

# Preclinical and clinical experience with dupilumab on the correlates of live attenuated vaccines



Michael E. Wechsler, MD,<sup>a</sup> Adelmir Souza-Machado, MD, PhD,<sup>b</sup> Christine Xu, PhD,<sup>c</sup> Xuezhou Mao, PhD,<sup>c</sup> Upender Kapoor, MD, DTCD,<sup>c</sup> Faisal A. Khokhar, MD,<sup>d</sup> John T. O'Malley, MD, PhD,<sup>e</sup> Christopher D. Petro, PhD,<sup>d</sup> Veronica Mas Casullo, MD,<sup>d</sup> Leda P. Mannent, MD,<sup>f</sup> Paul J. Rowe, MD,<sup>c</sup> Juby A. Jacob-Nara, MD, MPH, DHSc,<sup>c</sup> Marcella Ruddy, MD,<sup>d</sup> Elizabeth Laws, PhD,<sup>c</sup> Lisa A. Purcell, PhD,<sup>d\*</sup> and Megan Hardin, MD, MPH<sup>e\*</sup> *Denver, Colo; Salvador, Brazil; Bridgewater, NJ; Tarrytown, NY; Cambridge, Mass; and Chilly-Mazarin, France*

**Background:** The safety and tolerability of live attenuated vaccines in patients administered dupilumab for moderate-to-severe asthma have not been previously evaluated. During the LIBERTY ASTHMA TRAVERSE open-label extension study (ClinicalTrials.gov identifier NCT02134028), a yellow fever outbreak in Brazil required administration of a live attenuated vaccine to at-risk individuals.

**Objective:** Our aim was to evaluate immune response to a live attenuated vaccine in the context of IL-4 receptor blockade (REGN1103, a dupilumab surrogate) in mice and in dupilumab-treated patients with moderate-to-severe asthma who participated in TRAVERSE.

**Methods:** In the preclinical study, mice were coadministered REGN1103/isotype control and live attenuated influenza vaccine/control, followed by influenza virus challenge. During TRAVERSE, 37 patients discontinued dupilumab treatment and were administered 17D live attenuated yellow fever vaccine (YFV). Safety and tolerability data, dupilumab serum concentrations, and plaque reduction neutralization titers before and after vaccination were collected.

**Results:** In the preclinical study, there was no impact of REGN1103 on vaccine efficacy in mice. In TRAVERSE, all 37 patients who received YFV achieved seroprotection despite most having therapeutic levels of dupilumab, with the magnitude of response appearing unrelated to prevaccination dupilumab concentrations. No instances of vaccine-related adverse events or vaccine hypersensitivity were reported in 36 patients; 1 patient reported nonserious body ache, malaise, and dizziness 7 days after vaccination but recovered fully.

**Conclusion:** The preclinical model suggested that dupilumab does not affect the efficacy of live attenuated influenza vaccine. The live attenuated YFV did not raise safety concerns and appeared to be well tolerated in patients with asthma who recently discontinued dupilumab treatment, and dupilumab concentrations had no apparent impact on immunologic response to the vaccine. (J Allergy Clin Immunol Global 2022;1:9-15.)

**Key words:** Asthma, dupilumab, live attenuated vaccine, safety, immunogenicity, yellow fever, mouse model, influenza vaccine

From <sup>a</sup>the Division of Pulmonary, Critical Care and Sleep Medicine, National Jewish Health, Denver; <sup>b</sup>the Universidade Federal da Bahia, Salvador; <sup>c</sup>the Sanofi, Bridgewater; <sup>d</sup>Regeneron Pharmaceuticals, Inc, Tarrytown; and <sup>e</sup>Sanofi, Cambridge; and <sup>f</sup>Sanofi, Chilly-Mazarin.

\*These authors are co-senior authors.

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Corresponding author: Michael E. Wechsler, MD, Department of Medicine, National Jewish Health, 1400 Jackson St, Denver, CO 80206. E-mail: [WechslerM@NJHealth.org](mailto:WechslerM@NJHealth.org). Or: [MikeWechsler@gmail.com](mailto:MikeWechsler@gmail.com).

