ORIGINAL ARTICLE

# Phase 1 Trial of a Therapeutic Anti–Yellow Fever Virus Human Antibody

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## ABSTRACT

### BACKGROUND

Insufficient vaccine doses and the lack of therapeutic agents for yellow fever put global health at risk, should this virus emerge from sub-Saharan Africa and South America.

### METHODS

In phase 1a of this clinical trial, we assessed the safety, side-effect profile, and pharmacokinetics of TY014, a fully human IgG1 anti–yellow fever virus monoclonal antibody. In a double-blind, phase 1b clinical trial, we assessed the efficacy of TY014, as compared with placebo, in abrogating viremia related to the administration of live yellow fever vaccine (YF17D-204; Stamaril). The primary safety outcomes were adverse events reported 1 hour after the infusion and throughout the trial. The primary efficacy outcome was the dose of TY014 at which 100% of the participants tested negative for viremia within 48 hours after infusion.

### RESULTS

A total of 27 healthy participants were enrolled in phase 1a, and 10 participants in phase 1b. During phase 1a, TY014 dose escalation to a maximum of 20 mg per kilogram of body weight occurred in 22 participants. During phases 1a and 1b, adverse events within 1 hour after infusion occurred in 1 of 27 participants who received TY014 and in none of the 10 participants who received placebo. At least one adverse event occurred during the trial in 22 participants who received TY014 and in 8 who received placebo. The mean half-life of TY014 was approximately 12.8 days. At 48 hours after the infusion, none of the 5 participants who received the starting dose of TY014 of 2 mg per kilogram had detectable YF17D-204 viremia; these participants remained aviremic throughout the trial. Viremia was observed at 48 hours after the infusion in 2 of 5 participants who received placebo and at 72 hours in 2 more placebo recipients. Symptoms associated with yellow fever vaccine were less frequent in the TY014 group than in the placebo group.

### CONCLUSIONS

This phase 1 trial of TY014 did not identify worrisome safety signals and suggested potential clinical benefit, which requires further assessment in a phase 2 trial. (Funded by Tysana; ClinicalTrials.gov number, NCT03776786.)

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Yellow fever is an acute viral hemorrhagic disease. This disease is caused by the yellow fever virus, which is currently enzootic in the forests of South America and sub-Saharan Africa. Spillover transmission of yellow fever virus from the enzootic cycles into humans is now occurring at increasing frequency, with an estimated 20,000 cases of yellow fever occurring each year.[1] This trend is alarming because large outbreaks of yellow fever have occurred in urban centers in the past, in which transmission by the anthropophilic and highly domesticated *Aedes aegypti* mosquito enabled human–mosquito–human cycles of yellow fever virus transmission. The increased frequency of spillover transmission[2-4] thus threatens to resurrect such urban outbreaks throughout the tropics and wherever *A. aegypti* has gained a foothold, including in parts of the United States.[5] International travelers who were infected with yellow fever virus in Africa and South America have returned to their countries of origin with both the disease and yellow fever virus,[6,7] leading to a risk of further viral transmission. Yellow fever is associated with mortality of 20 to 50%, especially among persons whose infection in the liver is sufficiently extensive to cause liver failure.[1] Yellow fever is thus a major global health concern.

Although a safe and effective vaccine against yellow fever virus is licensed for use, global manufacturing capacity is insufficient to meet surges in demand, especially during outbreaks.[8,9] The vaccine is also contraindicated in infants, in pregnant women, and in persons older than 60 years of age, as well as in immunocompromised persons, because of the increased likelihood of vaccine-induced viscerotropic and neurotropic serious adverse events.[10,11] To date, there is no licensed antiviral therapy against yellow fever virus, so the management of severe disease, especially in these at-risk groups, involves supportive care. There is thus an unmet therapeutic and prophylactic need to manage yellow fever.

