Received: 21 June 2024 | Accepted: 10 July 2024

DOI: 10.1097/HC9.0000000000000524

PROTOCOL PAPER

OPEN

Zinc supplementation to improve prognosis in patients with compensated advanced chronic liver disease: a multicenter, randomized, double-blind, placebo-controlled clinical trial

Juan Bañares[1] | **Laia Aceituno**[1] | **Lourdes Ruiz-Ortega**[1] | **Mònica Pons**[1,2] | **Juan G. Abraldes**[3] | **Joan Genescà**[2,4]

[1]Liver Unit, Digestive Diseases Division, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca (VHIR), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain

[2]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Instituto de Salud Carlos III, Madrid, Spain

[3]Liver Unit, Division of Gastroenterology, University of Alberta, Edmonton, Alberta, Canada

[4]Liver Unit, Digestive Diseases Division, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca (VHIR), Vall d'Hebron Barcelona Hospital Campus, Universitat Autònoma de Barcelona, Barcelona, Spain

Correspondence
Juan G. Abraldes, Liver Unit, Division of Gastroenterology, University of Alberta, 1-38 Zeidler Ledcor Centre 8540 112 St NW Edmonton, AB, T6G 2X8 Edmonton, Canada.
Email: juan.g.abraldes@ualberta.ca

Abstract

Zinc homeostasis could play a role in compensated advanced chronic liver disease, and its supplementation has been linked to improvement in liver function, a decrease of hepatic complications, and reduction in HCC incidence. Compensated advanced chronic liver disease encompasses a heterogeneous group of patients with variable risks of clinically significant portal hypertension and clinical events. The ANTICIPATE model is a validated model for stratifying these risks. Our aim is to demonstrate that zinc administration can reduce the rate and risk of presenting clinical events (first decompensation, HCC, death, and liver transplantation). This study protocol describes an ongoing phase III, national, multicenter, randomized, double-blind clinical trial that will enroll 300 patients to receive either the trial treatment (zinc acexamate) or placebo. An inclusion period of 42 months is planned, with a minimum follow-up of 2 years. Our principal hypothesis is that zinc could modify the natural history of patients with compensated advanced chronic liver disease, with an overall improvement in prognosis.

Key Words: cirrhosis, first decompensation, hepatocellular carcinoma, portal hypertension, zinc

INTRODUCTION

Existing research and trial rationale

Zinc is a crucial trace element for essential biological functions mainly related to cell division, growth, and development. Many of the proteins and enzymes that use zinc as a cofactor are involved in beneficial antioxidant, anti-inflammatory, and apoptotic effects. A significant amount of evidence suggests that zinc homeostasis may play a role in liver diseases. In patients with cirrhosis, there is a high prevalence of zinc deficiency, probably

Abbreviations: ACLD, advanced chronic liver disease; ACZ, zinc acexamate; AEMPS, Agencia Española de Medicamentos y Productos Sanitarios; cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; EudraCT, European Union Drug Regulating Authorities Clinical Trials.

owing to a multifactorial cause.[1–3] There is a direct correlation between blood zinc levels and the worsening of advanced chronic liver disease, with a good correlation with the Child-Pugh score.[4,5] Furthermore, in patients with HCC, intracellular zinc levels in tumor tissue are consistently and markedly low.[6]

Several nonrandomized clinical studies have suggested that oral zinc supplementation may have a positive impact on the progression of advanced chronic liver disease (ACLD) differently assessed by (1) raising blood levels of zinc in patients with cirrhosis[7–10]; (2) improving liver function, evaluated by the Child-Pugh score[7,8,10,11]; (3) decreasing serum ammonia levels[7–9]; (4) decreasing the development of complications in ACLD (ascites and encephalopathy)[8]; and (5) reducing incidence of HCC.[10,12] Thus, zinc supplementation has the potential impact to modify the natural history and prognosis of patients with ACLD.

Compensated ACLD (cACLD) encompasses a heterogeneous group of patients at risk of developing clinically significant portal hypertension (CSPH) with a variable risk of clinical events. Of note, even when selecting patients with a high risk of events (HVPG $>$ 10 mm Hg, presence of varices, or increased Child-Pugh score), the estimated cumulative incidence of clinical events after a 2–3-year follow-up period is relatively low (20%–30%).[13,14] This incidence is even lower in patients with metabolic dysfunction–associated steatotic liver disease.[15] Nevertheless, developing a first decompensating event has a marked survival impact on these patients.[16] One of the main drawbacks in designing a clinical trial with clinical events in this compensated population is the need for large sample sizes, which might be unrealistic to accrue.[17,18]

Recently, the ANTICIPATE model (which includes liver stiffness by transient elastography (Fibroscan and platelet count) has been developed to predict the risk of having CSPH.[19] This model has now been externally validated.[15,20] A nomogram based on this model is shown in Figure 1.

