IL-1 Signal Inhibition in Alcohol-Related Hepatitis: A Randomized, Double-Blind, Placebo-Controlled Trial of Canakinumab

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BACKGROUND AND AIMS: **Short-term mortality in alcohol-related hepatitis (AH) is high, and no current therapy results in durable benefit. A role for interleukin (IL)-1β has been demonstrated in the pathogenesis of alcohol-induced steatohepatitis. This study explored the safety and efficacy of canakinumab (CAN), a monoclonal antibody targeting IL-1β, in the treatment of patients with AH.**

METHODS: **Participants with biopsy-confirmed AH and discriminant function ≥32 but Model for End-Stage Liver Disease ≤27 were randomly allocated 1:1 to receive either CAN 3 mg/kg or placebo (PBO). Liver biopsies were taken before and 28 days after treatment. The primary endpoint was the overall histological improvement in inflammation analyzed by the modified intention-to-treat principle.**

RESULTS: **Fifty-seven participants were randomized: 29 to CAN and 28 to PBO. Two participants had histology that did not corroborate the clinical diagnosis. Of the remaining 55 participants, paired histology data were evaluable from 48 participants. In CAN-treated participants, 14 (58%) of 24 demonstrated histological improvement compared with 10 (42%) of 24 in the PBO group ($P = .25$). There was no improvement in prognostic scores of liver function. Four (7%) of the 55 participants died within 90 days, 2 in each group. The number of serious adverse events was similar between CAN vs PBO. In post hoc exploratory analyses after adjustment for baseline prognostic factors, CAN therapy was associated with overall histological improvement ($P = .04$).**

Abbreviations used in this paper: AH, alcohol-related hepatitis; AHHS, Alcoholic Hepatitis Histology Score; AST, aspartate aminotransferase; CAN, canakinumab; CI, confidence interval; GAHS, Glasgow Alcoholic Hepatitis Score; IL, interleukin; IMP, investigational medicinal product; IQR, interquartile range; mDF, Maddrey's discriminant function; MELD, Model for End-Stage Liver Disease; mITT, modified intention to treat; NAS, NAFLD Activity Score; OR, odds ratio; PBO, placebo.

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CONCLUSIONS: **CAN therapy in severe AH participants with Model for End-Stage Liver Disease ≤27 did not alter biochemical or clinical outcomes compared with PBO. Nonsignificant histological improvements did not translate into clinical benefit. EudraCT, Number: 2017-003724-79; ClinicalTrials.gov, Number: NCT03775109.**

Keywords: Model for End-Stage Liver Disease; MELD; Interleukin-1b; Alcohol-Related Hepatitis.

Alcohol-related hepatitis (AH) is an acute and life-threatening form of alcohol-related liver disease. It is a clinical syndrome of jaundice and liver failure that occurs after heavy and prolonged alcohol drinking. Severity can be graded using the Maddrey's discriminant function (mDF) that comprises bilirubin and prothrombin time: a score 32 or greater indicates severe AH. Published short-term mortality rates for severe AH participants have improved in recent years, but the condition still results in death for up to 30% of participants within 3 months.

International guidelines recommend that corticosteroid therapy be considered in the treatment of severe AH because meta-analyses indicate a benefit at 28 days.[1] However, no benefit has been demonstrated beyond this time point. Further, 40% of participants show no biochemical response to this therapy at any time point.[2] Moreover, prednisolone is associated with a high rate of life-threatening nosocomial infections that no established biomarker can predict.[3] AH participants therefore remain in urgent need of new therapeutic options.

In addition to jaundice and liver failure, AH is characterized by hepatic and systemic inflammation that has diagnostic and prognostic relevance in AH.[4,5] Of the plethora of inflammatory cytokines that are elevated in the serum of participants with AH, data from mouse models of alcoholic steatohepatitis have suggested a pivotal role for interleukin (IL)-1β. Participants with alcohol-related hepatitis have serum IL-1β levels almost 10 times higher than found in healthy control subjects.[6] In mice, administration of IL-1β at physiological doses can induce hepatic steatosis and augment Toll-like receptor 4 signaling in macrophages.[7] Moreover, neutralization of IL-1β signaling by an IL-1 receptor antagonist reduces features of murine alcohol-related steatohepatitis,[7] suggesting a pivotal role for this cytokine. In humans, IL-1β may be responsible for many of the clinical and metabolic characteristics of AH including fever, neutrophilia, monocyte activation, anorexia, and muscle catabolism.[8]

Canakinumab (CAN) is a human anti-IL-1β monoclonal antibody. It is currently licensed not only for periodic syndromes including cryopyrin-associated periodic syndrome, tumor necrosis factor receptor–associated periodic syndrome, hyperimmunoglobulin D syndrome, and familial Mediterranean fever, but also for rheumatological disorders such systemic juvenile, idiopathic, and gouty arthritis. In these conditions and in over 10,000 participants with prior myocardial infarction, CAN has demonstrated a favorable risk-benefit profile.[9] However, AH represents a major challenge for immunosuppressive therapy because participants demonstrate numerous immune defects and high rates of life-threatening nosocomial infection. Previous studies of monoclonal anti-tumor necrosis factor α therapies, either alone and especially in combination with prednisolone, have resulted in high rates of infection and early trial termination.[10,11] By recruiting participants with a maximum Model for End-Stage Liver Disease (MELD) score of 27 and prohibiting concomitant use of corticosteroids, the ISAIAH trial sought to limit complications associated with AH.

The purpose of our exploratory phase 2 trial was to investigate the potential benefits of CAN therapy in a population of AH participants admitted to hospital with mDF $\geq$32 and MELD $\leq$27. As murine data demonstrated benefit from IL-1 signaling inhibition on liver histology,[7] we selected a histological endpoint for the trial. While this is commonly used in nonalcoholic steatohepatitis clinical trials, it is a novel primary endpoint in AH and was designed to explore the relationship between histological, biochemical, and clinical outcomes.

Materials and Methods

Patient eligibility, trial design, and endpoints for the trial have been described previously.[12] ISAIAH was a 2-arm, parallel, multicenter, randomized, double-blind, placebo (PBO)-controlled trial to evaluate the therapeutic benefits of CAN in the treatment of AH. A trial management group designed the study that was approved by the UK Health Research Authority (18/LO/0745). Clinical trials authorization was received from the Medicines and Healthcare Products Regulatory Agency. Written informed consent was obtained from each participant or from his or her legal representative until such time as the participant recovered mental capacity. The trial was conducted and reported as directed by the protocol, the Medicine for Human Use Regulations 2004, the European Union Clinical Trials Directive (Directive 2001/20/EC) guidelines, the principles of the International Conference of Harmonization Good Clinical Practice under the oversight of Imperial Clinical Trials Unit, and the provisions of the Declaration of Helsinki. An independent data monitoring committee, whose members were unblinded to group allocations, was convened at 3 time points to review the conduct and safety of the trial. The trial was registered with EudraCT (2017-003724-79).