TY014, a fully engineered human IgG1 monoclonal antibody against the yellow fever virus, is manufactured with the use of Chinese hamster ovary cells. It specifically targets a conserved epitope on the yellow fever virus envelope (E) protein. Nonclinical in vitro and in vivo studies showed a promising safety profile and efficacy in inhibiting yellow fever virus infection. Given the gap in the pharmacopeia regarding therapies for yellow fever, we explored the potential of TY014 as a postinfection therapy for yellow fever virus infection. We took advantage of the properties of the live attenuated yellow fever vaccine (YF17D-204 strain; referred to here as YF17D), which is one of the most effective licensed vaccines and which elicits detectable viremia in more than 80% of vaccine recipients.[12] It also elicits mild influenza-like symptoms at a median of 6 days after vaccination in approximately half the recipients.[13,14] We thus made use of these features of YF17D to test the safety and efficacy of TY014 in eliminating detectable YF17D viremia as a proof of concept for further clinical development.

## METHODS

### TRIAL OVERSIGHT

The trial was sponsored by Tysana and conducted at a single site at the Singapore Health Services (SingHealth) Investigational Medicine Unit, Singapore. The clinical protocol, which is available with the full text of this article at NEJM.org, was reviewed and approved by the SingHealth Centralized Institutional Review Board and the Health Sciences Authority of Singapore. The trial was designed and supervised by the authors, who vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol. The sponsor had no role in data collection. Data analysis was led by the principal investigator and was conducted jointly with the sponsor. Celerion, a contract research organization that was paid by the sponsor, managed the clinical trial and data collection but had no role in the preparation of the manuscript. A dose-escalation review committee met to review data regarding safety and overall trial progress, as well as to make decisions regarding dose escalations.

### PARTICIPANTS

Participants were eligible for inclusion in the trial if they were between 21 and 50 years of age, had no history of travel to countries where yellow fever is endemic, had not been vaccinated against or had previous exposure to yellow fever virus, and had a stable health status at baseline. Full lists of the inclusion and exclusion criteria are provided in the protocol. Written informed consent was provided by all the participants before enrollment.

### TRIAL DESIGN

This phase 1 trial of TY014 in humans was conducted in two parts (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Early discussions with the regulatory authority (Health Sciences Authority) in Singapore were initiated in July 2018. Once the clinical protocol design was approved by the regulatory authority, an Investigational New Drug (IND) package was submitted to the regulatory authority in October 2018. Concurrently, a clinical trial application was submitted to the SingHealth Centralized Institutional Review Board for ethics review. Approval from both bodies was granted on November 26, 2018.

TY014 was manufactured and packaged in a vial, with 100 mg of TY014 per 5 ml of aqueous buffered vehicle. Placebo was a 250-ml infusion of sodium chloride (Baxter USP, 0.9%). The solution (active treatment or placebo) was administered as a slow intravenous infusion through a peripherally inserted cannula over a period of 30 minutes according to body weight.

The safety phase (phase 1a) was a time-lagged, single-ascending-dose trial of TY014 involving 27 healthy adult participants across five dose cohorts and a placebo group. A double-blind design was applied to the first dose cohort (0.5 mg per kilogram of body weight), which consisted of 7 participants: 2 participants were randomly assigned to receive TY014 and 5 to receive placebo. In phase 1a, the remaining dose cohorts (in which the participants received 2, 5, 10 or 20 mg of TY014 per kilogram) were open-label and consisted of 5 participants each. The safety, side-effect profile, and pharmacokinetics of TY014 were assessed.

The efficacy phase (phase 1b) involved a sequential time-lagged, parallel-group, randomized, placebo-controlled, double-blind, single-ascending-dose trial of TY014. According to the protocol, we planned for up to 40 healthy adult participants to receive a full dose of YF17D (Stamaril) subcutaneously before TY014 or placebo was administered 24 hours later, across the four dose cohorts (2, 5, 10, and 20 mg per kilogram) in a 1:1 ratio. Each dose cohort involved 10 participants, with 5 randomly assigned to receive TY014 and 5 to receive placebo. We assessed safety, the side-effect profile, and the time to aviremia (defined as an absence of YF17D viral growth in cell culture [negative isolation] from a blood sample obtained after the infusion). The trial protocol for phase 1b also specified a priori that if 100% of the participants treated with TY014 in one dose cohort had undetectable viremia according to virus isolation within 48 hours after the infusion, further dose escalation would be stopped for futility.