The ANTICIPATE model allows the estimation of the risk of CSP, which has a marked prognostic value for clinical events in patients with cACLD.[21] Furthermore, liver stiffness measured using transient elastography is independently associated with clinical events in these patients.[13]

Endpoints based on ordinal scales have been proposed to capture more granularity in describing the clinical outcomes of patients in randomized trials while making them more efficient by substantially reducing the required sample size. This approach has been routinely used, for example, in stroke randomized trials (using the Rankin scale)[22] and COVID trials (using the WHO scale of severity).[23] We postulated that in trials of patients with compensated cirrhosis, we could add efficiency in detecting the effect of an intervention based on the distribution of patients according to an ordinal scale.[17] This scale would have the highest severity level defined by the development of clinical events but would also add granularity by ranking the patients not developing clinical events according to their risk of CSPH and clinical events (based on the ANTICIPATE model).

Therefore, we decided to conduct a clinical trial to investigate the efficacy of oral administration of zinc in the form of zinc acexamate (ACZ) (a soluble, well-tolerated salt) to improve prognosis in patients with cACLD. As this randomized trial will test an approved therapy (already on the market), the lack of constraints of a defined path for regulatory approval allowed us to use an innovative design based on the use of 2 co-primary endpoints. One would be the classic endpoint used in compensated cirrhosis trials, which is the "time to clinical events" (decompensation, HCC, transplantation, and liver death). The innovative contribution is the use of a co-primary endpoint (in which we based the sample size calculation) based on the distribution of patients on a 6-point ordinal scale of severity at the 2-year mark, which could potentially detect a similar given effect size with a much smaller sample size. This design will also allow us to test (if the trial shows benefit) if the effect size observed on the ordinal outcome is predictive of the effect size estimated from the traditional time to clinical events endpoint.

Study objectives

Main objective

The main objective of this clinical trial is to evaluate whether the oral administration of ACZ at a dose of 600 mg/d (equivalent to 100 mg/d of zinc element) to patients with cACLD improves prognosis by reducing the number of expected clinical events and the estimated risk of developing these events (evaluated with the ANTICIPATE model) during the study.

Secondary objective

As secondary objectives, we aim to evaluate whether the administration of ACZ (1) decreases the risk of having the first decompensation; (2) decreases the risk of CSPH estimated by the ANTICIPATE model; (3) reduces the risk of HCC; (4) reduces the risk of bacterial infections; (5) improves overall transplant-free survival and the risk of liver-related death; and (6) improves liver function as measured by Child-Pugh and MELD scores. In addition, we aim to evaluate the possible association between blood zinc levels and the study outcomes, as well as the possible adverse effects of treatment (Table 1).

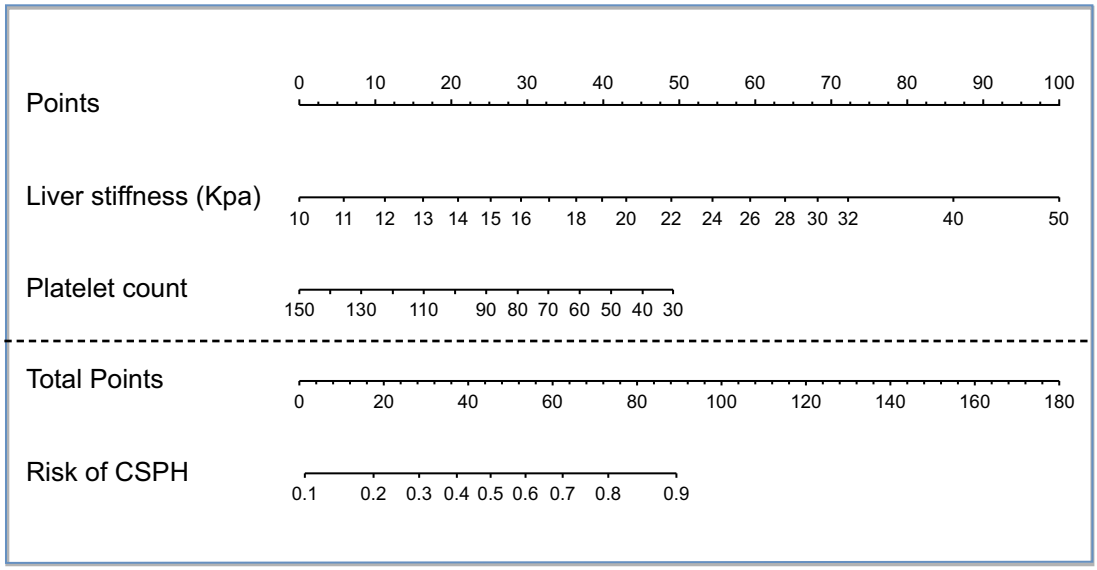

FIGURE 1 Nomogram for calculating the risk of CSPH using liver stiffness and platelet count, estimated by the ANTICIPATE model.

