PUBLICATION CARD

Safety and immunogenicity of a next-generation live-attenuated yellow fever vaccine produced in a Vero cell line in the USA: a phase 1 randomised, observer-blind, active-controlled, dose-ranging clinical trial

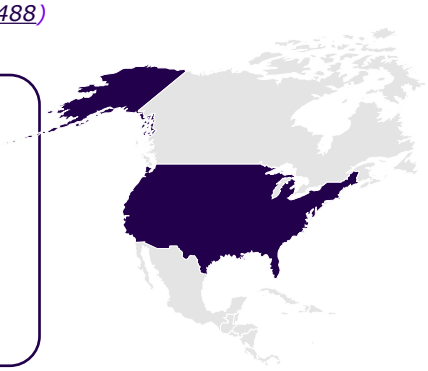
AUGUST 2024

Authors: Modjarrad K, Scott PT, McCauley M, Ober-Shepherd B, Sondergaard E, Amare MF, Parikh AP, Omar B, Minutello A-M*, Adhikarla H*, Wu Y*, Rojas P A*, Delore V*, Mantel N*, Morrison MN, Kourbanova KS, Martinez ME, Guzman I, Greenleaf ME, Darden JM, Koren MA, Hamer MJ, Lee CE, Hutter JN, Peel SA, Robb ML, Vangelisti M*, Feroldi E* *(*designates authors employed by Sanofi)*

Journal: *The Lancet Infectious Diseases* (https://pubmed.ncbi.nlm.nih.gov/39153488)

INTRODUCTION

- Yellow fever causes significant morbidity and mortality, with recent outbreaks highlighting vaccine shortages
- Current vaccines are effective but rely on century-old egg-based production methods with limited scalability
- The vYF vaccine candidate produced in Vero cells, offers rapid, scalable manufacturing with reduced contamination risk
- Preclinical studies evaluating vYF's immunogenicity and safety in mammalian models support this first-in-human trial to assess safety and immunogenicity



OBJECTIVE

- To report on the safety and immunogenicity of vYF in a North American adult human population with no self-reported history of previous yellow fever infection or vaccination

METHODS

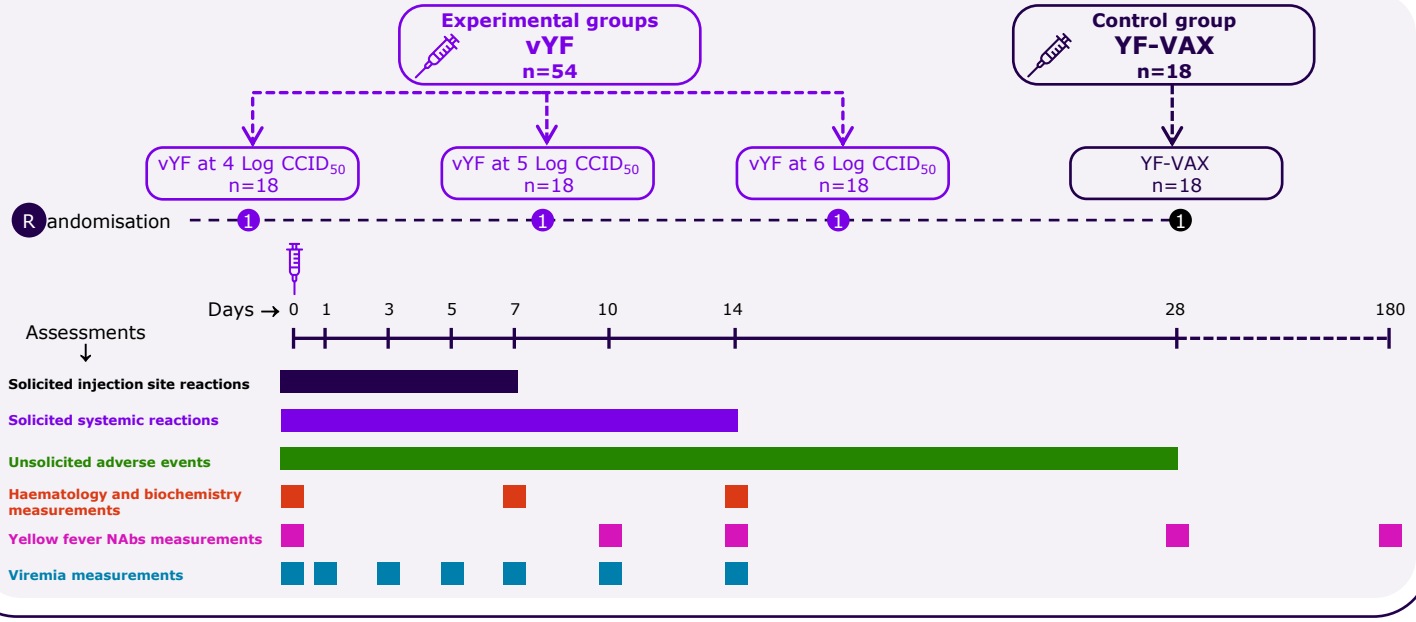
- First in-human phase 1 randomised, observer-blind, active-controlled, dose-ranging clinical trial was conducted at a single centre in the USA (NCT04142086)
- The vYF vaccine candidate (Sanofi, Neuville-sur-Saône, France) is a new live-attenuated YF-17D 204 substrain derived from the YF-VAX (Sanofi, Swiftwater, PA, USA) lineage
- Participants were randomly assigned to receive one dose of vYF at 4 Log $CCID_{50}$, 5 Log $CCID_{50}$, or 6 Log$CCID_{50}$ or YF-VAX (commercial control)