### PRIMARY OUTCOME MEASURES

#### *Safety Assessment (Phases 1a and 1b)*

The primary outcome measures for the safety and side-effect profile of TY014 were the percentage of participants with adverse events occurring within 1 hour after the completion of the infusion and the percentages of participants with adverse events and severe adverse events throughout the trial, according to dose cohort. All the adverse events (i.e., those listed in the protocol-specified questionnaire and those that were reported spontaneously by the participants) were identified with the use of adverse-event data from case-report forms and were categorized according to the *Medical Dictionary for Regulatory Activities*, version 23.0, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Safety assessments also included the monitoring of clinical laboratory variables, vital signs, 12-lead electrocardiography, and physical examination.

#### *Infectious Viremia (Phase 1b Only)*

The anti–yellow fever virus efficacy of TY014 was evaluated by determining the dose at which all the participants tested negative for viremia as assessed by virus isolation within 48 hours after the administration of TY014. The isolation of YF17D was carried out with the use of a protocol adapted from a previously described method to isolate dengue virus in *A. albopictus*–derived C6/36 cell cultures.[15] Full details of the virus isolation are provided in the Supplemental Methods section in the Supplementary Appendix.

### SECONDARY OUTCOME MEASURES

In the phase 1a trial, the pharmacokinetic variables of TY014 were determined with the use of high-performance liquid chromatography–tandem mass spectrometry. In the phase 1b trial, a previously described reverse-transcriptase–quantitative polymerase-chain-reaction method[16] was used to quantify serum levels of YF17D viral

RNA.[17] The results of this analysis were expressed as $\log_{10}$ genome copies per milliliter. Full details of these assessments are provided in the Supplemental Methods section.

#### EXPLORATORY OUTCOME MEASURES

In the phase 1b trial, the NanoString Human Immunology V2 panel was used to measure gene expression from participants' whole-blood samples, according to the manufacturer's instructions. Data were then analyzed by means of NanoString nSolver software, version 4.0, with the use of hierarchical clustering according to euclidean dissimilarity and average linkage. The bioactivity of circulating TY014 in serum was determined with the use of a plaque reduction neutralization test. Full details of these assessments are provided in the Supplemental Methods section.

#### STATISTICAL ANALYSIS

A sample of five participants in each dose cohort was considered to be sufficient to assess the trial objectives of safety and pharmacokinetics in a typical phase 1 design and was set empirically. For additional safety, a sentinel dose cohort consisted of two participants who received a dose of 0.5 mg of TY014 per kilogram along with five participants who received placebo. No formal sample-size calculation was performed, and the sample size did not provide the trial with sufficient power to show statistical significance in both the safety and efficacy evaluations. Data were summarized according to dose cohort and, where appropriate, according to trial group (TY014 or placebo). Descriptive statistics, frequency counts, and percentages are presented.

The pharmacokinetic variables of TY014, such as the maximum concentration, the time to maximum concentration, the area under the curve (AUC) extrapolated to infinity, the AUC calculated from the time of administration to the last measurable concentration, the half-life, the volume of distribution, and clearance in serum, were calculated with Kinetica software, version 5.0, with the use of noncompartmental methods that were based on serum concentration–time data from individual participants. All the pharmacokinetic variables were analyzed descriptively according to dose cohort. Additional linear regression analysis for all dose cohorts was applied for the AUC and maximum concentration. We conducted the efficacy analysis by comparing the percentage of participants in the TY014 group who had aviremia within 48 hours after the infusion with the percentage in the placebo group.

## RESULTS

#### CHARACTERISTICS OF THE PARTICIPANTS

The first participant underwent screening on November 29, 2018, and was enrolled on December 5, 2018. The trial ended on July 1, 2019. A total of 63 participants underwent screening, and 37 participants were enrolled. Of these 37 participants, 27 were randomly assigned to participate in the phase 1a trial and 10 in the phase 1b trial. In the phase 1a trial, 22 participants were randomly assigned to receive TY014 and 5 to receive placebo. In the phase 1b trial, 5 participants were randomly assigned to receive TY014 and 5 to receive placebo, according to the trial protocol. Details about the randomization and follow-up of the participants are provided in Figure S2. The demographic and clinical characteristics of the participants are outlined in Table S1.