Participants

The trial recruited participants from 11 hospitals across the United Kingdom between January 3, 2019, and October 21, 2020. Participants with appropriate written consent and a clinical diagnosis of AH in line with consensus criteria[13] that could be corroborated by the demonstration of steatohepatitis in the baseline liver biopsy were eligible. Inclusion criteria were age ≥18 years, an average alcohol consumption of ≥80 g ethanol per day for men and ≥60 g per day for women, and a serum bilirubin level ≥80 μmol/L (4.7 mg/dL). Eligible participants also had mDF ≥32 and MELD ≤27. Key exclusion criteria were jaundice for >3 months, cessation of alcohol consumption for >2 months before randomization, serum aspartate aminotransferase (AST) >500 IU/L or serum alanine aminotransferase >300 IU/L, or variceal hemorrhage during the current admission.

Infection. All participants were screened for infection prior to randomization. Participants with uncontrolled sepsis were excluded but could be screened again after ≥2 days of appropriate antibiotic therapy. Due to concerns about the risk of infection in the context of anticytokine therapy in AH,[10,11] all participants received cotrimoxazole for the first 14 days of treatment. Corticosteroids

Due to similar concerns about the risk of infection in the context of anticytokine therapy in AH,[10,11] use of either prednisolone or any systemic steroids (equivalent to a dose of prednisolone >20 mg) within 6 weeks of screening or during the study treatment period was not permitted.

Renal Impairment. Participants who were oligoanuric, had a creatinine >200 μmol/L (2.5 mg/dL), or required renal support were given resuscitation therapy for up to 1 week and could be rescreened for eligibility and randomization.

Randomization

An Internet-based randomization system (Inform; Oracle) was used to allocate participants to 1 of 2 study groups, CAN or PBO 1:1. Block randomization was used with variable block sizes (2, 4, and 6) to assist in concealing allocation. This was blinded to site staff, research team, and the patient by a unique code. Designated study personnel who prepared infusions were unblinded.

Investigational Medicinal Product

Participants allocated to CAN received a single 3 mg/kg infusion in 100 mL 5% dextrose solution at baseline. Participants allocated to PBO received a single infusion of 100 mL 5% dextrose solution at baseline. Participants with moderate to severe ascites underwent large volume paracentesis prior to administration of investigational medicinal product (IMP) to avoid potential loss of drug in ascitic fluid. Participants with AST >80 U/L at day 28 received a second infusion on day 28 at an identical dose and type to the first.

What You Need to Know

Background

Interleukin (IL)-1β is thought to be an important proinflammatory mediator of alcohol-related hepatitis. One previous trial using the IL-1 receptor antagonist anakinra failed to show a survival benefit in participants with severe alcohol-related hepatitis.

Findings

There was no improvement in mortality, Lille score, or delta Model for End-Stage Liver Disease in canakinumab-treated participants compared with placebo-treated control subjects, but there was a difference in the degree of histological resolution.

Implications for patient care

There remain insufficient data to support the use of IL-1 or IL-1β inhibition in the treatment of alcohol-related hepatitis.

Endpoints

The primary outcome of the trial was the histological response after 28 days, recorded as a binary outcome of "improved" or "not improved" global immune cell infiltrate. The NAFLD Activity Score (NAS) and the Alcoholic Hepatitis Histology Score (AHHS) incorporate lymphocytic and neutrophilic infiltrate components, respectively, and were evaluated separately as secondary endpoints.

The endpoint was determined by 3 expert liver histopathologists who scored slides independently. Slides Q15 were masked for treatment allocation but were read in pairs that were not masked to time point. A majority verdict was derived where possible. Where there was no consensus between the 3 histopathologists, R.D.G. acted Q16 as the adjudicating histopathologist. The assessment of improvement or not in total inflammation is independent of any specific scoring system and relates to the global assessment of disease activity used as the basis for developing the METAVIR algorithm.[14] Key secondary endpoints included histological improvements in fatty change and ballooning, change in serum bilirubin, Lille score at day 7, and changes in MELD and Glasgow Alcoholic Hepatitis Score (GAHS) from baseline to day 28 and 90.

Statistical Analysis

Sample Size. We estimated that improvement in histological steatohepatitis would occur in 40% of

participants treated with PBO and 80% of participants treated with CAN. Using the defined chi square test, a trial with 80% power to detect a difference at $P < .05$ (2-sided) would require 46 participants in total, allocated 1:1 (23 per group). Assuming a dropout rate of 10%, 52 participants would be randomized to a treatment strategy of either CAN or PBO. This sample size was deemed appropriate for an early phase trial that aimed to detect a signal of efficacy for the experimental therapy.

Primary Endpoint Analyses. Analyses were conducted on the modified intention to treat (mITT) population (ie, for participants where liver biopsy had corroborated a diagnosis of AH and had been randomized to either CAN or PBO). The difference in the proportion of participants showing histological improvement in CAN vs PBO groups was tested for statistical significance using a chi-square test, with 95% confidence intervals (CIs) provided for the difference in proportions (exact/Clopper-Pearson binomial confidence intervals).

Univariable logistic regression tested whether baseline MELD score, baseline AHHS, age, and sex were individually associated with histological improvement. Next, multivariable logistic regression models tested for association of the treatment group with histological improvement after adjustment for variables that were either statistically significant on univariable analysis or were a priori clinically relevant.[15,16]

Secondary Endpoint Analyses. Continuous secondary endpoints were analyzed using analysis of covariance models, with levels at days 28 and 90 being the dependent variables, while treatment and baseline measurements were covariates. Log transformation of mDF and Lille score was required to obtain normal distributions and satisfy the assumptions of the models. Mean Lille scores were compared between groups using an independent t test. Shapiro-Wilk and Shapiro-Francia tests were using to assess normality and variance-comparison and robust tests for equality and homogeneity of variance. For individual components of histology, such as neutrophil and mononuclear cell infiltrate, the between-group differences in the proportions of "improved" or "not improved" between baseline and 28 days was compared using chi-square tests and the difference in proportions presented with corresponding 95% CIs. Changes in binary variables from baseline to day 28 were analyzed using logistic regression models with treatment and baseline value as covariates. Changes in ordinal variables from baseline to day 28 were analyzed using ordinal logistic regression (proportional odds, after assessment of the proportional odds assumption) modeling of the variable at day 28, with treatment and baseline value at covariates. Mortality rate at day 90 was compared between groups using a chi square test; survival analysis was also conducted for 90-day mortality using a Cox proportional hazards model, fitted as a follow-up analysis for mortality at 90 days with treatment group as the indicator.

Results

Participants

Patient Flow. Over a 3-year period, 76 participants were assessed for eligibility and 57 met full eligibility criteria. Of these, 29 participants were randomized to CAN and 28 to PBO. Two participants were subsequently withdrawn from the study because of negative biopsy results, 1 in each arm, and were not included in the mITT analysis (n = 55). One patient did not receive the allocated intervention due to a serious adverse event and did not undergo further trial procedures such as dosing of IMP or second liver biopsy but was retained within the study for data collection. Therefore, 54 participants, 27 in each arm, received the allocated intervention. Two participants then went on to either deteriorate or die due to AH and were unable to undergo a second liver biopsy; these participants were categorized as treatment failures for primary endpoint analysis. A further 6 participants did not attend for second liver biopsy (3 in each arm).