METHODS

Study design and setting

This is a phase III, randomized, double-blind clinical trial with 2 parallel groups, controlled with a placebo. This is a low-level intervention clinical trial since the experimental drug is an authorized medication. This is a multicenter national study with 15 Spanish centers recruiting patients.

TABLE 1 Summary of the main and secondary objectives of the study

Main objective:
• Evaluate whether the oral administration of zinc in patients with cACLD improves prognosis, reducing the number of clinical events and the estimated risk of developing these events.
Secondary objectives:
• Evaluate if the administration of zinc decreases the risk of having the first decompensation. • Evaluate if the administration of zinc decreases the risk of CSPH estimated by the ANTICIPATE model. • Evaluate if the administration of zinc reduces the risk of HCC. • Evaluate if the administration of zinc reduces the risk of bacterial infections. • Evaluate if the administration of zinc improves overall transplant-free survival and the risk of liver-related death. • Evaluate if the administration of zinc improves liver function as measured by Child-Pugh and MELD score. • Evaluate the possible association between blood zinc levels and the study outcomes. • Evaluate possible adverse effects of treatment.

Abbreviations: cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension.

Participants recruitment and eligibility criteria

Eligible participants may be identified and recruited at all sites over the course of the study period, both from general cirrhosis outpatient clinics and from monographic consultations for the different causes of chronic liver disease, such as metabolic dysfunction–associated steatotic liver disease and alcohol-associated liver disease. Detailed inclusion and exclusion criteria are presented in Figure 2.

Study population and total number of patients

The study will be conducted on a total of 300 patients who will be randomly distributed into 2 arms.

The sample size was calculated based on the predicted distribution of patients on an ordinal scale with 6 levels (Table 2). This ordinal scale captures both the development of clinical events (level 6) and the risk of presenting them based on the ANTICIPATE model (levels 1–5 as defined in Table 2). Considering the sum of expected clinical events at 24 months of follow-up according to the PREDESCI study[14] and other studies on the natural history of liver cirrhosis[24–27] with the added effect of decompensation, HCC, and death, a total of 20% of clinical events are expected at 2 years of follow-up (16% decompensations, 2% HCCs, and 2% deaths). To estimate the distribution of liver-related events according to the ordinal scale (for those not developing a clinical event), we used data from Pons et al.[15]

The hypothesized effect of ACZ will be an OR of 0.55, which would result in a reduction in clinical events from 20% to 12% in the treated group and a shift in the