#### SAFETY OUTCOMES

During phases 1a and 1b, adverse events within 1 hour after the infusion were observed in 1 of 27 participants who received TY014 and in none of the 10 participants who received placebo. At least one adverse event occurred during the trial in 22 participants who received TY014 and in 8 who received placebo; at least one serious adverse event occurred during the trial in 1 participant who received TY014 and in no participants who received placebo.

In phase 1a, among 5 participants who received placebo, 3 adverse events were observed in 3 participants during the trial; among 22 participants who received TY014, a total of 18 adverse events were observed in 14 participants during the trial. All these adverse events were graded as being either mild or moderate. One participant (in the cohort that received 10 mg of TY014 per kilogram) had an adverse event (phlebitis with fever) within 1 hour after infusion.

One serious adverse event was reported in a participant in the cohort that received 2 mg of TY014 per kilogram. This participant had asymptomatic premature ventricular contractions, which were noted during cardiac monitoring at 2 hours

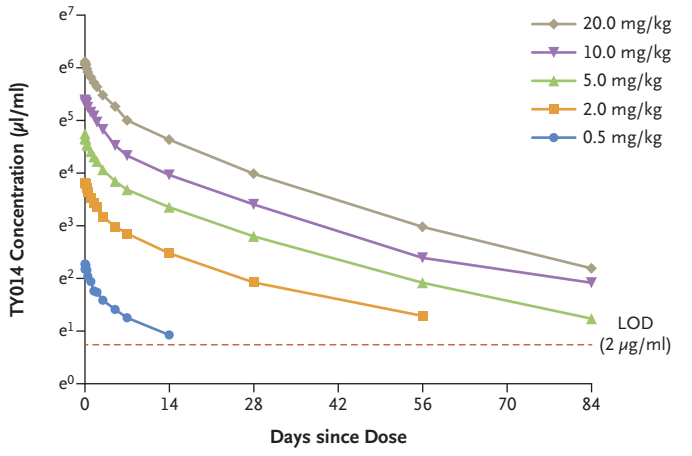


**Figure 1. Pharmacokinetic Profiles of a Single Ascending Dose of TY014 in the Safety Phase of the Trial.**

Serum samples for pharmacokinetic assessment were obtained before the administration of the dose; at 0.5 hours, 1 hour, and 2, 4, 8, 12, 24, 36, 48, 72, and 120 hours; and at 7, 14, 28, 56, and 84 days (symbols). The TY014 concentrations were natural log–transformed and are represented as the mathematical constant "e" on the y axis. The limit of detection (LOD) for the liquid chromatography–mass spectrometry method was 2 μg per milliliter (dashed line). The graphed lines for the cohorts that received 0.5 mg per kilogram or 2.0 mg per kilogram do not continue through the entire graph because values fell below the LOD.

after infusion that had been performed as part of the trial protocol; the adverse event led to hospitalization for further medical evaluation as a secondary precaution. The participant was subsequently found to have an existing benign cardiac abnormality that had not been declared at enrollment. A full listing of the adverse events reported during phase 1a is provided in Table S2.

In phase 1b, among 5 participants who received placebo, 21 adverse events were observed in all 5 participants during the trial; among 5 participants who received TY014, a total of 9 adverse events were observed in 4 participants during the trial. All these adverse events were graded as being either mild or moderate. There was no report of serious adverse events in phase 1b. A full listing of the adverse events reported during phase 1b is provided in Table S4.

### PHARMACOKINETICS OUTCOMES

The pharmacokinetics profile of TY014 across the range of doses tested is shown in Figure 1. The highest concentration of circulating TY014 was reached approximately 1.3 hours after the start of the infusion (Table S3). The pharmacokinetics assessment revealed biphasic concentration-time profiles, showing a multi-exponential disposition with a rapid distribution phase, followed by a slower elimination phase (Fig. 1). The concentration of circulating TY014 increased in an approximately dose-proportional manner across all five doses assessed, revealing linear pharmacokinetics in the dose range of 0.5 to 20 mg per kilogram. The half-life of TY014 ranged from 6.5 to 17.5 days among individual participants across the five dose cohorts.

