] for the placebo arm) as well as any moderate-severe events (22 [55.0%] and 22 [53.7%] CER-0001 and placebo, respectively). Two serious AEs were reported, one in a participant receiving CER-0001 (2.5%) (raised creatinine kinase, considered probably related to CER-0001) and one placebo (2.4%) (colitis considered probably related to CER-0001). Events leading to discontinuation of study were reported in 14 participants (35.0%) receiving CER-0001 treatment and in 15 participants

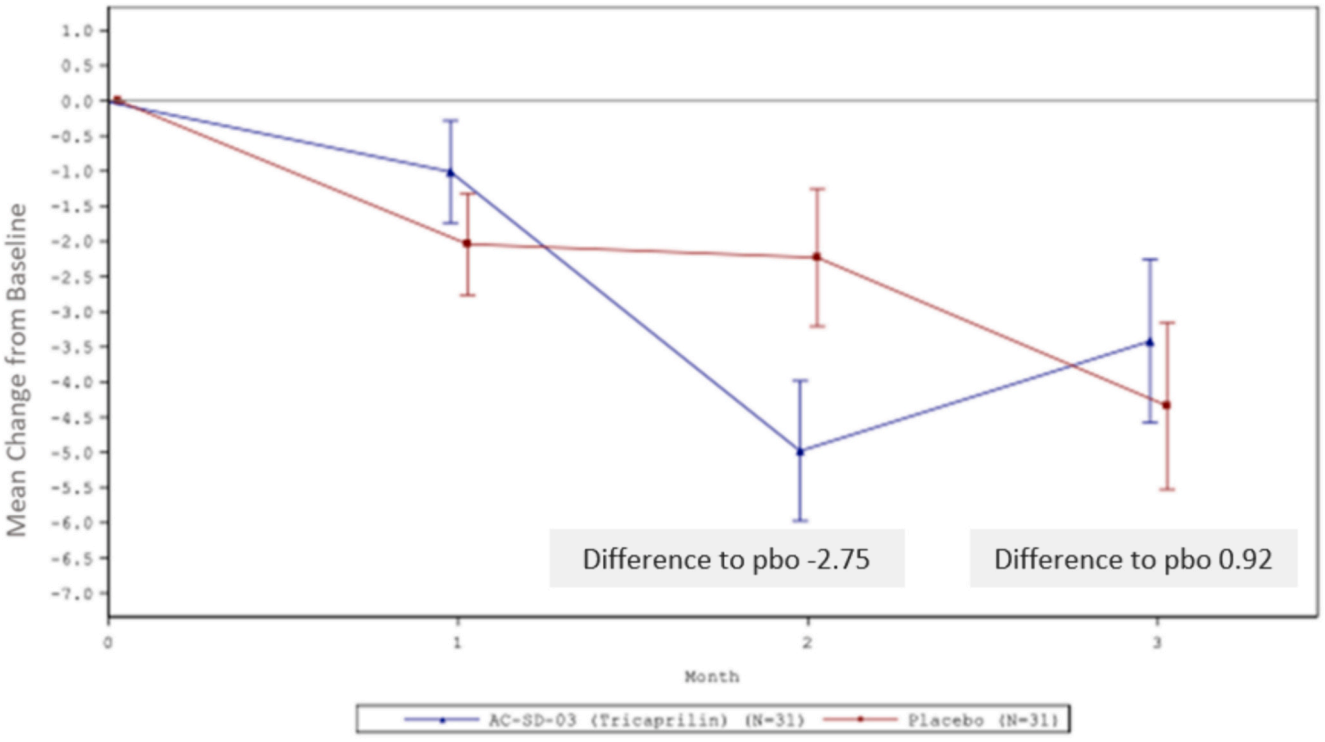


Fig. 3. Statistical analysis of the change from baseline in MHDs (MHDs ± SE) over time.
Primary endpoint: change from baseline in MHDs in Month 3, evaluable for efficacy set (EES); CER-0001 3.4 MHDs, placebo −4.3 MHDs, p = 0.586. NOTE: The baseline period is defined as the 28-day evaluation period prior to randomisation, i.e., study days −28 to −1. Months 1 to 3 are the subsequent 28-day evaluation periods, i.e., study days 1–28 (Month 1), study days 29–56 (Month 2) and study days 57–84 (Month 3). The model fitted included change in the number of MHD per month as the response variable, with treatment, visit, treatment*visit interaction, and a continuous fixed covariate of baseline number of MHD.