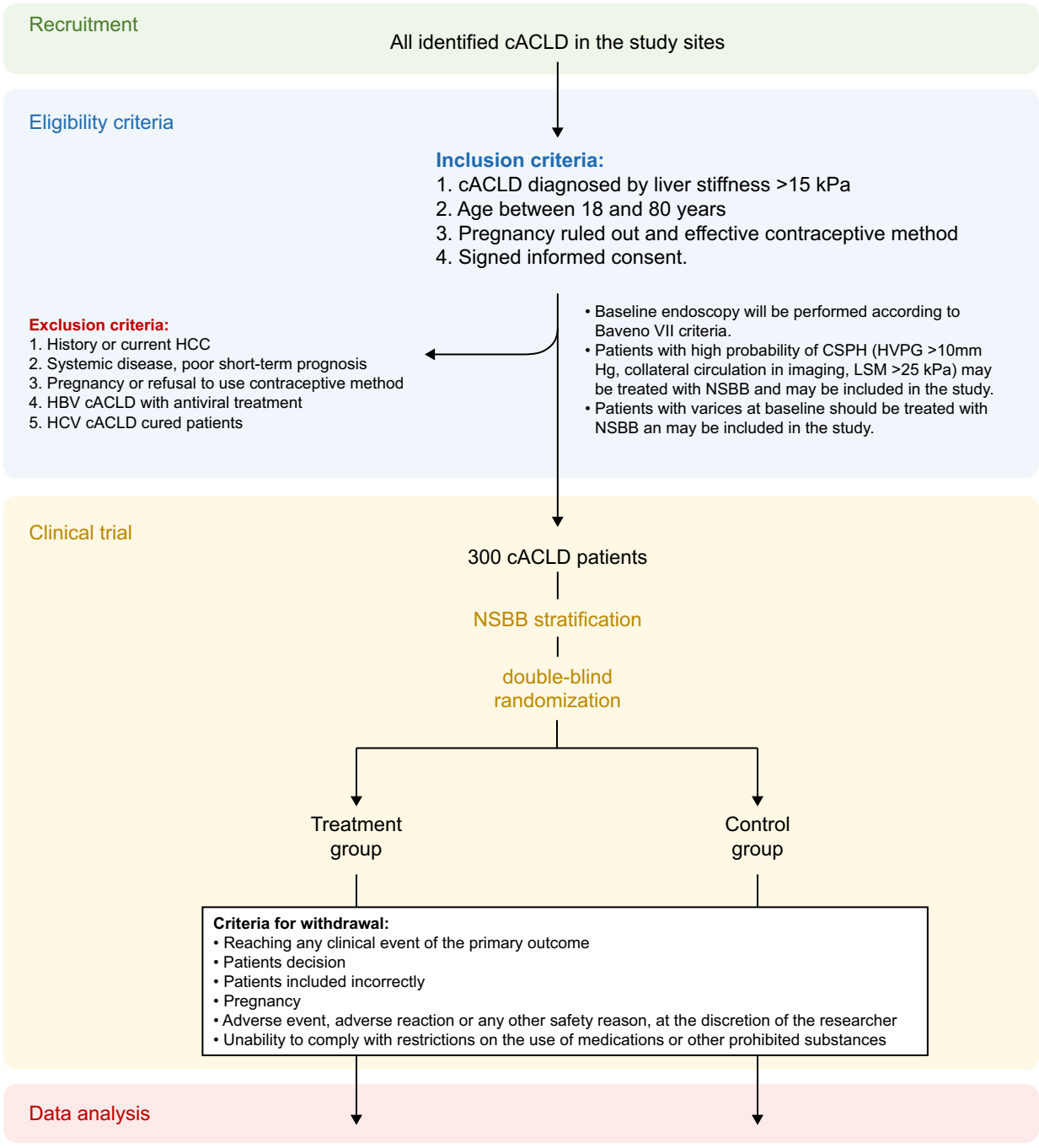

FIGURE 2 Workflow of the trial including inclusion/exclusion criteria and treatmemt arms.

TABLE 2 Ordinal scale to assess the efficacy of the intervention

Ordinal scale	1 ANTICIPATE < 0.30	2 ANTICIPATE 0.30–0.45	3 ANTICIPATE 0.45–0.60	4 ANTICIPATE 0.60–0.85	5 ANTICIPATE > 0.85	6 Clinical event
Placebo (%)	2	8	10	21	39	20
Treatment (%)	4	13	14	25	32	12

Note: This table also includes the expected distribution of patients on the ordinal scale in the placebo group at the 2-y mark, and the expected distribution of patients under a treatment with an effect size of an OR of 0.55.

distribution of the CSPH risk category, as shown in Table 2. This effect was a conservative estimation of a more than 60% reduction of clinical events in patients with cirrhosis treated with zinc for 3 years, as observed by Hosui et al.[10] Under these assumptions, 143 patients would be required per arm (with an α error of 0.05) to achieve a 0.80 power. Considering a 5% loss during follow-up, a total sample size of 300 patients will be included.

Randomization

Patients will be randomly assigned to the experimental or placebo groups. This randomization will be stratified according to the use of nonselective beta-blockers when entering the study. This process will be performed on a 1:1 ratio using a centralized network-based system with double-blind allocation through computer-generated electronic code (Figure 2).

Trial treatment and control

The experimental group will receive ACZ at a daily dose of 600 mg, equivalent to 100 mg of elemental zinc (1 hard gelatin capsule of 300 mg of ACZ twice a day). Treatment will be stopped when the patient presents with any of the events that define the main endpoint of the study.

ACZ is a soluble, well-tolerated salt that is commercialized and approved in Spain for the treatment of gastroduodenal ulcers. The dose chosen for the trial was based on the published clinical studies performed in patients with cirrhosis,[7–12] in which 33–150 mg per day of zinc element in different compositions were administered once or 3 times per day.

The control group will receive hard gelatin capsules orally twice a day, identical to those of ACZ, in color, weight, and nature, but containing an inert preparation (isomaltose).

