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<br>*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<br>*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 | msigdbr v7.5.1. GENCODE v45 (GRCh38) transcript set, Silva database v138.1 (silva_nr99_v138.1_wSpecies_train_set.fa, https://zenodo.org/records/4587955). |
| Data analysis | SAS® Software version 9.4, Trim Galore (v0.6.10), Bowtie2 (v 2.5.3), MetaPhlAn4.1.0, HUMAnN3 v.3.9, Salmon v 1.10.3, R v4.4.2, tximport v1.34.0, DESeq2 v1.46.0, ggplot2 v3.5.1., DADA2 R package v1.32.0, speedyseq R package v0.5.3.9021, Maaslin3 |

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

The datasets generated during the current study are not publicly available due to patient privacy considerations and sponsor contractual obligations but are available from the sponsor on reasonable request. Qualified researchers may request access to anonymized individual participant datas by contacting the corresponding author (bhadida@exeliombio.com). Requests are subject to review by a scientific review committee and the study sponsor (Exeliom Biosciences) to

ensure scientific merit and feasibility. Access will be granted following approval of a research proposal and execution of a data use agreement. The data use agreement includes restrictions to protect participant confidentiality, prohibits attempts at re-identification, and limits use of the data to the approved research purpose. Data will be shared within six months under agreements that data are provided in a secure research environment further protecting participant privacy.

## Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

| | |
|---|---|
| Reporting on sex and gender | This was a first-in-human phase 1 trial. There were no predefined inclusion/exclusion criteria or analysis criteria based on sex/gender. Sex is reported in the manuscript and reported as such. The sex of the participant at birth was reported. Gender was not documented in the eCRF; thus the study design did not consider participants that had undergone gender reassignment. No sex analysis were carried out due to the small population size which limit our ability to account for covariate. |
| Reporting on race, ethnicity, or other socially relevant groupings | This was a first-in-human phase 1 trial. Race and ethnicity were not predefined criterion. Ethnicity is only included as part of patient demographics. All patients reported they were white. |
| Population characteristics | Male or female adults with clinically active Crohn's disease (CDAI score >180 and <350) at baseline. As we have a small population size, we were limited in our ability to account for covariates. |
| Recruitment | Patients meeting the eligibility criteria were recruited from participating centers. Patients were recruited during regular follow-up visits in their centre. To boost recruitment, advertising fliers were prepared for notice boards within waiting rooms and for circulation by Patient Associations to members and displayed on their website.<br>We do not think there is self-selection bias or other biases that are likely to impact results. |
| Ethics oversight | Central IECs: Liège University Hospital Faculty Ethics Comitttee, Komisja Bioetyczna Okręgowej Izby Lekarskiej (OIL) w Warszawie (Bioethics Committee of the District Medical Chamber in Warsaw. Participants had provided documented informed consent for the study. No financial compensation was given to the participants, except for reimbursement of transportation-related costs. |

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 | TNBS colitis model in rats. Vehicle n=14; TNBS + Vehicle n=29; TNBS + EXL01 ≥10^10 n=28; TNBS + EXL01 ≥10^8 n=27; TNBS + EXL01 ≥10^6 n=30; TNBS + EXL01 ≥10^4 n=19; TNBS + EXL01 ≥10^2 n=9; TNBS + 5-ASA n=26. DNBS colitis model in mice. DNBS + Vehicle n= 8; DNBS + EXL01 n= 8; DNBS + 5-ASA n=8. DNBS colitis model with recovery in mice. DNBS + Vehicle n= 8; DNBS + EXL01 n= 7; DNBS + 5-ASA n=8. DSS colitis model in mice. DSS + Vehicle n= 5; DSS + EXL01 n= 5; DSS + ciclosporin n=8.<br>No statistical methods were used to pre-determine sample sizes, but the choice of sample sizes was based on our experience with the models and are in accordance with other similar studies.<br>Clinical trial, n=8, This number of evaluable participants is based on clinical and scientific judgement to meet the objectives of the study. As this is a Phase 1, proof-of-concept study, a formal sample size calculation was not performed. |
| Data exclusions | Patients who discontinued treatments were excluded to compare the evolution of gene expression, microbiome composition, and disease activity indexes. |
| Replication | As this is a Phase 1 Clinical Trial no replication was possible. |
| Randomization | NA- Phase 1, first-in-human trial; no blind group |
| Blinding | NA - Phase 1, first-in-human trial; dosing was open-label |

# 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 |
| ☒ | ☐ Plants |

## Methods

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

# Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

| | |
|---|---|
| Laboratory animals | Sprague Dawley rats (5 weeks old) and Mice C57BL/6J (7-10 weeks old) |
| Wild animals | The study did not involved wild animals |
| Reporting on sex | Male rats<br>Female mice |
| Field-collected samples | This study did not involve filed collection of samples |
| Ethics oversight | French government agreements APAFIS#7542-2017030609233680 and Apafis #16744-201807061805486. |

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

# 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 | NCT05542355 |
| Study protocol | Redacted trial protocol is provided |
| Data collection | Belgium and Poland, clinical trial sites; 20 March 2023 to 02 October 2024 |
| Outcomes | Predefined in the protocol; assessed by the investigator; endoscopy videos and histology were assessed by blinded central reviewers who were not involved in the study conduct.<br>This study has incorporated a number of clinical, endoscopic, and histologic assessments to assess disease activity in the study participants, all of which are standard for assessing disease activity in participants with CD in a clinical trial setting. In addition, the study has included biomarker assessments to investigate potential mechanisms of action and provide further information on the effects of EXL01 on disease activity. All clinical and laboratory procedures in this study are standard and generally accepted for the assessment of safety and efficacy of study participants. |

# Plants

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|---|---|
| Seed stocks | NA |
| Novel plant genotypes | NA |
| Authentication | NA |