Clearance rates of TY014 ranged from 2.82 to 5.98 ml per day per kilogram, with a geometric mean weight-adjusted clearance of 4.13 ml per day per kilogram. No meaningful difference was observed in weight-adjusted volume distribution across the five dose cohorts, with values ranging from 54.35 to 85.25 ml per kilogram and with a geometric mean weight-adjusted volume distribution of approximately 72 ml per kilogram (Table S3).

### EFFICACY PHASE

In the assessment of the primary efficacy outcome, viremia was observed in none of the participants who received TY014 and in 2 of the 5 who received placebo (i.e., virus isolation was negative for all 5 participants who received TY014 and for 3 who received placebo) at 48 hours after the infusion (72 hours after the YF17D challenge). By 72 hours after the infusion (96 hours after the YF17D challenge), virus isolation was negative for only 1 participant who received placebo and remained negative for all participants who received TY014 (Fig. 2A). The serum levels of YF17D RNA were uniformly negative in the TY014 group, whereas all the participants who received placebo were positive for YF17D RNA on day 5 after infusion (day 6 after the YF17D challenge) (Fig. 2B). Only 10 participants (those from dose cohort 1) were recruited in phase 1b because all 5 treated participants (100%) had undetectable viremia within 48 hours after the TY014 infusion at a dose of 2 mg per kilogram.

Four participants in the placebo group reported a total of 14 symptoms associated with YF17D infection, as compared with one participant who received TY014. Neutralizing antibody titers against YF17D were assessed at the end of the trial (day 84 after receipt of the dose) by means of the plaque reduction neutralization test. Neutralizing antibodies against YF17D developed in

