

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 (<i>n</i>) 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 <i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>
☐	☒ 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. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give P values as exact values whenever suitable.</i>
☒	☐ 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 <i>d</i> , Pearson's <i>r</i>), 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	Study data were collected and managed using REDCap electronic data capture tools hosted at CERMEL. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.
Data analysis	All analyses were performed using R version 4.6.1 (R Core Team, 2026).

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](#)

Requests for access to the individual deidentified trial participant dataset can be submitted to corresponding author GMN for a period up to 24 months after

publication of this article. Upon reasonable request (outlined proposal for the intended analysis and a list of variables required), the corresponding author will respond within a maximum of 4 weeks following a review and subject to approval by a committee from CERMEL. In addition, reported results from this trial are publicly available at <https://pactr.samrc.ac.za/Researcher/TrialRegister.aspx?TrialID=30503>. Supporting clinical documents (protocol and statistical analysis plan) are provided as Supplementary Information.

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	Sex was used
Reporting on race, ethnicity, or other socially relevant groupings	No socially relevant grouping was made except for sex/gender and age groups. There was no adjustment for confounders
Population characteristics	Age was categorized into 5 classes: <2 years; 3-5 years; 6-10 years; 11-20 years; and >20 years. These categories represent more or less the biological development and susceptibility described with malaria as the susceptibility is higher in the youngest ages and decreases as we get older, while inversely there is semi-immunity growing with the age. Adults are semi-immune. The location or site of the study was also described to eventually look at any difference between urban and rural settings as malaria is indeed more frequent in rural settings, while malaria parasites might be potentially more resistant in urban settings because of the drug pressure.
Recruitment	Participants were patients with malaria symptoms who presented at our health centers in the study sites. Following an informed consent process, malaria diagnosis was performed using a rapid diagnostic test or a microscopic detection on a thick blood slide. Those positive for malaria were screened for eligibility in the study. This was a pragmatic "real-world" study design including as much routine patients as possible, therefore limiting the potential selection bias. Patients were randomized and drug allocation was concealed. The microscopists in charge of determining the efficacy outcome were not aware of the treatment arm the participants were in.
Ethics oversight	The study protocol was approved by the Institutional Ethics Committee of CERMEL (OHRP registration: IORG0007336/IRB00008812)

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	With the non-inferiority margin of 5% (0.95 in success probability), a significance level of one-sided 2.5% ($\alpha = 0.025$), power 80% ($\beta = 0.2$), adjusting for 10% loss to follow-up, and a randomization ratio 1:1, the non-inferiority limit on the odds ratio scale is 0.474, the sample size per group is 329 participants, making a total sample size (both groups) of 658 participants. To allow for a more comprehensive safety evaluation of the new treatment regimen, the statistical analysis plan defined to enrol at least 1,000 patients leading at the same time to higher precision for the treatment outcomes. ACPRs are presented as n/N (%; 95% CI). Treatment difference is expressed as odds ratio and 95% CI.
Data exclusions	No data exclusion
Replication	Describe the measures taken to verify the reproducibility of the experimental findings. If all attempts at replication were successful, confirm this OR if there are any findings that were not replicated or cannot be reproduced, note this and describe why.
Randomization	After informed consent was signed, participants were attributed a study number and the corresponding sealed envelope was opened to reveal the assigned treatment group. Participants were randomly assigned (randomisation ratio 1:1) to single dose SPAP or twice-daily AL for three days. Allocation of participants to study arms was done centrally by the clinical sponsor using R software, generating site specific randomisation lists. The method employed was randomisation that assigned participants to treatment arms within specific trial sites without enforcing rigid, predefined block sizes.
Blinding	The investigators were not formally blinded but the study drugs were allocated and given by the pharmacists away from the investigators. The strict blinding was not done because SPAP was given as a single dose while AL was given twice daily for three days. However, the microscopists who determined the efficacy results were kept masked from the study drug allocation. We can therefore say that the study was assessor-blinded.

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

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

Study protocol

Data collection

Outcomes

Analysis of secondary efficacy outcomes

The secondary outcomes were:

- Crude Day 42 cure rate by species and PCR adjusted cure rate for Day 42 cure rate for *P. falciparum* [modified intention to treat and per-protocol population]
- Recurrence, reinfection and recrudescence rate until day 42.
- Gametocyte carriage up to day 42 by microscopy, (prevalence and density) at days 7, 28 and 42 after treatment.
- Time between malaria episodes and frequency of repeat episodes before and after Day 42
- Compliance of AL will be assessed by counting the number of tablets dispensed but not taken, when the CHW visits the patient at home.
- Safety (including hepatic safety) in retreated patients.
- Haematology recovery, that is, haemoglobin changes between day 0 and day 28.
- Changes in the frequency of mutations in the dihydrofolate (DHFR) gene at day 0 first follow-up and day of re-appearance of parasitaemia.

For the secondary outcomes, analyses were focus on estimating differences between treatments using 95% confidence intervals for (%) differences, odds-ratios or hazard-ratios rather than testing statistical hypotheses. If hypotheses are tested a P-value of 0.05 (5% level) was used to declare statistical significance. Rather than adjust for multiplicity, relevant results from other studies already reported in the literature were taken into account in the interpretation of these results.

Seed stocks

Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.

Novel plant genotypes

Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.

Authentication

Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosaicism, off-target gene editing) were examined.