Primary endpoint data were therefore evaluable in 48 participants, 24 in each group. This population was the same as the per-protocol population because the 1 patient withdrawn after randomization had no primary endpoint data to evaluate. For secondary endpoints, 28 CAN-treated and 27-PBO treated participants were compared by mITT (n = 55) (see the CONSORT diagram in Supplementary Figure 1).

Baseline Characteristics Between Study Arms. Table 1 shows that the study arms were similar in most parameters. Participants randomized to receive CAN were older (median 50.5 [interquartile range (IQR), 44.0–56.5] years vs 46.0 [IQR, 41.0–51.0] years), were more frequently male (60% [n = 17 of 28] vs 48% [n = 13 of 27]), and had a greater proportion with World Health Organization performance status 3 or higher (54% [n = 15 of 28] vs 33% [n = 9 of 29]). While histology scores were similar for CAN and PBO groups (median AAH score 5.5 vs 7.0 [Supplementary Table 1], median NAS score 5.0 vs 5.0 [Supplementary Table 3]), functional liver prognostic scores were higher for participants treated with CAN (median MELD score 23.45 [IQR, 21.91–25.22] vs 21.49 [IQR, 19.95–22.89], median GAHS 9 [IQR, 8.0–9.5] vs 8 [IQR, 7.0–8.0], median mDF 78.66 [IQR, 59.9–103.3] vs 73.2 [IQR, 45.46–112.44]).

Endpoints

Primary Endpoint Primary Analysis. At 28 days, histology had improved in 14 (58%) of 24 participants in the CAN group and 10 (42%) of 24 participants in the PBO group, representing a difference in the proportions of participants showing histological response of 17% (−11.20% to 44.51%; $P = .25$) (Figure 1). For 7 (12.3%) of 55 participants, primary endpoint data were missing,

Table 1. Summarized Baseline Characteristics and Prognostic Scores for mITT Population (With Positive Histology at Screening)

Variable/Component	Statistics	Canakinumab	Placebo	Total
Age	n	28	27	55
	Mean, y	50.61	46.33	48.51
	SD, y	9.10	7.84	8.70
	Median, y	50.50	46.00	47.00
	IQR, y	44.00–56.50	41.00–51.00	42.00–55.00
	Missing from eCRF	0	0	0
Sex	Male	17 (61)	13 (48)	30 (55)
	Missing from eCRF	0	0	0
WHO performance status	0—asymptotic	1 (4)	4 (15)	5 (9)
	1—symptomatic but completely ambulatory	5 (18)	6 (22)	11 (20)
	2—symptomatic <50% in bed	7 (25)	8 (30)	15 (27)
	3—symptomatic >50% in bed	13 (46)	9 (33)	22 (40)
	4—bedbound	2 (7)	0	2 (4)
	5—death	0	0	0
	Missing from eCRF	0	0	0
AHHS	0–3	2 (7)	0	—
	4–5	12 (43)	9 (33)	—
	6–9	14 (50)	18 (67)	—
	n	28	27	—
	Mean	5.93	6.22	—
	SD	1.70	1.09	—
	Median	5.50	7.00	—
	IQR	5.00–7.00	5.00–7.00	—
	Missing from eCRF	0	0	—
NAS	0–2	2 (7)	3 (11)	—
	3–4	8 (29)	2 (7)	—
	5–8	18 (64)	22 (82)	—
	n	28	27	—
	Mean	4.82	5.33	—
	SD	1.36	1.57	—
	Median	5.00	5.00	—
	IQR	4.00–6.00	5.00–6.00	—
	Missing from eCRF	0	0	—
MELD Score[a]	≤ 9	0	0	—
	>9–19	1 (4)	2 (7)	—
	>19–29	27 (96)	25 (93)	—
	>29–39	0	0	—
	>39	0	0	—
	n	28	27	—
	Mean	23.39	22.08	—
	SD	2.60	2.40	—
	Median	23.45	21.49	—
	IQR	21.91–25.22	19.95–22.89	—
	Missing from eCRF	0	0	—
GAHS	5–8	11 (39)	23 (85)	—
	9–12	17 (61)	4 (15)	—
	n	28	27	—
	Mean	8.75	7.67	—
	SD	1.32	0.92	—
	Median	9.00	8.00	—
	IQR	8.00–9.50	7.00–8.00	—
	Missing from eCRF	0	0	—
mDF score[a]	≤45	5 (18)	6 (22)	—
	>45–60	2 (7)	4 (15)	—
	>60–75	6 (21)	4 (15)	—
	>75–90	3 (11)	1 (4)	—
	>90	12 (43)	11 (41)	—
	n	28	27	—

Table 1. Continued

Variable/Component	Statistics	Canakinumab	Placebo	Total
	Mean	81.76	83.54	—
	SD	28.89	46.14	—
	Median	78.66	73.20	—
	IQR	59.91–103.34	45.46–112.44	—
	Missing from eCRF	0	1 (4)	—

Values are n (%), unless otherwise indicated. Baseline characteristics were collected for all randomized participants, regardless of their histology results at screening. Baseline characteristics were summarized for the mITT population (with positive histology results at screening) only (n = 55).
AHHS, Alcoholic Hepatitis Histology Score; eCRF, •••; mDF, Maddrey's discriminant function; MELD, Model for End-Stage Liver Disease; mITT, modified intention to treat; NAS, NAFLD Activity Score; WHO, World Health Organization.
[a]mDF and MELD scores were given explicitly at screening (recorded in eCRF).

4 allocated to CAN and 3 to PBO. A sensitivity analysis of the 20 possible outcomes for these missing data are described in Supplementary Table 5.

Primary Endpoint After Adjustment. Univariable logistic regression for the treatment effect of CAN on histological response gave an odds ratio (OR) of 1.96 (95% CI, 0.60–6.20; $P = .25$). After adjustment for age and baseline MELD, CAN was associated with histological improvement (OR, 5.0; 95% CI, 1.06–23.30; $P = .04$) (Table 2).

Histological Endpoints. There was no difference in the proportion of biopsies showing a reduction in neutrophilic infiltrate at 28 days after CAN therapy (OR, 1.29; 95% CI, 0.38–4.36, $P = .68$). However, the proportion of participants showing improvement in mononuclear cell infiltrate at 28 days in CAN treated group was numerically higher than in the PBO-treated group; this did not reach statistical significance (OR, 5.87; 95% CI, 0.96–35.7, $P = .055$). There were no differences in steatosis, ballooning, bilirubinostasis, or megamitochondria between groups. CAN therapy was not associated with improvements in AHHS nor NAS score (Supplementary Tables 1–4).