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Dupilumab, a fully human VelocImmune-derived<sup>1,2</sup> mAb, blocks the shared receptor component (IL-4R $\alpha$ ) for IL-4 and IL-13, which are key and central drivers of type 2 inflammation in multiple diseases.<sup>3,4</sup> Dupilumab is approved for patients with type 2 inflammatory diseases, including atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyps.<sup>5-10</sup>

In the spring of 2016, a yellow fever outbreak in Brazil required administration of yellow fever vaccine (YFV) to people at risk of infection. As the possible effects of dupilumab on live attenuated vaccines have not been studied, at-risk patients who were participating in the ongoing TRAVERSE open-label extension study were instructed to discontinue dupilumab treatment before receiving the YFV. YFV is a live attenuated vaccine that is generally represented as being safe and well tolerated and generates a robust and broad adaptive immune response<sup>11</sup> that can be evaluated by using the plaque reduction neutralization titer (PRNT), which quantifies yellow fever–neutralizing antibodies and is a measure of protection against infection. Most studies show seroconversion in more than 90% of exposed patients. The US Food and Drug Administration approved a log<sub>10</sub> neutralization index higher than 0.7 as a surrogate of protection against yellow fever, and approximately 75% to 100% of patients who receive the YFV have been shown to be seroprotected for at least 10 years after vaccination.<sup>12</sup> Vaccine-related adverse events are typically minor and most commonly include headache, myalgia, low-grade fever, and discomfort at the injection site.<sup>13</sup> Serious

**Abbreviations used**

PRNT: Plaque reduction neutralization titer  
 PRNT<sub>50</sub>: Reciprocal of the highest plaque reduction neutralization titer serum dilution for which the virus infectivity is reduced by 50%  
 YFV: Yellow fever vaccine

adverse effects with YFV are rare; they include YFV-associated neurotropic disease and YFV-associated viscerotropic disease.<sup>14</sup>

Although nonlive vaccination has previously been shown to be unaffected by dupilumab treatment,<sup>15</sup> the potential impact of dupilumab on live attenuated vaccines has not previously been evaluated, and immune response to live vaccines following IL-4R $\alpha$  blockade has not been studied. To better understand the potential impact of dupilumab on the immune response to a live attenuated vaccine, a preclinical study was first conducted to evaluate the response to live attenuated influenza vaccine in the setting of REGN1103, a surrogate dupilumab mouse antibody. We also conducted a *post hoc* analysis using data from patients in the TRAVERSE study who stopped taking dupilumab and were subsequently administered YFV to describe the safety and tolerability of live attenuated YFV.

**METHODS****Preclinical immunization and infection**

All animal procedures were performed in a facility accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International in accordance with protocols approved by the Regeneron Animal Care and Use Committee and the principles outlined in the Guide for the Care and Use of Laboratory Animals by the Institute for Laboratory Animal Resources, National Research Council. From week -5 to week -1, a total of 20 female BALB/c mice (approximately 6 weeks old at the study's start, with 5 mice per treatment group) were administered subcutaneous injections of 25 mg/kg of REGN1103 (a dupilumab mouse homologue) or REGN1094 (isotype control) mAb every week. A quantity of 33  $\mu$ L (equivalent to one-fifth of the human dose of 0.2 mL) of the live attenuated influenza vaccine (FluMist, live attenuated influenza vaccine [MedImmune, Gaithersburg, Md]) or PBS was coadministered intranasally at weeks -4 and -2. The animals underwent influenza virus challenge with 5 times the median lethal dose of the H1N1 A/California/07/2009 influenza virus strain. The virus was administered intranasally at week 0, and survival was subsequently assessed for 2 weeks (Fig 1). After influenza virus challenge, the mice were monitored daily for weight loss and morbidity. The mice that lost 25% or more of their starting weight were considered moribund and were euthanized.

**Clinical study design**

The study participants were taking part in LIBERTY ASTHMA TRAVERSE (NCT02134028) at the time of administration of the YFV. TRAVERSE was a multinational, multicenter, single-arm, open-label extension study evaluating subcutaneously administered dupilumab (300 mg every 2 weeks) for up to 2 years in patients with moderate-to-severe or oral corticosteroid-dependent severe asthma who had previously completed the EXPEDITION (NCT02573233), phase 2b (NCT01854047), QUEST (NCT02414854), or VENTURE (NCT02528214) studies. The patients included in the current analysis were previously enrolled in QUEST or VENTURE and had received either dupilumab (QUEST [200 mg or 300 mg every 2 weeks for 52 weeks] or VENTURE [300 mg every 2 weeks for 24 weeks]) or placebo in these studies.