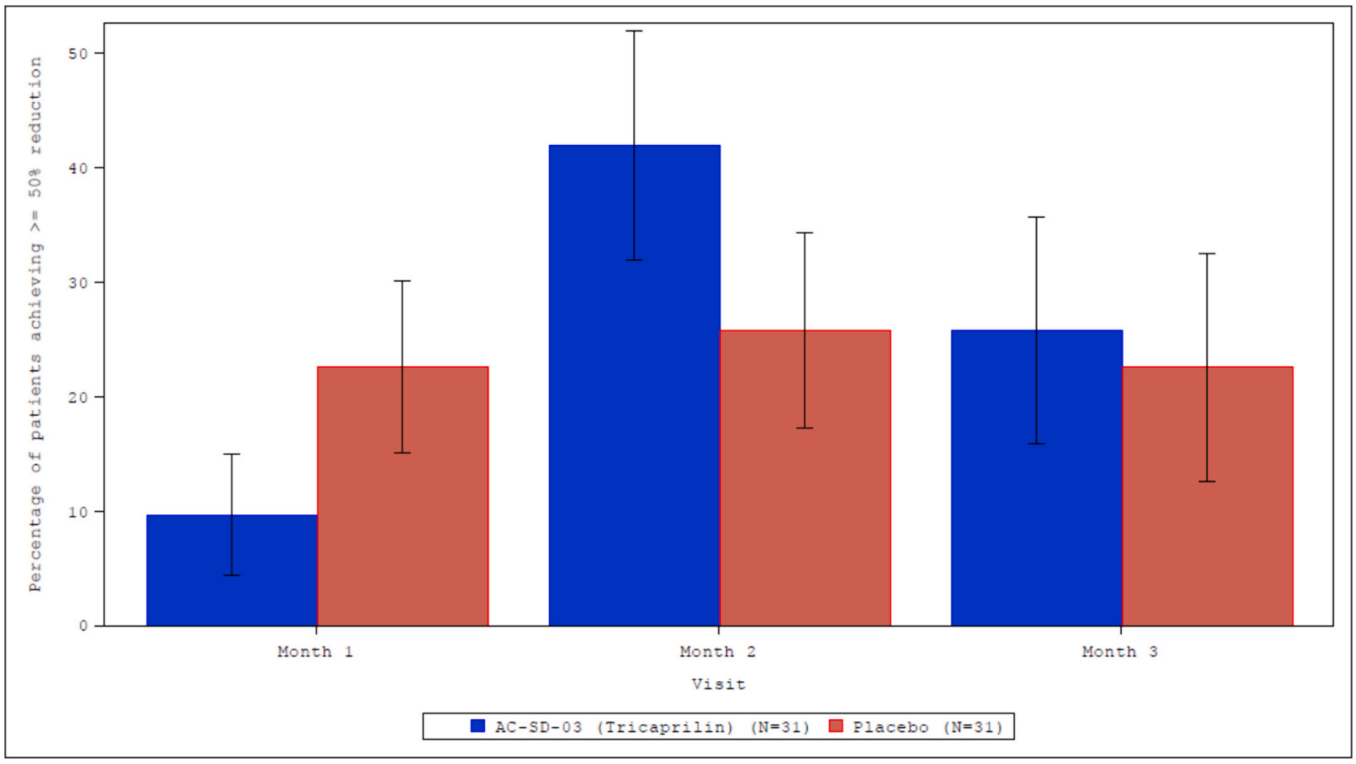


Fig. 4. Proportion (±SE) of Participants with 50% Reduction From Baseline in MHD Over Time - Evaluable for Efficacy Set.
NOTE: The Baseline period is defined as the 28-day evaluation period prior to randomisation, i.e., Study Days −28 to −1. Months 1 to 3 are the subsequent 28-day evaluation periods i.e., Study Days 1–28 (Month 1), Study Days 29–56 (Month 2) and Study Days 57–84 (Month 3).