Liver Function. Treatment was not associated with a difference in Lille score after 7 days (mean Lille score CAN 0.37 [range, 0.24–0.49] vs PBO 0.31 [range, 0.19 to 0.43]). Treatment was also not associated with a difference in serum bilirubin at 28 or 90 days, after adjustment for baseline values (serum bilirubin: day 28, $P = .27$; day 90, $P = .45$) (Figure 2*A*), nor with a difference in

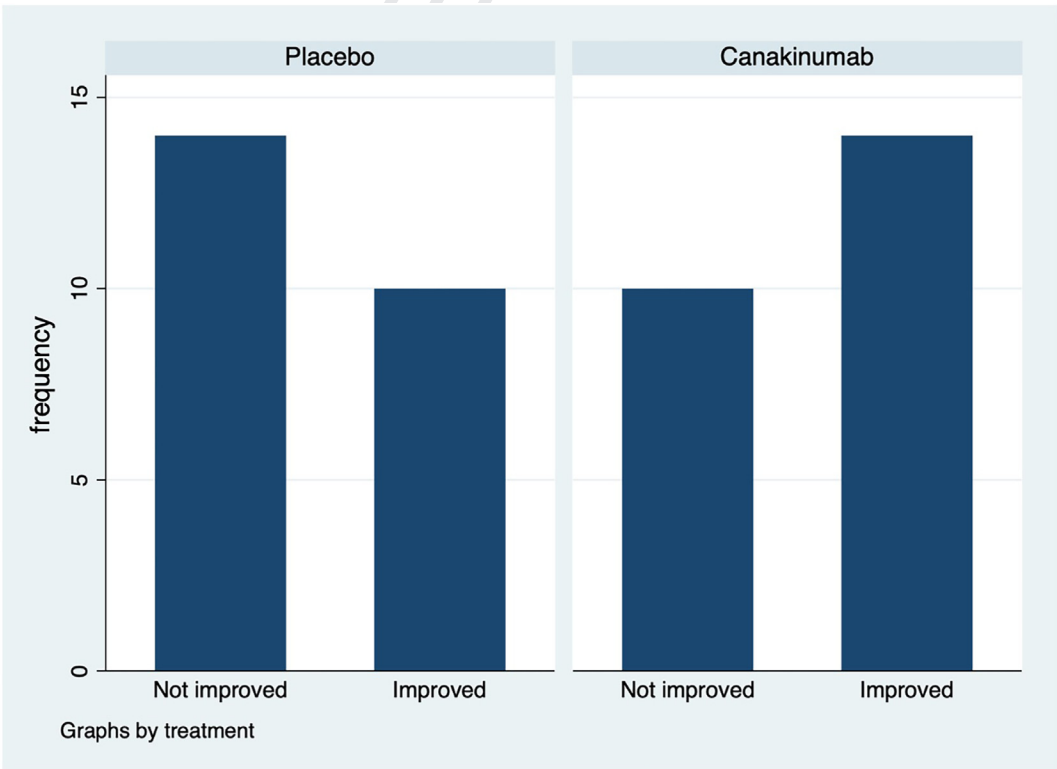

Figure 1. Primary endpoint analysis. Histological improvement occurred in 58% in the CAN group and 42% in the PBO group ($P = .25$).

Table 2. Unadjusted and Adjusted Factors Associated With Improvement in Histology

	Univariable		Multivariable	
Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
CAN therapy	1.96 (0.62–6.18)	.25	4.97 (1.1–23.3)	.04
Age	0.93 (0.87–1.01)	.07	0.88 (0.80–0.98)	.02
Baseline MELD	1.06 (0.85–1.31)	.62	0.85 (0.63–1.13)	.26
Baseline AHHS	0.88 (0.59–1.31)	.54	—	—
Sex	0.51 (0.16–1.61)	.25	—	—

AHHS, Alcoholic Hepatitis Histology Score; CAN, canakinumab; CI, confidence interval; MELD, Model for End-Stage Liver Disease; OR, odds ratio.

the delta serum bilirubin between groups (mean delta bilirubin CAN vs PBO: day 7, −56.0 (range, −89.0 to −23.1) vs −47.8 (range, −78.5 to −17.1) ($P = .71$); day 28, −167.1 (range, −211.9 to −122.3) vs −200.1 (range, −268.2 to −133.7) ($P = .39$); day 90, −234.6 (range, −290.6 to −178.5) vs −289.0 (range, −376.4 to −201.6) ($P = .28$). Similar results were obtained for the change in mean MELD score over the follow-up period (Figure 2*B*). Unexpectedly, CAN therapy was associated with higher MELD and GAHS at 28 days and higher GAHS at 90 days after adjustment for baseline MELD and GAHS (for MELD: $P = .035$ and $P = .11$ at days 28 and 90, respectively; for GAHS at 28 days: OR, 5.1; $P = .007$; and at 90 days: OR, 5.64; $P = .04$).

Biomarkers of Systemic and Hepatic Inflammation. CAN therapy was associated with numerically lower C-reactive protein values, especially between day 7 and day 21 compared with PBO-treated participants (Supplementary Figure 2). However, there was no statistically significant association between treatment and C-reactive protein at any time point. No between-group difference was detected in the proportion of participants who had resolved the systemic inflammatory response syndrome by days 28 or 90. A significant improvement in serum AST was observed in participants treated with CAN after adjusting for baseline AST, age, and MELD ($P = .02$). Indeed, by day-28 PBO-treated participants more frequently had serum AST > 80 IU/L and therefore more frequently required a second dose of IMP than CAN-treated participants (n = 14 of 27 [52%] vs 7 of 28 [25%]).

Mortality. Two participants died within 90 days for each group. Of the 4 participants who died in total, 1 from each group died of liver failure and 1 from each group died from infection. Of the 4 deaths, 1 occurred within 28 days and 3 occurred between 28 and 90 days. There were no differences in time to death between the 2 groups (Cox proportional hazards model beginning at baseline and ending 90 days after randomization, $P = .97$) (Figure 3, Supplementary Table 5).

Other Adverse Events. A total of 216 adverse events occurred during the study, of which 114 occurred in 26 CAN-treated participants and 102 occurred in 24 PBO-treated participants. There were a total of 49 SAEs in 20 (36%) of 55 participants (Table 3), of which 20 events occurred in 10 CAN-treated participants and 29 occurred in 10 PBO-treated participants. Of special interest, 1 infection occurred in 1 of the 28 CAN-treated participants while 5 infections occurred in 2 PBO-treated participants. There was 1 (of 29) acute kidney injury occurring in 1 of 28 CAN-treated participants and

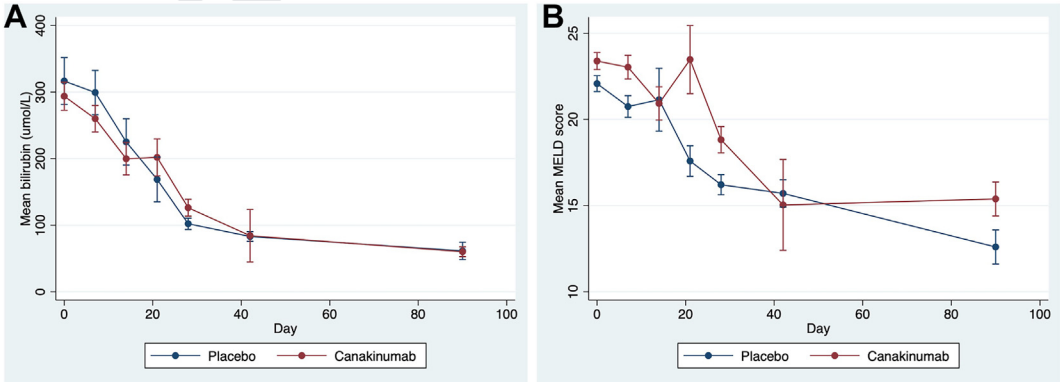

Figure 2. (*A*) Change in mean levels of serum bilirubin (and corresponding 95% CIs) from baseline to days 7, 14, 21, 28, 42, and 90 (intention-to-treat population for efficacy). (*B*) Change in mean MELD scores (and corresponding 95% CIs) from baseline to days 7, 14, 21, 28, 42, and 90 (intention-to-treat population for efficacy).