The study design and methods of the TRAVERSE clinical trial have been reported elsewhere.<sup>16</sup> TRAVERSE was conducted in accordance with the

Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guideline, and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of the patient safety data. The local institutional review board or ethics committee at each study center oversaw trial conduct and documentation. All patients, or their parents or guardians, provided written informed consent before participation in the trial.

**Patients and yellow fever vaccination**

The patient population consisted of patients in the TRAVERSE study who were living in the outbreak-affected areas in Brazil and were administered a live attenuated YFV. Following the yellow fever outbreak, a regional protocol amendment and updated informed consent form were issued, addressing the discontinuation of dupilumab treatment before vaccine receipt and the need for additional blood sampling for drug pharmacokinetics and immunogenicity assessments, as well as prevaccination and postvaccination antibody titers. The patients had discontinued dupilumab treatment for at least 7 days before YFV administration. A single dose of YFV (YF-17D, Stamaril; Sanofi Pasteur, France) was administered in line with local practice guidelines. Blood samples for determination of dupilumab concentrations were collected on or before the vaccination, as well as 28 to 54 days after vaccination, and required additional patient consent. The amounts of blood drawn during the study were 285 mL and 315 mL for 1 year and 2 years of treatment, respectively. Samples were collected in red-top tubes and stored at -20°C to -70°C.

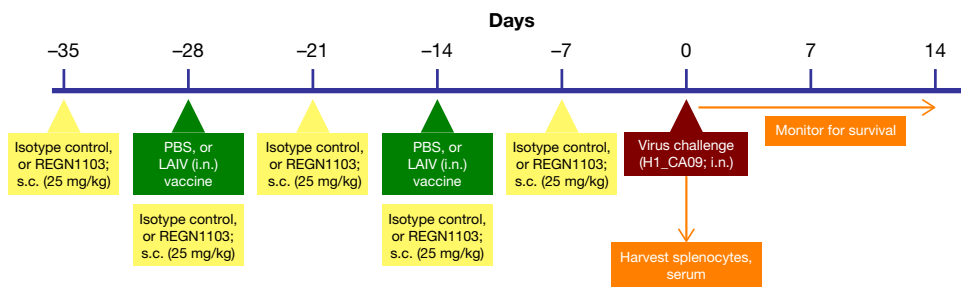
**Clinical outcomes**

**Dupilumab serum concentrations.** Serum concentrations of functional dupilumab were assessed by using a validated ELISA method (Regeneron Pharmaceuticals, Tarrytown, NY) with dupilumab as the assay standard and IL-4R $\alpha$  as the capture reagent.<sup>17,18</sup> Concentrations of dupilumab with 1 or 2 unoccupied binding sites were measured. The lower limit of quantification was 0.078 mg/L. Dupilumab concentrations were anticipated to have reached steady state (the time at which dupilumab intake is equal to dupilumab elimination from the body, resulting in consistent dupilumab concentrations) in patients with asthma by week 24 of the parent study. For the purpose of this evaluation, the mean therapeutic concentration of dupilumab for patients with asthma was considered to be 37.4 mg/L (data not shown).

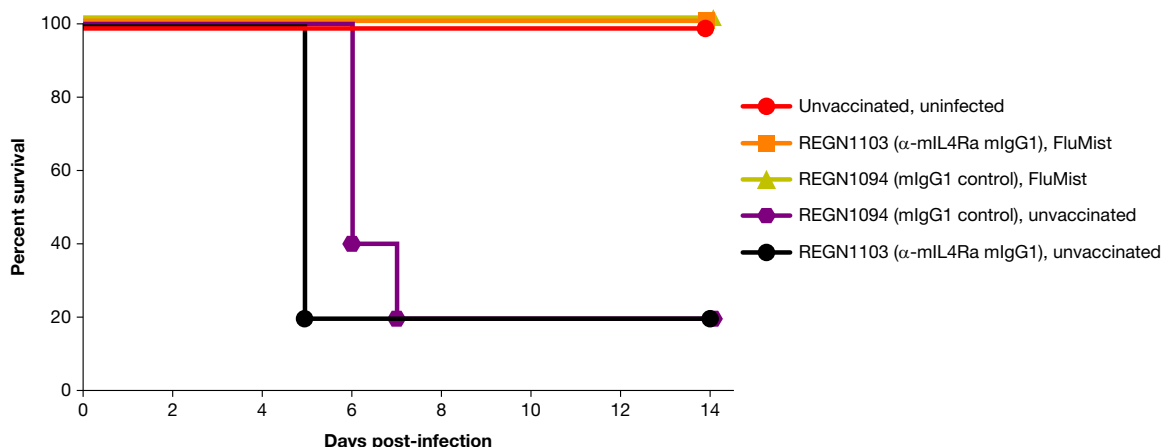
**PRNTs.** The humoral immune response to YFV was determined 28 to 42 days after vaccination by using a PRNT assay (performed externally by Q<sup>2</sup> Solutions, Valencia, Calif) that calculated the reciprocal dilution neutralizing 50% of the virus (PRNT<sub>50</sub>). Seroprotection was defined as a PRNT<sub>50</sub> value higher than 1:10.<sup>13</sup>