INCLUSION CRITERIA:

- Adults aged 18–60 years

EXCLUSION CRITERIA:

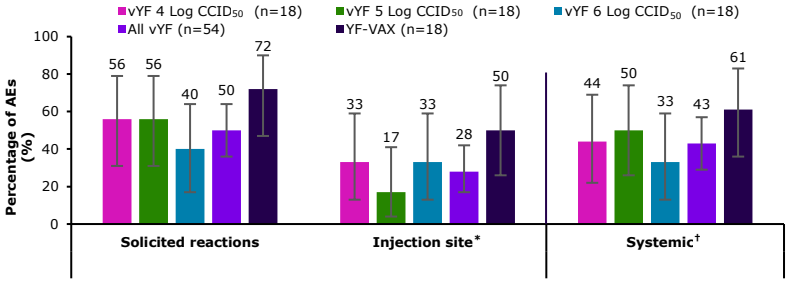
- Participants with a known history or previous vaccination for a flavivirus disease or previously known flavivirus infection
- Known or suspected congenital or acquired immunodeficiency; receipt of immunosuppressive therapy within the preceding 6 months
- Known or suspected HIV infection
- Pregnancy, lactation or not using an effective method of contraception at least 4 weeks before and after vaccination, if of childbearing potential
- Receipt of immune globulins, blood, or blood-derived products in the previous 6 months
- Chronic illness
- Moderate or severe acute illness or infection
- Receipt of any antiviral in the 2 months preceding vaccination and up to 6 weeks after
- Planned travel to yellow fever endemic countries within 6 months of the vaccination



RESULTS

Demographics were well balanced between arms

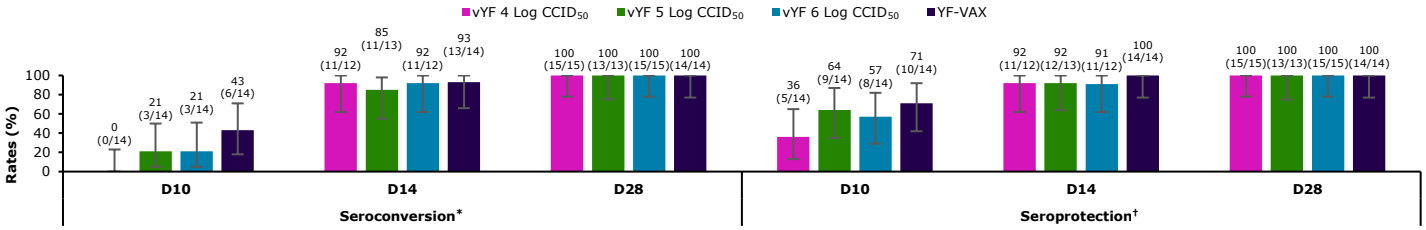
Safety profile of vYF 4, 5, 6 Log $CCID_{50}$ and YF-VAX in the safety analysis set for participants with at least one event (N=72)



Data presented in % and 95% CI. *Within 7 days after vaccination. †Within 14 days after vaccination.