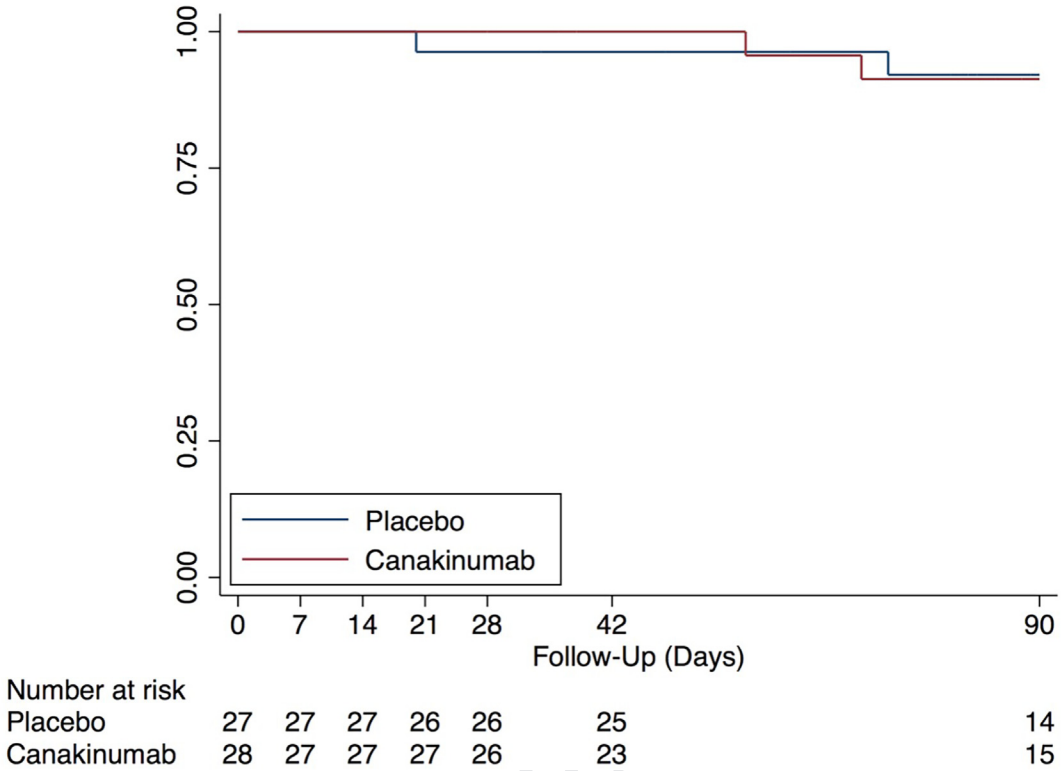

Figure 3. Kaplan-Meier graph showing overall mortality over 90 days (intention-to-treat population for efficacy).

1 (of 20) acute kidney injury occurring in 1 of 27 PBO-treated participants. Investigators reported similar instances of variceal hemorrhage, ascites, and encephalopathy in both arms of the trial.

Discussion

In this exploratory phase 2 study, treatment with CAN resulted in histological improvement in alcohol-related hepatitis[17] without affecting clinical outcomes such as Lille score, MELD, or mortality. Histological improvement predominantly comprised a reduction in the frequency of mononuclear cells, rather than neutrophils, in liver tissue. In addition to the histological changes, an improvement in serum AST, indicating resolution of liver injury and/or inflammation, was also demonstrated for CAN-treated participants.

Regardless of the effect of CAN on liver histology, there was no signal of benefit for any of the clinical parameters of liver function measured. While the small sample size predisposes to type II error, if anything prespecified analyses indicated worsening of liver function, specifically MELD and GAHS, in CAN-treated participants compared with PBO treatment. In this regard, we highlight recent data from a similar trial of the IL-1 receptor antagonist anakinra, inhibiting both IL-1α and IL-1β signaling, that identified worse clinical outcomes at 90 days for participants receiving IL1 signal inhibition therapy.[18]

Mortality in the ISAIAH trial was low, at 7%. From the outset, the ISAIAH trial sought to recruit a subpopulation of AH participants for whom the risk of infectious complications, which might be exacerbated by anti-IL-1β therapy, was limited. However, the ceiling MELD score of 27 at recruitment only partially explains the high survival rate in the ISAIAH trial. Subset analysis of the STOPAH participants with MELD $\leq$27 predicts an expected mortality of 22% at 90 days.

Several differences in trial design may explain the higher survival in the ISAIAH trial compared with the STOPAH trial. First, all participants in the ISAIAH trial received at least 14 days of prophylactic antibiotics, in contrast to the STOPAH trial, in which antibiotic prescription was directed by the attending physician.[3] Second, the STOPAH trial recruited participants using strict clinical criteria, while the ISAIAH trial used both strict clinical criteria and confirmation of steatohepatitis on liver biopsy. The requirement for liver biopsy in and of itself required participants to be fit enough to undergo the procedure.

Other limitations concern the uncertainty surrounding the 7 (12%) of 55 of participants without primary endpoint data. These missing data raise the possibility of selection and/or attrition biases within the study. However, the constructed scenario sensitivity analysis (Supplementary Table 3) is instructive in this regard. It highlights that of the 20 possible outcomes for these 7 missing datapoints only the best-case scenario, that all CAN-treated participants and no PBO-treated

Table 3. Summary of the Events Reported on the Serious Adverse Event Form (Sorted by % of Total Events) (mITT Population)