**IgG measurements.** Yellow fever-specific antibody responses were measured by using a modified multiplexed Luminex immunoassay with Luminex FLEXMAP 3D and associated xPONENT software, as described previously.<sup>11</sup> Luminex assays provide a semiquantitative measurement; they are not Good Laboratory Practice-validated and were conducted in a research laboratory setting at Regeneron Pharmaceuticals, Inc. For the Luminex assay, yellow fever antigens (Yellow Fever 17D vaccine viral lysate, yellow fever envelope protein, and yellow fever NS1 protein [The Native Antigen Company, Kidlington, United Kingdom]) along with irrelevant proteins (*Felinus domesticus* 1, Vero lysate, and tetanus toxoid [List Biologicals, Campbell, Calif]) as internal negative controls were coupled to fluorescent barcoded MagPlex microspheres (Luminex Corporation, Austin, Tex). Serially diluted human serum samples were then added to the Ag-coupled bead mixture and incubated overnight at 4°C. Antibody-bound beads were detected via phycoerythrin-conjugated anti-human IgG1 (clone HP6001 [Southern Biotech, Birmingham, Ala]), anti-human IgG2 (clone 31-7-4 [Southern Biotech]), anti-human IgG3 (clone HP6050 [Southern Biotech]), anti-human IgG4 (clone HP6025 [Abcam, Cambridge, United Kingdom]), and anti-human IgG (clone JDC-10 [Southern Biotech]). Antibody levels for each antigen-coated bead are represented as the net median fluorescence intensity at a given dilution of serum.

**Statistical analysis.** Descriptive statistics (mean, SD, frequency, and proportion) were used to analyze dupilumab serum concentrations in the



**FIG 1.** Design of the preclinical mouse study. *H1\_CA09*, H1N1 A/California/07/2009 influenza virus strain; *i.n.*, intranasal; *LAIV*, live attenuated influenza vaccine (FluMist); *REGN1103*, dupilumab mouse surrogate; *s.c.*, subcutaneous.



**FIG 2.** Postchallenge survival in mice subjected to a postvaccination influenza virus challenge. *REGN1103*, Dupilumab mouse surrogate–treated animals; *REGN1094*, animals administered isotype control antibodies.

mouse model. Kaplan-Meier analysis was performed to analyze survival following influenza virus challenge.

Descriptive statistics (mean, SD, frequency, and proportion) were used to analyze serum dupilumab concentrations and PRNTs in the 37 patients exposed to the live attenuated YFV. Vaccine safety was evaluated in all 37 patients vaccinated.

**Role of the funding source.** The external authors and study sponsors participated in the study design, data collection, data analysis, data interpretation, and development of the report and gave approval to submit the article for publication. The report was written by an independent medical writing company and funded by the study sponsors. All authors had full access to the study data and had final responsibility for the decision to submit for publication.

## RESULTS

### Preclinical study data

In the murine model evaluating coadministration of a live attenuated influenza vaccine and the *REGN1103* dupilumab surrogate, 1 of 5 of the unvaccinated animals (20%) survived after influenza challenge, whereas there was 100% survival during the 2 weeks after influenza challenge in all vaccinated animals irrespective of whether they were administered *REGN1103* or the isotype control (Fig 2). These results suggest that IL-4R $\alpha$  blockade had no impact on postchallenge survival of mice immunized with the live attenuated influenza vaccine.