Compliance assessment (adherence to treatment)

To assess compliance, the medication count method will be used at each of the control visits, recording the number of capsules consumed and the expected number of capsules consumed, thereby obtaining a ratio or compliance percentage (current number of capsules consumed/expected number $\times$ 100). Adherence will be considered good when at least 70% of capsules are consumed.

Adverse events and reactions

All adverse events will be recorded, regardless of their possible association with the study treatment. Degrees of a causal relationship between adverse events and study medication will be established (from no relationship to very likely related). A specific record will be included in the clinical report form to register all the possible adverse events and the imputability criteria at every scheduled visit. Suspected serious and unexpected adverse reactions will be reported to the Spanish Agency of Drugs and Sanitary Products (AEMPS). The AEMPS qualified the study of a low level of intervention and a Data Safety Monitoring Board was not needed. Copper deficiency might be caused by zinc treatment; the risk in patients seems to be very low.[7,11] Copper levels will be assessed several times during follow-up.

Criteria for withdrawal of study subjects

Every patient may suspend participation in the study at any time without needing additional explanation and without prejudice to optimal subsequent treatment. Other criteria for withdrawal of the study are detailed in Figure 2.

OUTCOMES MEASURES AND STUDY PROCEDURES

Primary endpoint

The primary endpoint will be assessed at the 2-year mark as the distribution of patients on the 6-value ordinal scale shown in Table 2. The most severe category (level 6) will be the development of clinical events. These clinical events are defined as follows:

(1) First decompensation:

   (a) Ascites, are defined by clinical signs within the physical examination and confirmation by ultrasound or paracentesis. The sole presence of malleolar edema or the detection of i.p. fluid only by imaging techniques (subclinical ascites) will not be considered an event.
   (b) Gastrointestinal bleeding due to portal hypertension, defined as any episode of hematemesis or melena (or both) and endoscopic criteria according to Baveno consensus.
   (c) Overt HE, according to the West Haven criteria (equal or greater than grade II).

(2) HCC.
(3) Liver-related death (non–liver-related deaths will be considered as non-events).
(4) Liver transplantation.

Patients free of a liver-related event at 2 years will be classified according to the risk of CSPH and clinical

events estimated by the ANTICIPATE model value (Figure 1), distributing the patients on an ordinal scale with ascending hierarchy of CSPH risk (Table 2): level 1, <0.30 risk; level 2, 0.30–0.45 risk; level 3, 0.45–0.60 risk; level 4, 0.60–0.85 risk; and level 5, >0.85 risk.

Since patients will be followed up for clinical events until the study termination, there will be a co-primary outcome defined as the time to occurrence of the composite endpoint of clinical events. Superiority in any of the co-primary outcomes will define the success of the study intervention.

Secondary outcomes

The secondary outcomes will consist of the evolutionary development of each of the secondary objectives (Table 1).

Expected duration of inclusion period and treatment

An inclusion period of 42 months is planned, with a minimum of 24 months of follow-up for the last patient included. Therefore, the minimum follow-up would be 24 months, with a maximum of 66 months. Patients will receive their assigned treatment for the entire duration of the study. The expected median follow-up would be 45 months. The first patient was included in June 2022, and the predicted recruitment of the last patient will be in December 2025, with the last follow-up at the end of 2027. As of June 2024, 136 patients had already been randomized.

Schedule of assessments

The schedule of assessment is detailed in Table 3.

DATA ANALYSIS PLAN

Statistical considerations

A final detailed statistical analysis plan will be finalized before the lock of the database. All data will be collected in an electronic format (clinical report form) in an anonymized form. We will consider a type I error of 5%. For each variable, a descriptive analysis will be carried out, expressing the qualitative variables as the absolute number of cases and percentage of each of the categories in each group and overall. For the quantitative variables, means (standard deviations), medians (interquartile range), minimum, and maximum will be calculated.

Primary outcome measures

Both co-primary endpoints will be analyzed simultaneously at the end of the trial without adjustment for multiplicity. The superiority of the intervention will be declared with a p value <0.05 in any of the 2 co-primary outcomes.

The primary inferential analysis for the primary outcome based on the distribution of patients on the ordinal scale at 2 years will be conducted using a proportional odds model, in which the effect of the ACZ will be adjusted by the randomization strata (treatment with nonselective beta-blockers) and baseline ANTICIPATE model value. A single OR with a 95% CI will be used as a summary of treatment efficacy.