System Organ Class and MedDRA Event	Events			Participants[a]		
	Canakinumab	Placebo	Total	Canakinumab	Placebo	Total
Total	20 (41)	29 (59)	49 (100)	10 (36)	10 (37)	20 (36)
Blood and lymphatic disorders	1 (5)	0	1 (2)	1 (10)	0	1 (5)
Anemia	1 (5)	0	1 (2)	1 (10)	0	1 (5)
Cardiac disorders	2 (10)	0	2 (4)	2 (20)	0	2 (10)
Cardiac arrest	1 (5)	0	1 (2)	1 (10)	0	1 (5)
Palpitations	1 (5)	0	1 (2)	1 (10)	0	1 (5)
Gastrointestinal disorders	4 (20)	3 (10)	7 (14)	4 (40)	3 (30)	7 (35)
Abdominal distension	1 (5)	0	1 (2)	1 (10)	0	1 (5)
Abdominal pain	0	1 (3)	1 (2)	0	1 (10)	1 (5)
Gastrointestinal hemorrhage	0	1 (3)	1 (2)	0	1 (10)	1 (5)
Hematemesis	1 (5)	0	1 (2)	1 (10)	0	1 (5)
Pancreatitis acute	1 (5)	0	1 (2)	1 (10)	0	1 (5)
Rectal hemorrhage	1 (5)	0	1 (2)	1 (10)	0	1 (5)
Upper gastrointestinal hemorrhage	0	1 (3)	1 (2)	0	1 (10)	1 (5)
General disorders and administration site conditions	1 (5)	0	1 (2)	1 (10)	0	1 (5)
Edema	1 (5)	0	1 (2)	1 (10)	0	1 (5)
Hepatobiliary disorders	7 (35)	6 (21)	13 (27)	5 (50)	5 (50)	10 (50)
Alcoholic liver disease	1 (5)	0	1 (2)	1 (10)	0	1 (5)
Ascites	0	1 (3)	1 (2)	0	1 (10)	1 (5)
Hepatic failure	2 (10)	5 (17)	7 (14)	2 (20)	4 (40)	6 (30)
Hepatic encephalopathy	2 (10)	0	2 (4)	2 (20)	0	2 (10)
Esophageal varices hemorrhage	2 (10)	0	2 (4)	1 (10)	0	1 (5)
Infections and infestations	1 (5)	5 (17)	6 (12)	1 (10)	2 (20)	3 (15)
Peritonitis bacterial	0	2 (7)	2 (4)	0	2 (20)	2 (10)
Pneumonia	1 (5)	2 (7)	3 (6)	1 (10)	2 (20)	3 (15)
Urinary tract infection	0	1 (3)	1 (2)	0	1 (10)	1 (5)
Injury, poisoning and procedural complications	1 (5)	4 (14)	5 (10)	1 (10)	2 (20)	3 (15)
Hemoperitoneum	1 (5)	0	1 (2)	1 (10)	0	1 (5)
Postprocedural hemorrhage	0	2 (7)	2 (4)	0	1 (10)	1 (5)
Skull fracture	0	1 (3)	1 (2)	0	1 (10)	1 5)
Subarachnoid hemorrhage	0	1 (3)	1 (2)	0	1 (10)	1 (5)
Metabolism and nutrition disorders	1 (5)	3 (10)	4 (8)	1 (10)	2 (20)	3 (15)
Hypernatremia	0	1 (3)	1 (2)	0	1 (10)	1 (5)
Hypokalemia	0	2 7)	2 (4)	0	2 (20)	2 (10)
Metabolic acidosis	1 (5)	0	1 (2)	1 (10)	0	1 (5)
Nervous system disorders	0	1 (3)	1 (2)	0	1 (10)	1 (5)
Hypoesthesia	0	1 (3)	1 (2)	0	1 (10)	1 (5)
Renal and urinary disorders	1 (5)	1 (3)	2 (4)	1 (10)	1 (10)	2 (10)
Acute kidney injury	1 (5)	1 (3)	2 (4)	1 (10)	1 (10)	2 (10)
Respiratory, thoracic, and mediastinal disorders	1 (5)	3 (10)	4 (8)	1 (10)	2 (20)	3 (15)

Table 3. Continued

System Organ Class and MedDRA Event	Events			Participants[a]		
	Canakinumab	Placebo	Total	Canakinumab	Placebo	Total
Acute respiratory distress syndrome	0	1 (3)	1 (2)	0	1 (10)	1 (5)
Dyspnea	1 (5)	1 (3)	2 (4)	1 (10)	1 (10)	2 (10)
Pneumonia aspiration	0	1 (3)	1 (2)	0	1 (10)	1 (5)
Vascular disorders	0	3 (10)	3 (6)	0	1 (10)	1 (5)
Hematoma	0	1 (3)	1 (2)	0	1 (10)	1 (5)
Hypotension	0	1 (3)	1 (2)	0	1 (10)	1 (5)
Soft tissue necrosis	0	1 (3)	1 (2)	0	1 (10)	1 (5)

Values are n (%). The data include all randomized participants, with positive histology results at screening, followed up for 90 days.
mITT, modified intention to treat.
[a]A total of 55 participants were in the mITT population with positive histology results at screening (canakinumab: n = 28; placebo: n = 27).

participants showed histological improvement, would result in a statistically significant benefit for CAN therapy in AH. The possibility that selection and/or attrition biases have substantially altered the conclusions of this study therefore appear remote. In addition, secondary endpoint comparisons between CAN and PBO groups are uncontrolled for type I and II errors and should be viewed as exploratory.

The failure of CAN therapy to improve clinical outcomes questions the role of IL-1β in the pathogenesis and prognosis of AH, despite strongly supportive preclinical data.[7] In this regard, we note that in CAN-treated participants, C-reactive protein levels fell by 18% after 7 days, while in PBO-treated participants a 7% rise was observed. In contrast, C-reactive protein fell by 89% over 7 days for CAN-treated participants with cryopyrin-associated periodic syndrome.[19] Furthermore, in the CANTOS study those participants with the lowest C-reactive protein after CAN therapy gained the most clinical benefit.[20] This suggests either that the dose of CAN was insufficient for participants with AH or that redundancy in cytokine pathway–maintained inflammation in the face of IL-1β inhibition.

Although there was some evidence of improvement in mononuclear infiltrate, the lack of improvement in neutrophilic infiltrate, ballooning, and cholestasis concords with the lack of improved clinical outcomes. In the ISAIAH trial, there was no excess of infections in CAN-treated participants despite the well-documented immune paresis in participants with AH. This may reflect the judicious use of prophylactic antibiotics.

Conclusions

In summary, the ISAIAH trial did not detect a signal of clinical efficacy for CAN in participants with mDF $\geq$32 and MELD $\leq$27.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2024.07.025.

References

1. Louvet A, Thursz MR, Kim DJ, et al. Corticosteroids reduce risk of death within 28 days for patients with severe alcoholic hepatitis, compared with pentoxifylline or placebo-a meta-analysis of individual data from controlled trials. Gastroenterology 2018; 155:458–468.e8.
2. Louvet A, Naveau S, Abdelnour M, et al. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. Hepatology 2007;45:1348–1354.
3. Vergis N, Atkinson SR, Knapp S, et al. In patients with severe alcoholic hepatitis, prednisolone increases susceptibility to infection and infection-related mortality, and is associated with high circulating levels of bacterial DNA. Gastroenterology 2017; 152:1068–1077.e4.
4. Altamirano J, Miquel R, Katoonizadeh A, et al. A histologic scoring system for prognosis of patients with alcoholic hepatitis. Gastroenterology 2014;146:1231–1239.e1–e6.
5. Michelena J, Altamirano J, Abraldes JG, et al. Systemic inflammatory response and serum lipopolysaccharide levels predict multiple organ failure and death in alcoholic hepatitis. Hepatology 2015;62:762–772.
6. Tilg H, Wilmer A, Vogel W, et al. Serum levels of cytokines in chronic liver diseases. Gastroenterology 1992;103:264–274.
7. Petrasek J, Bala S, Csak T, et al. IL-1 receptor antagonist ameliorates inflammasome-dependent alcoholic steatohepatitis in mice. J Clin Invest 2012;122:3476–3489.
8. Tilg H, Moschen AR, Szabo G. Interleukin-1 and inflammasomes in alcoholic liver disease/acute alcoholic hepatitis and nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. Hepatology 2016;64:955–965.
9. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377:1119–1131.