The changes in the IgG isotype IgG1, IgG2, and IgG3 titers in response to vaccination were similar irrespective of whether the

mice had received *REGN1103* or the isotype control, whereas the variability in IgA titer appeared higher in mice receiving the control rather than *REGN1103* (see Fig E1 in this article’s Online Repository at [www.jaci-global.org](http://www.jaci-global.org)). Coadministration of *REGN1103* and live attenuated influenza had little effect on the body weight of the mice, whereas the unvaccinated mice administered *REGN1103* lost more than 25% of their body weight by day 5 after infection (see Fig E2 in this article’s Online Repository at [www.jaci-global.org](http://www.jaci-global.org)).

### Clinical study data: Baseline patient characteristics

This analysis includes 37 patients who participated in TRAVERSE and received YFV. Of these patients, 33 were rolled over from the QUEST study and 4 were rolled over from the VENTURE study. Their baseline characteristics were comparable to those of the overall TRAVERSE non–oral corticosteroid–dependent population. The mean patient age was 46.5 years with an SD of 12.0 years (range 24–68 years), and 32.4% of the patients were male (Table I).

### Dupilumab serum concentrations before and after YFV administration

Before YFV administration, patients had been exposed to dupilumab for at least 24 weeks (mean = 0.7 years) and had reached steady state with a mean trough concentration of

**TABLE I.** Patient demographics and disease characteristics

Characteristic	Patients from QUEST		Patients from VENTURE		Combined All (N = 37)
	Placebo/ dupilumab (n = 11)	Dupilumab/ dupilumab (n = 22)	Placebo/ dupilumab (n = 3)	Dupilumab/ dupilumab (n = 1)	
Age (y), mean (SD)	48.1 (11.3)	44.9 (11.8)	47.0 (17.1)	63.0 (NC)	46.5 (12.0)
Min-max	30-65	24-68	33-66	N/A	24-68
Male (%)	5 (45.5)	5 (22.7)	1 (33.3)	1 (100)	12 (32.4)
Dupilumab serum concentration at last visit before yellow fever vaccination (mg/L), mean (SD)	56.4 (41.0)	58.0 (35.8)	85.6 (33.2)	45.2 (NC)	59.5 (36.7)
Min-max	0.039:112	0.039-127	59.4-123	N/A	0.039-127
Race					
White, no. (%)	5 (45.5)	14 (63.6)	2 (66.7)	0	21 (56.8)
Black/of African descent, no. (%)	3 (27.3)	5 (22.7)	1 (33.3)	1 (100)	10 (27.0)
Other, no. (%)	3 (27.3)	3 (13.6)	0	0	6 (16.2)
Ethnicity					
Hispanic, no. (%)	7 (63.6)	17 (77.3)	0	0	24 (64.9)
Not Hispanic, no. (%)	4 (36.4)	5 (22.7)	3 (100)	1 (100)	13 (35.1)
BMI, mean (SD)	31.52 (5.27)	29.52 (6.21)	28.65 (5.64)	30.23 (NC)	30.06 (5.74)
Ongoing atopic medical condition, no. (%)	9 (81.8)	21 (95.5)	3 (100)	1 (100)	34 (91.9)
Ongoing atopic dermatitis, no. (%)	1 (9.1)	2 (9.1)	0	0	3 (8.1)
Ongoing allergic rhinitis, no. (%)	7 (63.6)	21 (95.5)	3 (100)	1 (100)	32 (86.5)
Ongoing chronic rhinosinusitis, no. (%)	2 (18.2)	1 (4.5)	0	0	3 (8.1)
Ongoing hives, no. (%)	1 (9.1)	1 (4.5)	1 (33.3)	0	3 (8.1)
Baseline IgE level $\geq 100$ IU/mL AND $\geq 1$ baseline aeroallergen specific-IgE level $\geq 0.035$ IU/mL, no. (%)	6 (54.5)	14 (63.6)	2 (66.7)	0	22 (59.5)

BMI, Body mass index; N/A, not applicable; NC, not calculated.