A sensitivity analysis of the main variable will be carried out, in which the proportional odds assumption will be relaxed, using a Bayesian constrained partial proportional odds model as described in https://www.fharrell.com/post/yborrow/. This analysis will assess a special OR for the treatment effect on the highest level of the ordinal scale (level 6). In addition, it will assess the departure from the proportional odds assumption (represented by the log of the ratio of the OR for clinical events to the OR for the general effect of treatment), using a skeptical prior (0.9 chance that is in the interval 0.5–2). This analysis assesses how likely it is for the effect of the treatment on clinical events (level 6) to be different from the effect on the levels defined by the ANTICIPATE-CSPH (levels 1–5). We will provide the probability of an overall effect, a treatment effect on clinical events, and the probability that the differential treatment effect on clinical events versus overall is by more than a factor of 1.2.

For the co-primary outcome (time to a clinical event across all follow-ups), we will use a Cox proportional hazards model (stratified by baseline beta-blocker treatment).

Secondary outcomes measures

The analysis of secondary outcomes will be based on a time-to-event analysis, using Kaplan-Meier curves for description, and analyzing treatment effects using the Cox proportional hazards model. In addition, a complementary analysis of competitive risks will be carried out using the Fine and Gray method. Specifically, we will assess (a) the effect of treatment in preventing mortality from liver causes and transplantation, considering nonhepatic mortality as a competing risk, and (b) the effect on decompensation/transplant or death, considering the development of HCC as a competing risk.

TABLE 3 Schedule of assessments

	Minimal duration of treatment									Extended follow-up till the end of the study		
	Baseline	3 mo	6 mo	9 mo	12 mo	15 mo	18 mo	21 mo	24 mo	30 mo 42 mo 54 mo	36 mo 48 mo 60 mo	End of follow-up (66 mo)
Confirm eligibility	✓											
Information /informed consent	✓											
Randomization	✓											
Medical history	✓											
Physical examination	✓											
Signs and symptoms	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Standard care blood test	✓		✓		✓		✓		✓	✓	✓	✓
Blood Zn, Cu, and Fe levels	✓		✓		✓		✓		✓			
Child-Pugh/MELD	✓				✓				✓		✓	✓
Liver ultrasound[a]	✓		✓		✓		✓		✓	✓	✓	✓
Endoscopy[b]	✓											✓
Liver stiffness with Fibroscan	✓				✓				✓		✓	✓
Control of alcohol consumption	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Control of contraceptive measures[c]	✓		✓		✓		✓		✓	✓	✓	✓
Dispense trial medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Adverse event evaluation		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adherence		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Note: In case of event development, nonprogrammed visits will be conducted. If there is an abandonment during the study, there will be an intent to arrange an end of a follow-up visit with a blood test and liver stiffness measurement.

[a]Including ultrasound performed in a 3-month period before the visit.

[b]Endoscopy will be performed according to Baveno VII consensus recommendations.

[c]Only women of childbearing age.

Planned analysis of abandonments, missing data, and sensitivity analysis

In principle, no imputation of missing data will be performed. As this is a survival analysis, the management of lost patients is controlled in the analysis as long as the censoring is not informative. The main reasons for censoring will be losses to follow-up.

Patients who abandon treatment voluntarily, present serious deviations from the protocol, lack of compliance (adverse effects, change of residence, and loss of interest), and those lost to follow-up will be analyzed by intention to treat. In the event of patient withdrawal due to the appearance of adverse reactions or events, an assessment of imputability will be carried out, and follow-up will be attempted.

An analysis of missing cases will be performed depending on the treatment. Missing data $>10\%$ in the relevant variables will not be allowed, in which case the results will be considered invalid. All analyses will be performed on an intention-to-treat basis. A sensitivity analysis will be performed in the final analysis. First, the results will be compared by assigning the worst and the best results to all the lost cases. Second, the best result will be assigned to the untreated and the worst to the treated group to compare the differences in the effects of the treatment.

ETHICS, CLINICAL TRIAL REGISTRATION, AND DISSEMINATION

Ethical consideration

The trial will be conducted in accordance with the ethical requirements expressed in the Declaration of Helsinki (Edinburgh revision, Scotland, October 2000), the current Spanish regulations on Clinical Research, and the European Union (EU) Good Clinical Practice standards and the ethical approval of the Ethics Committee of the participants' centers.

Candidate patients will be proposed to voluntarily participate in the trial after being informed (both orally and with an informative sheet) about the trial procedures, possible adverse events, detailed information on scheduled assessments, and the possibility of withdrawing at any time during the study. Written consent will be provided in writing to all subjects, and signing will be held after they have read and understood the trial information.

The data will be codified and strictly confidential (the anonymity of the subjects participating in the trial will always be maintained). The promoter and the center will comply with the data protection regulations of Spain and the EU regarding data protection.