- There were no deaths, serious adverse events, or adverse events of special interest reported during the study through D180 of follow-up
- The overall proportion of solicited reactions was 50% across the vYF groups compared with 72% in the YF-VAX group
- Most frequently reported solicited injection site reactions (vYF groups vs. YF-VAX group): pain (22% vs. 28%) and erythema (13% vs. 39%)
- Most frequently reported solicited systemic reactions (vYF groups vs. YF-VAX group): headache (32% vs. 44%) and malaise (26% vs. 33%)

Seroconversion and seroprotection rates after the yellow fever vaccination in the per-protocol analysis set (yellow fever-naïve participants; N=57)

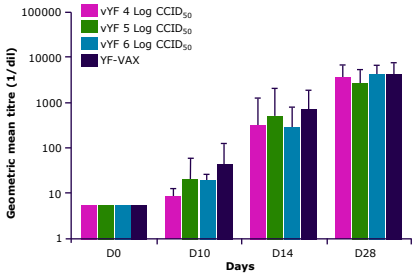


Data presented in %(n/N) and 95% CI. The per-protocol analysis set comprised yellow fever-naive participants who met all protocol-specified inclusion criteria, did not meet any specified exclusion criteria, received the vaccine they were randomised to receive, and provided blood samples within the specified time windows. n=number of participants experiencing the endpoint listed. N=number of participants with available data.
*Seroconversion was defined as at least a four-fold increase in NAb titres compared with pre-vaccination; specifically, if a pre-vaccination titre of less than 10 (1/dil) and post-injection titre of at least 40 (1/dil), or pre-vaccination titres of at least 10 (1/dil) at D0 and at least four-fold rise in titre (1/dil) post-injection.
†Seroprotection was defined as yellow fever NAb titres of at least 10 (1/dil).

- All participants seroconverted by D28 and were seroprotected (NAb titres ≥10 [1/dil])
- **Seroprotection:** 100% (vYF 4 Log), 89% (vYF 5 Log), 100% (vYF 6 Log), and 94% (YF-VAX) remained seroprotected through D180

Geometric mean titres of yellow fever neutralising antibodies in the per-protocol analysis set (yellow fever-naïve participants; N=57)

- Geometric mean titres of yellow fever NAbs increased at post-vaccination timepoints and were similar across all groups
- Waning of NAb titres was observed from D28 through D180, and all YF-naïve participants, but 3, maintained titres above the threshold of seroprotection



Viremia

- Viremia assessed via qRT-PCR was observed in 50 participants, mostly from D4 to D10 post-vaccination in all groups, with levels generally too low to be quantifiable in terms of genome equivalents
- It was more frequently detectable or lasted longer in the vYF 6 Log $CCID_{50}$ and YF-VAX groups
- Viremia detection and clearance guided the selection of the vYF 5 Log $CCID_{50}$ dose for further development over the 6 Log $CCID_{50}$ dose

LIMITATIONS

- The study had a small sample size, typical for a first-in-human phase 1 study, and was not powered for a definitive safety assessment
- The diversity of the study population might not be representative of the overall US population
- Further large-scale studies are needed to better define the safety profile and assess the non-inferiority of vYF to licensed yellow fever vaccines

1 The vYF vaccine candidate produced in a Vero cell line demonstrated a similar safety profile to the licensed YF-VAX vaccine, with no serious adverse events reported

2 All vYF dose groups achieved 100% seroconversion by D28, and most participants remained seroprotected through D180

3 The vYF 5 Log $CCID_{50}$ dose was identified as the optimal dose due to its favorable balance of safety, immunogenicity, and low levels of viremia, supporting its further clinical development

Scan the QR code to access the manuscript

Glossary: AEs, adverse events; CCID, cell culture infectious dose; D, day; HIV, human immunodeficiency virus; NAb, neutralising antibody; vYF, yellow fever vaccine.

References: 1. Modjarrad K, et al. Lancet Infect Dis. 2024; Online ahead of print.

Declaration: This study was funded by Sanofi.

Scan the QR code to access the editorial by Dr. Anna Roukens and Dr. Leo Visser for the manuscript