73.3 mg/L. Of the 37 patients who received YFV, 35 had dupilumab concentrations measured before the YFV was administered and all 37 had dupilumab concentrations measured after administration of the YFV. The mean interval between prevaccine sampling of dupilumab concentration and YFV administration was 4.3 ( $\pm 6.4$ ) days (range 0-25 days), whereas the mean duration of postvaccine dupilumab concentration sampling was 35.2 ( $\pm 6.4$ ) days (range 28-54 days). The mean interval between the last dose of dupilumab and YFV administration was 22.3 ( $\pm 11.9$ ) days (range 7-51 days). The mean interval between the last administration of dupilumab and the prevaccination sampling of serum dupilumab concentrations was 18.4 ( $\pm 8.5$ ) days (range 7-44 days). The mean prevaccination serum dupilumab concentration was 59.5 mg/L ( $\pm 36.7$  mg/L) (see [Table E1](#) in this article's Online Repository at [www.jaci-global.org](http://www.jaci-global.org)). The mean interval between administration of the last dupilumab dose and collection of the postvaccination serum sample was 57.5 ( $\pm 8.8$ ) days (range 39-79 days), and the mean postvaccination serum dupilumab concentration had decreased to 13.7 mg/L ( $\pm 15.3$  mg/L) (see [Table E1](#)).

### Vaccine-induced humoral immune response

**Yellow fever neutralization titers.** The immune response to YFV administration was assessed by PRNT assay in 37 patients who received the YFV after discontinuation of dupilumab treatment. On the basis of their postvaccination PRNT<sub>50</sub> value, all 37 patients had seroprotective levels of anti-yellow fever antibodies (PRNT<sub>50</sub> > 1:10; mean titer = 1:7699  $\pm$  10951 [[Fig 3](#)]).

Prevaccination PRNT<sub>50</sub> values were available for 23 of the 37 patients ([Table II](#)). After YFV administration, the PRNT<sub>50</sub> value increased in 21 of these 23 patients (91.3%) and remained stable in 2 patients (8.7%) ([Fig 3](#)). Of note, the 2 patients for whom the

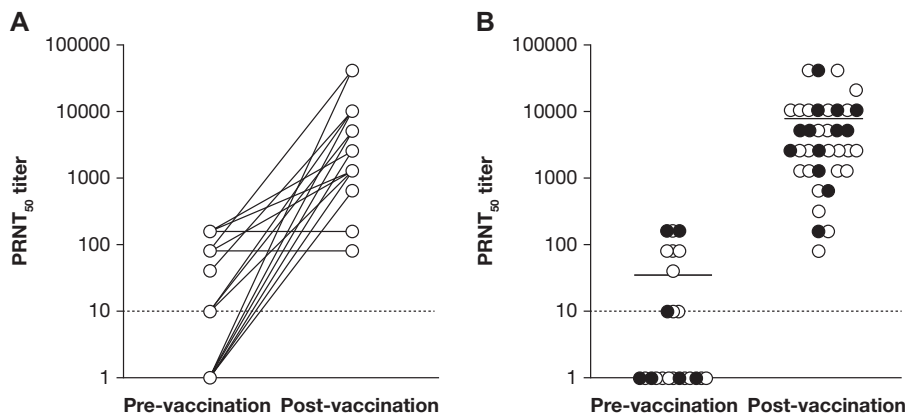
PRNT<sub>50</sub> value did not increase had seroprotective values before vaccine administration.

Of the 23 patients for whom prevaccination and postvaccination PRNT<sub>50</sub> values were available, 15 had available dupilumab serum concentrations on the day of vaccination. Both in the population of 15 patients with same-day data available and in the remaining 8 patients, the vaccine-induced neutralizing antibody response appeared to be independent of prevaccination dupilumab concentration ([Fig 4](#)). The mean prevaccination dupilumab concentration in the subgroup of 15 patients with same-day dupilumab serum concentrations was 76.4 mg/L. Of the 15 patients, 13 (86.7%) had dupilumab concentrations above the steady-state mean trough concentration of 37.4 mg/L.

**Anti-yellow fever antibody responses.** An increased IgG immune response to different yellow fever antigens was observed for all 37 patients, with a median fold change from before to after yellow fever vaccination of 1.2 for YFV lysate (interquartile range [IQR] = 0.9-1.4 [25th and 75th quartile]), 1.4 for yellow fever envelope protein (IQR = 1.1-2.1), and 7.3 for yellow fever NS1 (IQR = 3.5-19.7). There was no observed increase in irrelevant antigens (eg, 1.0 for tetanus toxoid [0.9-1.1]). Additionally, when measuring different yellow fever-specific IgG subclasses, we observed increased IgG1 and IgG3 concentrations but not increased IgG4 concentrations (see [Fig E3](#) in this article's Online Repository at [www.jaci-global.org](http://www.jaci-global.org)).

### Safety

Of the 37 patients administered the YFV, 1 reported a vaccine-related adverse event. The patient reported body ache, malaise, and dizziness that were nonserious and resolved within 2 weeks. There were no reports of vaccine hypersensitivity.