Clinical trial versions and registration

The first version of the protocol was approved by the AEMPS on August 28, 2021, and registered in the EU Clinical Trials Register (EudraCT Number: 2021-000680-74). This version included clinical events during follow-up as the only primary endpoint. Version 2.0 was approved by the AEMPS on April 25, 2022. In this first amendment, the primary endpoint was switched to the ordinal 1–6 scale, as described in the Methods section. The second amendment (current version 3.0) was approved by the AEMPS on April 14, 2024, and registered in ClinicalTrials-gov (NCT06434753). This amendment included the co-primary endpoints (the ordinal scale at 2 y, and the time to event during the full follow-up).

AUTHOR CONTRIBUTIONS

Juan Bañares and Laia Aceituno contributed equally to the drafting of this manuscript. Lourdes Ruiz-Ortega and Mònica Pons were responsible for revising the final manuscript and contributing with important intellectual content. Joan Genescà and Juan G. Abraldes were responsible for the original idea, study design, revising the final manuscript, and contribution with important intellectual content.

FUNDING INFORMATION

Joan Genescà was partially funded by grant PI21/00691 from Instituto de Salud Carlos III and co-funded by the European Regional Development Fund/European Social Fund (ERDF/ESF, "A way to make Europe/Investing in your future"). Mònica Pons is funded by a grant contract, Joan Rodés from the Instituto de Salud Carlos III. CIBERehd is supported by Instituto de Salud Carlos III.

CONFLICTS OF INTEREST

Joan Genescà has received consulting fees from Boehringer Ingelheim, speaking fees from Echosens and travel expenses from Gilead and Abbie. MP reports CSL Behring speaking fees and consulting fees from Takeda. Juan G. Abraldes consults for 89bio, Boehringer Ingelheim, AstraZeneca, AMGEN, Boston Pharmaceuticals, and Novo Nordisk and received consulting fees from Boehringer Ingelheim, Agomab, 89bio, Boston Pharmaceutics, AstraZeneca, and Novo Nordisk. He received grants from Gilead and Cook, paid to the University of Alberta. The remaining authors have no conflicts to report.

ORCID

Juan Bañares https://orcid.org/0000–0002–1966–1947
Laia Aceituno https://orcid.org/0000–0001–5414–2408
Lourdes Ruiz-Ortega https://orcid.org/0000–0003–3636–3367

Mònica Pons https://orcid.org/0000–0002–0985–3320
Juan G. Abraldes https://orcid.org/0000–0003–3421–937X
Joan Genescà https://orcid.org/0000–0002–0831–8422