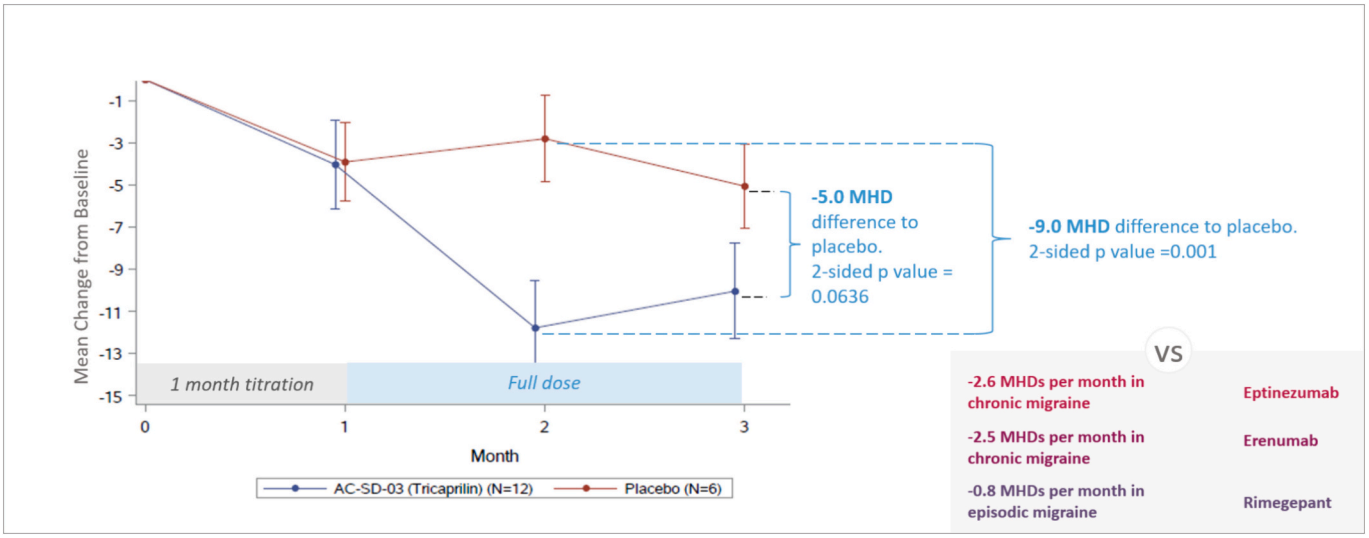


Fig. 5. Change from Baseline in Migraine Headache Days (MHDs) in Chronic Migraine Subset Over time.

(36.6%) receiving placebo; no life-threatening events or deaths were reported. The withdrawal rate in the study was high in both arms, 45.0% vs 53.7% (CER-0001 vs placebo), primarily due to AEs.

Overall, the most frequently reported TEAEs were GI disorders (135 events in 63 participants [77.8%]), as expected, followed by nervous system disorders (12 events in 11 participants [13.6%]). Constipation was the most frequently reported TEAE across the study, with similar rates in both arms (Table 4).

4. Discussion

There is a significant unmet medical need in migraine treatment and a clear need for new and better drugs. The targets of the traditional preventive treatments for migraine are the brain's excitation/inhibition balance and/or serotonin metabolism and come with associated side effect profiles. In small sample sizes, CER-0001 showed a 9.0 MHDs reduction at Month 2 and 5.0 MHDs at Month 3, compared to CGRP larger sample sizes with effect sizes ranging from a − 0.8 (rimegepant, episodic and chronic migraine) to −2.6 MHDs (eptinezumab, chronic migraine) difference to placebo [14,15]. Although CGRP agents offer a

Table 4
Incidence of TEAEs.