10. Boetticher NC, Peine CJ, Kwo P, et al. A randomized, double-blinded, placebo-controlled multicenter trial of etanercept in the treatment of alcoholic hepatitis. Gastroenterology 2008; 135:1953–1960.
11. Naveau S, Chollet-Martin S, Dharancy S, et al. A double-blind randomized controlled trial of infliximab associated with prednisolone in acute alcoholic hepatitis. Hepatology 2004; 39:1390–1397.
12. Vergis N, Patel V, Bogdanowicz K, et al. IL-1 Signal Inhibition In Alcoholic Hepatitis (ISAIAH): a study protocol for a multicentre, randomised, placebo-controlled trial to explore the potential benefits of canakinumab in the treatment of alcoholic hepatitis. Trials 2021;22:792.
13. Crabb DW, Bataller R, Chalasani NP, et al. Standard definitions and common data elements for clinical trials in patients with alcoholic hepatitis: recommendation from the NIAAA Alcoholic Hepatitis Consortia. Gastroenterology 2016;150:785–790.
14. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 1996;24:289–293.
15. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. Am J Epidemiol 1993;138:923–936.
16. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. Am J Epidemiol 1989;129:125–137.
17. Greenland S, Mansournia MA, Joffe M. To curb research misreporting, replace significance and confidence by compatibility: a preventive medicine Golden Jubilee article. Prev Med 2022; 164:107127.
18. Szabo G, Mitchell M, McClain CJ, et al. IL-1 receptor antagonist plus pentoxifylline and zinc for severe alcohol-associated hepatitis. Hepatology 2022;76:1058–1068.
19. Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, et al. Use of canakinumab in the cryopyrin-associated periodic syndrome. N Engl J Med 2009;360:2416–2425.
20. Ridker PM, MacFadyen JG, Everett BM, et al. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. Lancet 2018; 391:319–328.

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CRediT Authorship Contributions

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Vishal Patel (Data curation: Supporting; Formal analysis: Supporting; Investigation: Supporting; Methodology: Supporting; Project administration: Supporting; Writing – review & editing: Supporting)

Karolina Bogdanowicz (Data curation: Equal; Investigation: Supporting; Methodology: Supporting; Project administration: Lead; Writing – review & editing: Supporting)

Justyna Czyzewska-Khan (Data curation: Supporting; Investigation: Supporting; Project administration: Supporting; Writing – review & editing: Supporting)

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Conflicts of Interest
These authors disclose the following: Karolina Bogdanowicz is an employee of Novartis Pharmaceuticals. Nikhil Vergis is an employee of GSK. The remaining authors disclose no conflicts.

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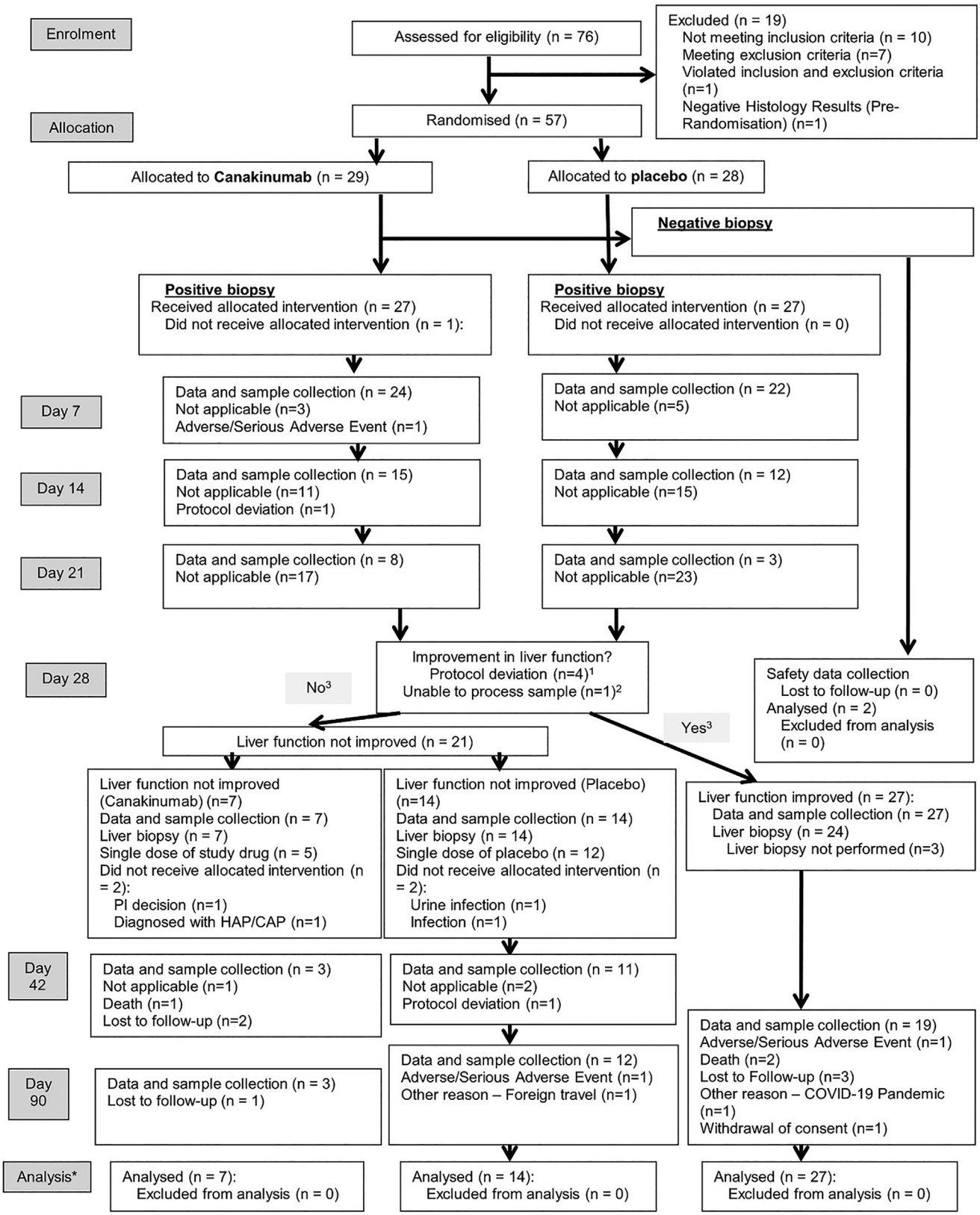
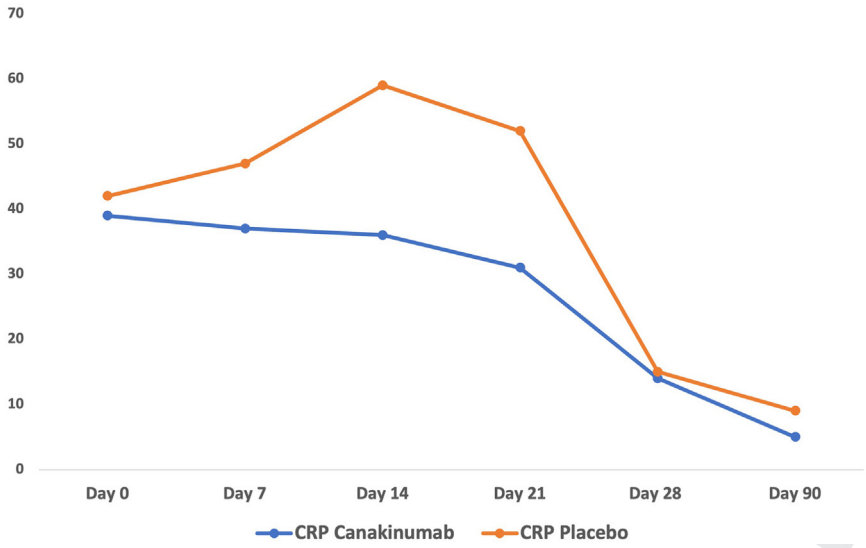
Supplementary Data

