nature portfolio

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☒	☐ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Laboratory data including hematology, clinical chemistry, urinalysis, and genetic testing data were collected in Eurofins' Fetch database. ECGs were collected and transmitted using Spaulding Electrocardiograph Model 2100iQ. Data were transmitted via Spaulding ECG (Android version 1.2.6.1), a client application that connects via Bluetooth to the Spaulding Electrocardiograph and transmits the ECG data to the database. The database used was Spaulding Medical's webECG Management system (webECG version 1.4.7.8). All other data was collected on electronic case report forms through IBM Clinical Development provided by Merge, an IBM Company. The initial version was 2019.6.0.1 and the final version was 2022.4.0.1.
Data analysis	All data analyses were performed using SAS v9.4.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Patient-related data not included in the paper were generated as part of a clinical trial and may be subject to patient confidentiality. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	The findings apply to all genders. Gender was determined based on self-reporting. As provided in Table 1, 214 participants identified as male, and 87 participants identified as female. Participants were stratified by gender to allow for a similar number of males and females in each treatment group. No gender-specific analyses were conducted.
Population characteristics	Adults enrolled into AD04-301 were required to have expressed a wish to reduce or stop alcohol consumption, a willingness to participate in behavioral and medicinal treatments for AUD, a moderate or severe diagnosis of alcohol use disorder (AUD) using Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria, ≥6 heavy drinking days (HDDs) (60 g/day or more for males and 40 g/day or more for females) in the 4 weeks prior to the Screening Visit, an average alcohol consumption at the medium risk level (defined by the WHO "International guide for monitoring alcohol consumption and related harm" as >40 g of ethanol/day for males and >20 g of ethanol/day for females) for the 4 weeks prior to the Screening Visit, ≤14 consecutive abstinent days in the 4 weeks preceding the Screening Visit, and have at least one of the following genotypes as measured by Adial's validated method: • rs4795541-LL genotype of the insertion-deletion polymorphism (5′-HTTLPR) in the 5′-regulatory region and the rs1042173-TT SNP in the 3′-untranslated region of SLC6A4 gene that encodes the serotonin transporter, • rs1150226-AG SNP in HTR3A, the gene that encodes subtype A of the serotonin-3 receptor, • rs1176713-GG SNP in HTR3A, the gene that encodes subtype A of the serotonin-3 receptor, • rs17614942-AC in HTR3B, the gene that encodes subtype B of the serotonin-3 receptor.
Recruitment	Patients were recruited through patient databases, referral networks, and advertisements. Because patients were self-selecting to participate in a clinical trial to reduce alcohol consumption, self-selection bias likely contributed to an increased placebo effect.
Ethics oversight	Ethics oversight was provided by regulatory authority and ethics committee for each country as follows: Bulgaria: Ethics committee: Republic of Bulgaria Ministry of Health Ethics Committee for Clinical Trials Regulatory authority: Republic of Bulgaria Bulgarian Drug Agency Croatia: Ethics committee: HALMED Agency for Medicinal Products and Medical Devices Regulatory authority: Republic of Croatia Ministry of Health Finland: Ethics committee: TUKIJA National Committee on Medical Research Ethics Regulatory authority: Finnish Medicines Agency FIMEA Latvia: Ethics committee: Ethics Committee for Clinical Trials of Medicinal Products Regulatory authority: State Agency of Medicines Poland: Ethics committee: Ethics Committee at the Regional Medical Chamber in Lublin Regulatory authority: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products Sweden: Ethics committee: Swedish Ethical Review Authority Regulatory authority: Medical Products Agency

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The primary endpoint is the change from baseline in the PHDD between the two treatment groups analyzed using a mixed-model for repeated measures (MMRM) controlling for the stratification factors of baseline DDD category and gender as discussed in Section 4.2. Sample size and power calculations were performed utilizing a t-test and a 5% two-sided alpha level. This sample size provides 95% power with an assumed difference in PHDD between AD04 and placebo of 11.08% with a standard deviation of 26.3, as estimated from a previous study with AD04 modeling for the genetic population of interest.
Data exclusions	None
Replication	Statistical analyses were conducted by three separate statistical groups. Data were only accepted if all three statisticians agreed with the results. All results were fully replicated.
Randomization	Subjects will be randomized in a 1 to 1 ratio to one of the following groups: Group 1: AD04 0.33 mg BID Group 2: Placebo Randomization will be stratified by the following criteria: - Two levels of risk drinking (average of <10 DDD vs. ≥10 DDD for the 28 days prior to baseline) - Gender (female vs. male) There will be up to four strata total: 1: average of <10 DDD for the 28 days prior to baseline, female 2: average of <10 DDD for the 28 days prior to baseline, male 3: average of ≥10 DDD for the 28 days prior to baseline, female 4: average of ≥10 DDD for the 28 days prior to baseline, male Subjects within each stratum will be randomized using a permuted block randomization and administered by the EDC software.
Blinding	This was a double-blind, randomized, placebo-controlled study. Subjects, investigators, study site personnel, Sponsor and contract research organization staff involved in the conduct of the study were blinded to the subject treatment assignments with the exception of the data monitoring committee unblinded statistician and unblinded data manager.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT04101227
Study protocol	The full study protocol was provided as part of the manuscript submission. All pertinent information from the study protocol, including inclusion/exclusion criteria and the efficacy and safety assessments used at each study visit are described within the manuscript or provided in the supplemental information.
Data collection	Data was collected at the clinical trial sites or from a participant's home via telephone and entered into the IBM Clinical Development electronic data capture system as noted above. Lab and ECG data was only collected at the clinical trial sites. Data collection began at the beginning of the recruitment period in March 2020 and ended at the end of the treatment period in March 2022.
Outcomes	The primary outcome measure was the change from baseline in the monthly percent of heavy drinking days (PHDD) in Study Months 5 and 6 combined, where heavy drinking is defined as the consumption of ≥ 60 g alcohol/day (if male) or ≥ 40 g alcohol/day (if female). Drinking amounts were assessed using the timeline follow-back (TLFB) method.

Secondary endpoints for analyses of efficacy included:
1. Change from baseline in PHDD at each study month. Drinking amounts were assessed using the TLFB method.
2. Change from baseline in AUD symptoms and clinical status (<2 symptoms, Mild, Moderate, or Severe) at Weeks 12 and Week 24. AUD symptoms and clinical status was assessed by the Investigator using DSM-V criteria for AUD.
3. Change from baseline in Drinking Risk Levels (DRL), 1-level shift at Week 24. Drinking levels were assessed by applying TLFB drinking amounts to the WHO drinking level criteria.
4. Change from baseline in Drinking Risk Levels (DRL), 2-level shift at Week 24. Drinking levels were assessed by applying TLFB drinking amounts to the WHO drinking level criteria.
5. Change from baseline in total alcohol consumption (TAC), defined as the mean daily alcohol consumption expressed in g/day, at Weeks 16 to 24. Drinking amounts were assessed using the TLFB method.
6. Change from baseline in the Patient Health Questionnaire-9 (PHQ-9) at Week 24.
7. Change from baseline in risk alcohol consumption responders at Weeks 16 and 24. Drinking amounts were assessed using the TLFB method.
8. Change from baseline in percent reduction in monthly total alcohol consumption (TAC) at Weeks 20 to 24. Drinking amounts were assessed using the TLFB method.
9. Change from baseline in the percent of non-drinking days (PNDD) at Weeks 16 to 24. Drinking amounts were assessed using the TLFB method.
10. Change from baseline in drinks per drinking day (DDD) at Weeks 16 to 24. Drinking amounts were assessed using the TLFB method.