REFERENCES

1. Ozeki I, Arakawa T, Suii H, Tatsumi R, Yamaguchi M, Nakajima T, et al. Zinc deficiency in patients with chronic liver disease in Japan. Hepatol Res. 2020;50:396–401.
2. Kim MC, Lee JI, Kim JH, Kim HJ, Cho YK, Jeon WK, et al. Serum zinc level and hepatic fibrosis in patients with nonalcoholic fatty liver disease. PLoS One. 2020;15:e0240195.
3. Miwa T, Hanai T, Toshihide M, Ogiso Y, Imai K, Suetsugu A, et al. Zinc deficiency predicts overt hepatic encephalopathy and mortality in liver cirrhosis patients with minimal hepatic encephalopathy. Hepatol Res. 2021;51:662–73.
4. Sengupta S, Wroblewski K, Aronsohn A, Reau N, Reddy KG, Jensen D, et al. Screening for zinc deficiency in patients with cirrhosis: When should we start? Dig Dis Sci. 2015;60:3130–5.
5. Prystupa A, Kiciński P, Luchowska-Kocot D, Błażewicz A, Kurys-Denis E, Niedziałek J, et al. Relationships between serum selenium and zinc concentrations versus profibrotic and proangiogenic cytokines (FGF-19 and endoglin) in patients with alcoholic liver cirrhosis. Ann Agric Environ Med. 2017;24:544–8.
6. Costello LC, Franklin RB. The status of zinc in the development of the hepatocellular cancer. Cancer Biol Ther. 2014;15:1–8.
7. Marchesini G, Fabbri A, Bianchi G, Brizi M, Zoli M. Zinc supplementation and amino acid nitrogen metabolism in patients with advanced cirrhosis. Hepatology. 1996;23:1084–92.
8. Takuma Y, Nouso K, Makino Y, Hayashi M, Takahashi H. Clinical trial: Oral zinc in hepatic encephalopathy. Aliment PharmacolTher. 2010;32:1080–90.
9. Katayama K, Saito M, Kawaguchi T, Endo R, Sawara K, Nishiguchi S, et al. Effect of zinc on liver cirrhosis with hyperammonemia: A preliminary randomized, placebo-controlled double-blind trial. Nutrition. 2014;30:1409–14.
10. Hosui A, Kimura E, Abe S, Tanimoto T, Onishi K, Kusumoto Y, et al. Long-term zinc supplementation improves liver function and decreases the risk of developing hepatocellular carcinoma. Nutrients. 2018;10:1955.
11. Somi MH, Rezaeifar P, Ostad Rahimi A, Moshrefi B. Effects of low dose zinc supplementation on biochemicals markers in non-alcoholic cirrhosis: A randomized clinical trial. Arch Iran Med. 2012;15:472–6.
12. Matsumura H, Nirei K, Nakamura H, Arakawa Y, Higuchi T, Hayashi J, et al. Zinc supplementation therapy improves the outcome of patients with chronic hepatitis C. J Clin Biochem Nutr. 2012;51:178–84.
13. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Abraldes JG, et al. Baveno VII. Faculty. Baveno VII—Renewing consensus in portal hypertension. J Hepatol. 2022;76:959–74.
14. Villanueva C, Albillos A, Genescà J, Garcia-Pagan JC, Calleja JL, Aracil C, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): A randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2019;393:1597–608.
15. Pons M, Augustin S, Scheiner B, Guillaume M, Rosselli M, Rodrigues SG, et al. Noninvasive diagnosis of portal hypertension in patients with compensated advanced chronic liver disease. Am J Gastroenterol. 2021;116:723–32.
16. Jalan R, D'Amico G, Trebicka J, Moreau R, Angeli P, Arroyo V. New clinical and pathophysiological perspectives defining the trajectory of cirrhosis. J Hepatol. 2021;75(suppl 1):S14–26.
17. Abraldes JG, Trebicka J, Chalasani N, D'Amico G, Rockey DC, Shah VH, et al. Prioritization of therapeutic targets and trial design in cirrhotic portal hypertension. Hepatology. 2019;69:1287–99.
18. Pericàs JM, Anstee QM, Augustin S, Bataller R, Berzigotti A, Ciudin A, et al. A roadmap for clinical trials in MASH-related compensated cirrhosis. Nat Rev Gastroenterol Hepatol. 2024. doi:10.1038/s41575-024-00955-8
19. Abraldes JG, Bureau C, Stefanescu H, Augustin S, Ney M, Blasco H, et al. Noninvasive tools and risk of clinically significant portal hypertension and varices in compensated cirrhosis: The "Anticipate" study. Hepatology. 2016;64:2173–84; Erratum in: *Hepatology*. 2017;66:304–5.
20. Rabiee A, Deng Y, Ciarleglio M, Chan JL, Pons M, Genesca J, et al. Noninvasive predictors of clinically significant portal hypertension in NASH cirrhosis: Validation of ANTICIPATE models and development of a lab-based model. Hepatol Commun. 2022;6:3324–34.
21. Pons M, Rivera-Esteban J, Ma MM, Davyduke T, Delamarre A, Hermabessière P, et al. Point-of-care noninvasive prediction of liver-related events in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2024;22:1637–645.e9.
22. Bath PM, Lees KR, Schellinger PD, Altman H, Bland M, Hogg C, et al. Statistical analysis of the primary outcome in acute stroke trials. Stroke. 2012;43:1171–8; Erratum in: *Stroke*. 2012;43:e100.
23. WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis. 2020;20:e192–7; Erratum in: *Lancet Infect Dis*. 2020;20:e250.
24. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. J Hepatol. 2006;44:217–31.
25. D'Amico G, Morabito A, D'Amico M, Pasta L, Malizia G, Rebora P, et al. Clinical states of cirrhosis and competing risks. J Hepatol. 2018;68:563–76.
26. Sanyal AJ, Harrison SA, Ratziu V, Abdelmalek MF, Diehl AM, Caldwell S, et al. The natural history of advanced fibrosis due to nonalcoholic steatohepatitis: Data from the simtuzumab trials. Hepatology. 2019;70:1913–27.
27. Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Metwally M, et al. Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease: A multi-national cohort study. Gastroenterology. 2018;155:443–457.e17.

How to cite this article: Bañares J, Aceituno L, Ruiz-Ortega L, Pons M, Abraldes JG, Genescà J. Zinc supplementation to improve prognosis in patients with compensated advanced chronic liver disease: A multicenter, randomized, double-blind, placebo-controlled clinical trial. Hepatol Commun. 2024;8:e0524. https://doi.org/10.1097/HC9.0000000000000524