Preferred tern	CER-0001 (n = 40) n (%) episode	Placebo (n = 41) n (%) episode
Constipation	11 (27.5%) 13	12 (29.3%) 14
Nausea	10 (25.0%) 10	12 (29.3%) 13
Abdominal distension	13 (32.5%) 16	7 (17.1%) 7
Diarrhoea	8 (20.0%) 10	8 (19.5%) 9
Abdominal pain	6 (15.0%) 7	1 (2.4%) 1
Vomiting	1 (2.5%) 1	6 (14.6%) 6
Abdominal pain upper	6 (15.0%) 7	0 (0%) 0
Dizziness	3 (7.5%) 3	2 (4.9%) 2
Dyspepsia	3 (7.5%) 3	2 (4.9%) 2
Gastrooesophageal reflux disease	3 (7.5%) 3	2 (4.9%) 2

new option, additional treatments are needed due to migraines' multifactorial nature and varying responses among different migraine types. A valid and viable target that has not yet been fully explored is the metabolic pathway, which is supported by data from case studies and controlled trials of the KD [7–10]. CER-0001 being a ketogenic therapy without dietary modifications or restrictions offers a different target to the established migraine preventive therapies.

The results of this study did not demonstrate a statistically significant difference between CER-0001 and placebo on the primary 3-month endpoint, with a high withdrawal rate in both treatment arms. On average, the dose intensity was low in both arms, with a mean exposure of 47.9 days. The decrease in dose intensity was observed in both intended dose and relative dose intensity percentages, where the former measures the dose intensity as a proportion of the intended 84-day treatment duration, and the latter measures it from starting treatment until the participant's last day of dosing. The review of the dose intensity figures over time revealed decreasing intensity, indicating considerable dose reductions and increased dose interruptions.

The TEAE with the highest incidence was constipation (27.5% CER-0001, 29.3% placebo), which was not expected based on previous studies with CER-0001 and could have been due to the silicon dioxide as an excipient in the formulation. GI-related events are a known side effect of ingestion of MCTs, including CER-0001; however, ingestion 30 min after completion of a meal and a slow titration schedule was expected to mitigate these events. During the study, a high level of GI TEAEs with this CER-0001 formulation (and the matching placebo) led to participant withdrawals due to tolerability issues between Month 2 and Month 3.

Though not powered for the primary endpoint, promising Month 2 results and a post hoc per-protocol analysis suggests further exploration of CER-0001 in prevention of migraine is warranted. The tolerability and subsequent withdrawal rates in both arms created data variability, impacting study conclusions alongside the small sample size at the primary timepoint. Despite the small sample size, the observed effect magnitude provides a rationale for further exploration in this indication, along with a formulation review and update.

5. Conclusions

The interpretation of this pilot study is not solely reliant on statistically significant differences due to its design and limited statistical power. This pilot trial found no significant safety issues, but both CER-0001 and matching placebo showed poor tolerability. Although the Month 3 primary endpoint showed no significant difference between arms, Month 2 (EES, EEITS) and Month 3 (EEITS) results suggest an efficacy signal. The high incidence of causally related TEAEs seen in both arms suggest that they may be due to the formulation rather than the active ingredient. Results of the pilot suggest directional promise over 2–3 months for oral CER-0001, and a new formulation will be used for larger, fully powered phase 2/3 studies.

Funding

The authors disclosed receipt of the following financial support for this article's research, authorship, and/or publication: Cerecin.

CRediT authorship contribution statement

Lilian Chow: Investigation, Methodology, Project administration, Writing – review & editing. **Julia Presanis:** Methodology, Software. **Nikki McIntyre:** Investigation, Methodology, Writing – review & editing. **Samuel Henderson:** Formal analysis, Methodology. **Mark Bloch:** Investigation, Validation, Writing – review & editing. **Elspeth Hutton:** Investigation, Project administration, Visualization, Writing – review & editing. **Marc Cantillon:** Conceptualization, Data curation, Formal analysis, Writing – original draft.

Declaration of competing interest

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MB has no conflicts of interest; EH has no conflicts of interest; all other authors are or were employees or consultants of Cerecin.

Acknowledgements

The authors thank the participants and the sites that participated in this study. Medical writing services were provided by Christina Green (My Medical Department) and supported by the study funder Cerecin.

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