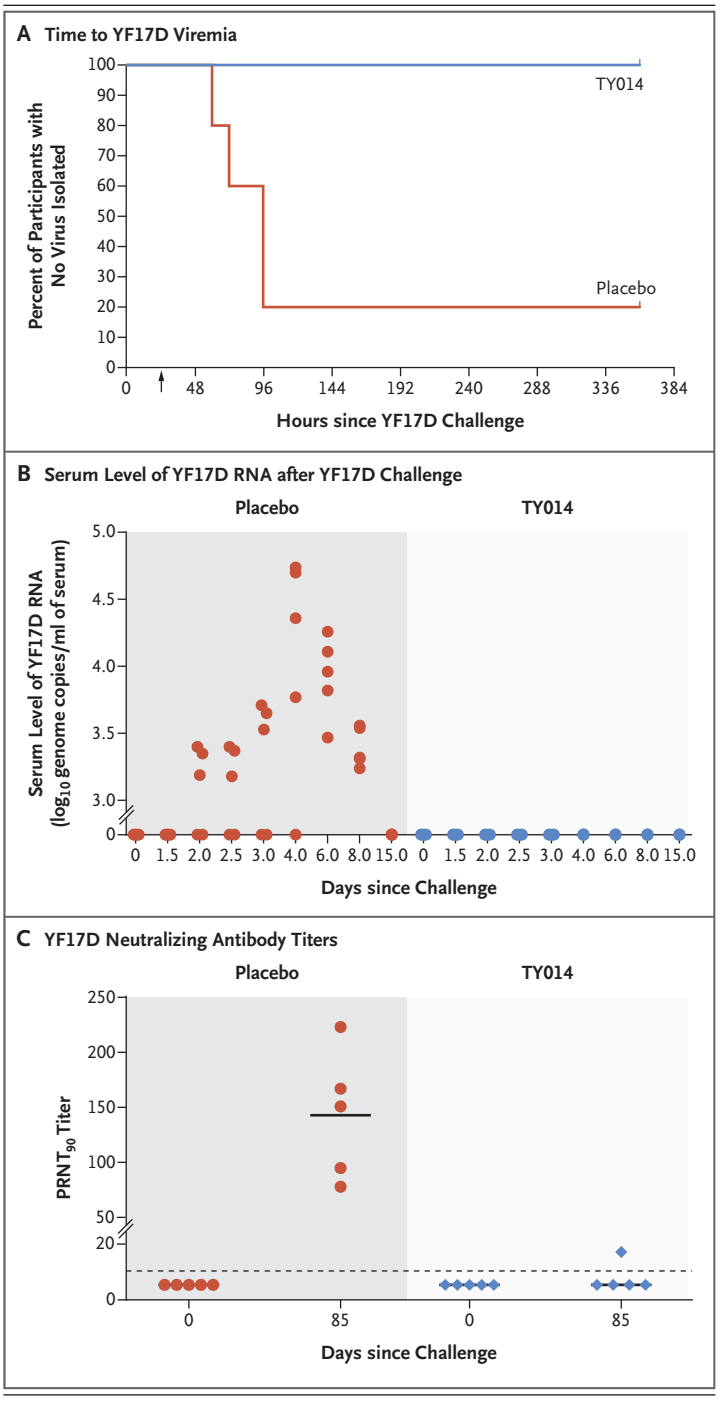


**Figure 2. Pharmacodynamic Outcomes of TY014 in the Efficacy Phase of the Trial.**

The Kaplan–Meier plot shows the percentages of the participants in the TY014 group and the placebo group who were negative for virus isolation after the YF17D challenge (Panel A). TY014 or placebo was administered to the participants 24 hours after the YF17D challenge (arrow). The primary efficacy outcome was the dose of TY014 at which 100% of the participants tested negative for viremia within 48 hours after infusion (72 hours after the challenge). The serum level of YF17D RNA (measured as $\log_{10}$ genome copies per milliliter of serum) was determined with the use of reverse-transcriptase–quantitative polymerase-chain-reaction testing before the challenge and at days 1.5, 2, 2.5, 3, 4, 6, 8, and 15 after the challenge (Panel B). All five participants who received placebo were positive for viral RNA on days 6 and 8 after the YF17D challenge (days 5 and 7, respectively, after receipt of the infusion), with the earliest detected YF17D RNA occurring on day 2 after the YF17D challenge (in three participants on day 1 after the infusion). None of the participants who received TY014 were positive for viral RNA. Neutralizing antibody titers to YF17D at 3 months after infection were assessed by a plaque reduction neutralization test (Panel C). Immunity against YF17D developed at the end of the trial, as an expected outcome of vaccination, in all five participants who received placebo. Low immunity against YF17D (i.e., a titer of 17 on a plaque reduction neutralization test with a cutoff of 90% [$PRNT_{90}$]) developed in one participant who received TY014. None of the participants had received YF17D previously (according to a $PRNT_{90}$ titer, <10; dashed line) before the challenge on day 0. We assigned an arbitrary value of 5 to reflect $PRNT_{90}$ titers that were less than 10 (dotted lines).

all the participants who received placebo, whereas four participants who received TY014 had undetectable levels of neutralizing antibodies against YF17D, as assessed on the plaque reduction neutralization test with a 90% cutoff ($PRNT_{90}$ titer, <10); one participant who received TY014 had a $PRNT_{90}$ titer of 17 against YF17D (Fig. 2C). This finding is consistent with a previously observed correlation between YF17D viremia and an eventual neutralizing antibody titer.[12]

### HOST RESPONSE TO YF17D

We also explored the effect of the administration of TY014 on the host response to YF17D infection. From a panel of 594 immune genes, including 15 housekeeping genes, 24 immune genes were found to be differentially expressed between the TY014 group and the placebo group, starting as early as day 2 after receipt of the dose. All these 24 genes were consistently up-regulated (by a factor of up to 64) across all the participants and time points in the placebo group. By contrast, the expression of these same genes was reduced in the TY014 group and was even down-regulated in one participant in the TY014 group (Fig. S3). A complete heat map of all the genes analyzed

and the gene expression levels ($log_2$ counts) are provided in Figure S4 and Table S5, respectively.

## DISCUSSION

The lack of a therapeutic agent against yellow fever leaves vaccination as the only sustainable and effective measure to prevent the reemergence of epidemic yellow fever that once plagued the Western world.[18] The imposing geographic footprint of *A. aegypti*, which is evident given the annual burden of dengue, also places much of Asia at risk for unprecedented outbreaks of yellow fever. The availability of a therapeutic agent to treat yellow fever would alleviate the stress on global health care systems in managing outbreaks. Moreover, the yellow fever vaccine is also contraindicated in certain population subgroups — namely, infants, pregnant women, the elderly, and immunocompromised persons. A therapeutic agent to treat yellow fever would thus fill gaps in public health that cannot be safely addressed by vaccination alone.