Missing Primary Outcome Data

Missing primary outcome data were assumed to be missing completely at random. However, the sensitivity of the primary endpoint analysis to a scenario in which data were not missing completely at random was also tested. A worst-case scenario was constructed that assumed all missing data for canakinumab-treated participants were no histological improvement and that all missing data for placebo-treated participants were histological improvement. A best-case scenario was also constructed that assumed all missing data for canakinumab-treated participants were histological improvement and that all missing data for placebo-treated participants were no histological improvement. Intermediate cases assumed all possible allocations of histological improvement in both treatment groups. The estimated treatment effect and 95% confidence intervals for each constructed scenario are presented. Missing data for secondary endpoints were analyzed under the missing completely at random assumption as a complete case analysis.



Supplementary Figure 1. CONSORT flow diagram.



Supplementary Figure 2. ●●●. CRP, C-reative protein.

Supplementary Table 1. Scores for Individual Components of AHHS at Baseline for the mITT Population (With Positive Histology at Screening)

Component	Statistics	Canakinumab	Placebo
Fibrosis stage	0	0	0
	3	28 (100)	27 (100)
	n	28	27
	Missing from eCRF	0	0
Bilirubinostasis	0	15 (54)	15 (56)
	1	6 (21)	7 (26)
	2	7 (25)	5 (19)
	n	28	27
	Missing from eCRF	0	0
Polymorphonuclear infiltration	2	14 (50)	17 (63)
	0	14 (50)	10 (37)
	n	28	27
	Missing from eCRF	0	0
Megamitochondria	2	17 (61)	18 (67)
	0	11 (39)	9 (33)
	n	28	27
	Missing from eCRF	0	0

Values are n (%)**, unless otherwise indicated**. Baseline measurements were collected for all randomized participants, regardless of their histology results at screening. **Measurements at baseline and day 28 were summarized for the mITT population (with positive histology at screening) only.** A total of 55 participants had at baseline.

AHHS, Alcoholic Hepatitis Histology Score; eCRF, •••; mITT, modified intention to treat.

Supplementary Table 2. Scores for Individual Components of AHHS at Day 28 for the mITT Population (With Positive Histology at Screening)

Component	Statistics	Canakinumab	Placebo
Fibrosis stage	0	0	1 (4)
	3	23 (100)	22 (96)
	n	23	23
	Missing from eCRF	0	0
Bilirubinostasis	0	14 (61)	16 (70)
	1	3 (13)	3 (13)
	2	6 (26)	4 (17)
	n	23	23
	Missing from eCRF	0	0
Polymorphonuclear infiltration	2	21 (91)	17 (74)
	0	2 (9)	6 (26)
	n	23	23
	Missing from eCRF	0	0
Megamitochondria	2	21 (91)	19 (83)
	0	2 (9)	4 (17)
	n	23	23
	Missing from eCRF	0	0

Values are n (%), unless otherwise indicated. Measurements at baseline and day 28 were summarized for the ITT population (with positive histology at screening) only. A total of 46 participants underwent day 28 biopsy.

AHHS, Alcoholic Hepatitis Histology Score; eCRF, •••; ITT, intention to treat; mITT, modified intention to treat.

Supplementary Table 3. Scores for Individual Components of NAS at Baseline for the ITT Population (With Positive Histology at Screening)

Component	Statistics	Canakinumab	Placebo
Steatosis	0	10 (36)	4 (15)
	1	10 (36)	3 (11)
	2	7 (25)	12 (44)
	3	1 (4)	8 (30)
	n	28	27
	Missing from eCRF	0	0
Lobular inflammation	0	0	0
	1	6 (21)	12 (44)
	2	14 (50)	8 (30)
	3	8 (29)	7 (26)
	n	28	27
	Missing from eCRF	0	0
Hepatocyte ballooning	0	0	1 (4)
	1	6 (21)	8 (30)
	2	22 (79)	18 (67)
	n	28	27
	Missing from eCRF	0	0

Values are n (%), unless otherwise indicated**. Baseline measurements were collected for all randomized participants, regardless of their histology results at screening.** Measurements at baseline and day 28 were summarized for the ITT population (with positive histology at screening) only. A total of 55 participants had data at baseline.
eCRF, •••; ITT, intention to treat; NAS, NAFLD Activity Score.

Supplementary Table 4. Scores for Individual Components of NAS at Day 28 for the ITT Population (With Positive Histology at Screening)

Component	Statistics	Canakinumab	Placebo
Steatosis	0	18 (78)	14 (61)
	1	2 (9)	5 (22)
	2	3 (13)	3 (13)
	3	0	1 (4)
	n	23	23
	Missing from eCRF	0	0
Lobular inflammation	0	1 (4)	0
	1	10 (44)	14 (61)
	2	11 (48)	7 (30)
	3	1 (4)	2 (9)
	n	23	23
	Missing from eCRF	0	0
Hepatocyte ballooning	0	1 (4)	3 (13)
	1	15 (65)	11 (48)
	2	7 (30)	9 (39)
	n	23	23
	Missing from eCRF	0	0

Values are n (%), unless otherwise indicated. Measurements at baseline and day 28 were summarized for the ITT population (with positive histology at screening) only. A total of 46 participants underwent day 28 biopsy.
eCRF, •••; ITT, intention to treat; NAS, NAFLD Activity Score.

Supplementary Table 5. Sensitivity Analysis: Status of Patients at Day 90 (ITT Population)

Status at Day 90	CAN	PBO	Total
Alive	19 (68)	20 (74)	39 (71)
Deceased	2 (7)	2 (7)	4 (7)
Total[a]	21 (75)	22 (82)	43 (78)
Unknown (status of patient is not known at day 90)	7 (25)	5 (19)	12 (22)
Adverse/serious adverse event	2 (29)	1 (20)	3 (25)
Lost to follow-up	4 (57)	2 (40)	6 (50)
Other reason	1 (14)	1 (20)	2 (17)
Withdrawal of consent	0	1 (20)	1 (8)

Values are n (%).
CAN, canakinumab; ITT, ITT, intention to treat; PBO, placebo.
[a]Data include all randomized participants with positive histology results at screening.