

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
<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. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P 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 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 No commercial, open source, or custom made code was used to collect data for this study.

Data analysis SAS software (9.04 version), R (Version 4.5.1, GraphPad Prism (Version 10.4.2) and Excel (Version 2505) was used to analyze data and to generate graphical plots.

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](#)

Source data are provided with this paper. Johnson & Johnson has an agreement with the Yale Open Data Access (YODA) Project to serve as the independent review panel for evaluation of requests for clinical study reports and participant level data from investigators and physicians for scientific research that will advance medical knowledge and public health. Data will be made available following publication and approval by YODA of any formal requests with a defined analysis plan. YODA aims to handle requests within 30 days of receipt and make data available for approved requests within 30 days from the signing of a Data Use Agreement. For

more information on this process or to make a request, please visit The YODA Project site at yoda.yale.edu. The data sharing policy of Johnson & Johnson is available online at <https://www.janssen.com/clinical-trials/transparency>.

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	Selected immunogenicity data was reported by self-reported gender (female and male). Sex or gender was not considered in the study design as this was a Phase 1/2a study focused on the safety and immunogenicity profile for the vaccine in healthy adults. However, data disaggregated by gender is now included in the manuscript
Reporting on race, ethnicity, or other socially relevant groupings	No other variables were identified as a relevant subgroup due to a homogeneous study population (generally healthy male and female participants of 18-45 years of age).
Population characteristics	Information on the study population characteristics can be found within the manuscript and on ClinicalTrials.gov (NCT05901636). Population characteristics of the immunogenicity comparator group selected from COV3005 (NCT05091307) can also be found within the published primary manuscript which has been cited. All covariate-relevant population characteristics were well-balanced among study participants in all groups (Supplementary Table 1).
Recruitment	The target of 170 participants was enrolled in the study. The study design included 2 sequential cohorts comparing INFLUENZA G1 mHA (with or without Al(OH) ₃ adjuvant) at 2 dose levels. Screening for eligible participants was performed within 42 days before administration of the study vaccine. The inclusion and exclusion criteria for enrolling participants in the study are described in the Study Protocol submitted as Supplementary Information. Participants were randomly assigned to study vaccine groups. The participants, study-site personnel (including vaccine administrator) and investigator were blinded to study vaccine allocation throughout the study, except for the pharmacist or qualified staff member with primary responsibility for study vaccine preparation and dispensing.
Ethics oversight	The studies were conducted in accordance with the Declaration of Helsinki, Good Clinical Practices, and applicable regulatory guidelines. Study protocols were approved by institutional review boards at each study site. Participants provided written informed consent to participate in the study.

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	This was a first-in-human study with no formal statistical hypothesis testing for safety or immunogenicity outcomes between the groups. However, given 25 participants assigned to each vaccine regimen, the observation of no adverse reactions after the first vaccination would be associated with a 95% confidence that the true rate of adverse reactions is less than 11.3% for this sample size. Across active regimens with a sample size of 150, the observation of no adverse reactions after the first vaccination would be associated with a 95% confidence that the true rate is less than 2.0%.
Data exclusions	No data were excluded from safety analysis. For Per-protocol immunogenicity analysis, samples taken on or after the date when a participant experiences a major protocol deviation expected to impact the immunogenicity outcomes were excluded. In addition, samples obtained after missed doses or after natural infection were excluded.
Replication	Immunogenicity assays used for the study were appropriately developed, qualified or validated to assess among other parameters, repeatability and precision, such that expected assay variation was known.
Randomization	All randomization procedures are fully described in the protocol submitted with the manuscript. Participants were randomly assigned into vaccine groups, based on a computer-generated randomization schedule using randomly permuted blocks prepared under the sponsor's supervision. Participants were assigned into 3 groups in Cohort 1 (60 adults) and 5 groups in Cohort 2 (110 adults), at an overall ratio of 7.5:1 to receive study vaccine or placebo (0.9% saline) (Fig. 1b) using a staggered approach (Supplementary Fig. 1)
Blinding	All blinding procedures are fully described in the protocol submitted with the manuscript. The investigator was not provided with randomization codes. Data that may have potentially unblinded the intervention assignment was handled with special care to maintain the blind and to minimize potential bias. The participants, study-site personnel (including vaccine administrator) and investigator were blinded to study vaccine allocation throughout the study, except for the pharmacist or qualified staff member with primary responsibility for study vaccine preparation and dispensing.

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

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)	Madin-Darby Canine Kidney cells expressing human 2,6-sialtransferase (MDCK-SIAT1) were purchased from ATCC. Madin-Darby Canine Kidney cells stably expressing H5 hemagglutinin (MDCK-H5-HA) were generated at Janssen Vaccines and Prevention with the MDCK cell line purchased from ATCC.
Authentication	Cell lines were not further authenticated following purchase from vendor.
Mycoplasma contamination	Cell lines were confirmed mycoplasma free from vendor, and not further tested thereafter.
Commonly misidentified lines (See ICLAC register)	Not applicable.

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	BALB/c AnNCrI (SPF) mice, that were 6 weeks old on day of arrival ,were used in the passive serum transfer study to evaluate protective capacity of FLZ1001 serum against influenza H5N1 challenge.
Wild animals	The study did not involve animals captured in the wild.
Reporting on sex	Only female BALB/c AnNCrI (SPF) mice (N=116) were used in the passive serum transfer study. The serum samples came from N=32 female participants and N=18 male participants.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	The Animal Welfare Application for this study was approved by the Dutch Central Authority for Scientific Procedures on Animals (CCD) prior to study start and registered under number AVD4010020185285. The study protocol was approved by the Wageningen BioVeterinary Research Animal Welfare Body under permit number 2017.D-0030.017.

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	NCT05901636
Study protocol	The protocol has been submitted with the manuscript as Supplementary Information.
Data collection	The FLZ1001 study was conducted in 4 sites in the USA with recruitment between 31 May 2023 and 25 Aug 2023. Screening for eligible participants was performed within 42 days before administration of the study vaccine. The inclusion and exclusion criteria for enrolling participants in the study are described in the Study Protocol submitted as Supplementary Information. Participants were randomly assigned to study vaccine groups. The participants, study-site personnel (including vaccine administrator) and investigator were blinded to study vaccine allocation throughout the study, except for the pharmacist or qualified staff member with primary responsibility for study vaccine preparation and dispensing. Data collection continued until the end of the study on 19 Aug 24. No

formal statistical testing of safety or immunogenicity data was planned.

Outcomes

Primary (descriptive analysis of safety data) and secondary (descriptive analysis on immunogenicity data) outcomes measured were pre-defined in the Protocol and their assessment outlined in the Statistical Analysis Plan (SAP); both documents have been submitted with the manuscript as Supplementary Information. All covariate-relevant population characteristics were well-balanced among study participants in all groups.

Plants

Seed stocks

N/A

Novel plant genotypes

N/A

Authentication

N/A