To address these issues, we embarked on a program to develop a therapeutic monoclonal antibody for yellow fever. TY014 was developed with the use of a computational approach to epitope identification and antibody engineering to target a highly conserved epitope on domain II of the yellow fever virus E protein. Although this epitope is a well-known neutralization target among flaviviruses, including related Zika and dengue viruses,[19-21] it is conserved in yellow fever virus but not in other flaviviruses. TY014 neutralized nonmutated yellow fever virus and the YF17D strain in vitro and elicited 100% protection against the YF17D strain in a lethal mouse model, both as prophylaxis and as therapy. Together, these characteristics supported its potential to be an effective candidate therapy for or prophylaxis against yellow fever.

We used the YF17D vaccine as a challenge virus to assess the intervention. The percentages of participants with viremia and the symptomatic outcomes from YF17D vaccination were both consistent with what have been previously reported.[12-14] TY014 was able to abrogate viremia and to reduce the incidence of YF17D-induced symptoms. The virologic and clinical outcomes were further supported by the changes in host response to YF17D vaccination; YF17D infection induces innate immune and proinflammatory response genes in approximately half the recipients of the vaccine, and such responses underpin symptomatic infection.[13,14] Such proinflammatory responses have also been found to be associated with severe yellow fever.[22] The finding that TY014 treatment not only lowered the percentage of patients with detectable viremia but also prevented the induction of such innate immune and proinflammatory response genes, in contrast to the participants who received placebo, further supports the potential of TY014 to alter infection outcome. Likewise, the lack of detectable neutralizing antibody at 1 month after infection suggests that TY014 treatment not only prevented viremia but also abrogated infection in the draining lymph nodes. Collectively, these findings suggest the potential of TY014 as a therapeutic monoclonal antibody to interrupt yellow fever pathogenesis.

The results of this small, phase 1b trial are preliminary, and a phase 2 trial to be conducted in geographic areas in which yellow fever is endemic is needed to assess the efficacy of TY014 as a treatment for this disease. The peak viremia of YF17D on vaccination is significantly lower (by four to five orders of magnitude) than those attained by infection by nonmutated yellow fever virus.[3] Moreover, during a clinical yellow fever virus infection, the administration of the dose would only be initiated several days after infection, when symptoms manifest after an incubation period.[23] In such contexts, a higher dose of TY014 may be needed to reduce yellow fever viremia rapidly and to interrupt disease progression. Because the primary outcome of 100% of the participants testing negative for viremia was observed with the dose of 2 mg per kilogram, the evaluation of the effects of higher doses of TY014 was not conducted in the present trial, as prespecified in the protocol. The findings of this trial justify the further development of TY014 as a prophylaxis against or postexposure treatment for yellow fever.

After the reports of outbreaks of yellow fever in South America in 2017 and 2018, we embarked in mid-March 2018 to develop TY014 against yellow fever in preparation for a potential outbreak in 2019. The average industry standard from DNA sequencing of the monoclonal antibody to the filing of an IND application is approximately 18 to 20 months. To be ready for a potential start of a 2019 outbreak in Brazil in January

2019, we set ourselves a goal of having material for studies involving humans in approximately 9 months. We were able to get from the monoclonal antibody candidate to the filing of the IND application in 7 months and started the trial in December 2018 as planned. This timeframe was possible because of a development process we had put in place that carefully monitored product quality and correlated product quality with safety toxicologic and pharmacokinetic studies using redundant orthogonal analytic methods. This approach enabled a rapid-response strategy of producing a clinical batch of TY014 within 5 months after the initial transfection. This phase 1a–1b trial was completed within approximately 7 months, between the receipt of regulatory approval (November 26, 2018) and the last visit of a participant (July 1, 2019).

Many of the elements of the rapid-response strategy that we used can be extended to other infectious disease indications. The integration of drug discovery, innovative manufacturing processes, and adaptive clinical studies as presented here can reduce timelines for the production of antibody biologic agents for potential pandemic response such as what we are currently encountering with coronavirus disease 2019 (Covid-19). We anticipate that with these advancements, a rapid-response platform that can enable sequence-to-clinic translation of promising antibody biologic agents within 3 months is feasible.

The views expressed in this article are those of the authors and do not necessarily represent the official position of Tysana.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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