**FIG 3.** PRNT<sub>50</sub> values in patients for whom both pre- and post-yellow fever vaccination data were available (n = 23) (A) and the overall population (N = 37) with available prevaccination and postvaccination neutralizing titers and prevaccination serum dupilumab concentration data (B). B, White circles denote patients with prevaccination dupilumab concentrations lower than the therapeutic concentration of 37.4 mg/L; black circles denote patients with prevaccination dupilumab concentrations of 37.4 mg/L or higher. A prevaccination titer less than 1:10 was used to calculate the titer increase.

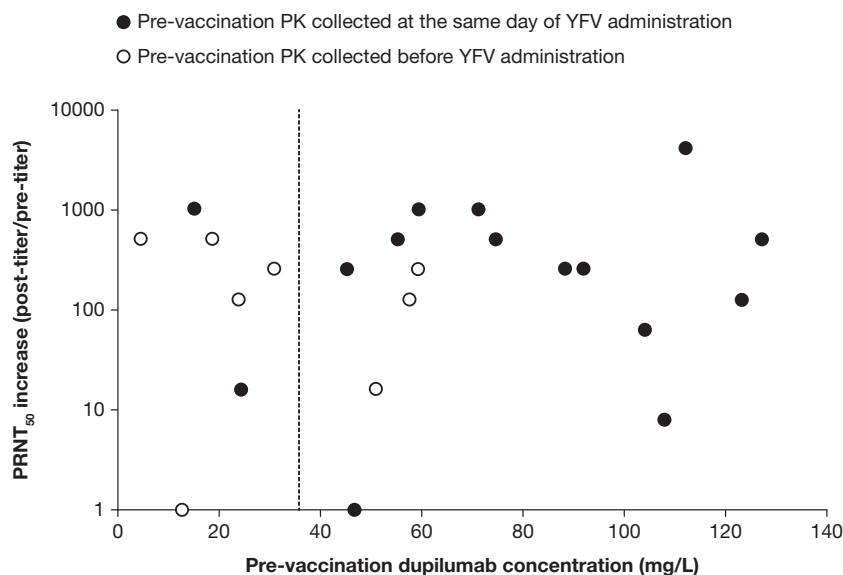
**TABLE II.** Serum dupilumab concentrations and vaccine seroprotection in the study patient populations

No.	Patients with available data on serum dupilumab, no. (%)		Serum dupilumab concentration (mg/L), mean (SD)		Patients with seroprotection (PRNT <sub>50</sub> >1:10), n (%)	
	Before vaccination	After vaccination	Before vaccination	After vaccination	Before vaccination	After vaccination
37*	35 (94.5)	37 (100)	59.5 (36.1)	13.7 (15.3)	N/A	37 (100)
23†	23	23	61.0 (37.2)	12.5 (15.0)	10 (43.5)	23 (100)

N/A, Not available.

\*All patients who discontinued dupilumab treatment and received the YFV for whom postvaccination serum dupilumab concentrations and plaque reduction neutralization titers were available.

†Patient subgroup excluding patients with a missing prevaccination PRNT<sub>50</sub> value.



**FIG 4.** Increase in plaque reduction neutralizing titer serum dupilumab concentrations after vaccination versus before vaccination. The dotted line denotes therapeutic dupilumab concentration (37.4 mg/L). White circles denote patients from whom prevaccination serum dupilumab samples were collected before the day of YFV administration; black circles denote patients from whom prevaccination serum dupilumab samples were collected on the day of vaccination. PK, Pharmacokinetic.

To the sponsor's knowledge, during a mean follow-up period of 186.6 ( $\pm 72.3$ ) days after vaccination (range 98-553 days), there were no cases of yellow fever among the 37 patients assessed.

## DISCUSSION

This article provides preclinical and clinical data to present a descriptive summary of whether the mechanism of action of dupilumab by dual inhibition of IL-4 and IL-13 via IL-4R $\alpha$  blockade potentially affects the safety, tolerability, and efficacy of live attenuated vaccines. Although the exact roles of IL-4 and IL-13 in vaccine-induced immunity are not clear, they are thought to be involved in the immune cell-activating cytokine response that occurs after vaccination and contributes to generation of robust long-term immunity.<sup>15,19</sup>

In a mouse model, survival after an influenza virus challenge was not affected when animals were coadministered a dupilumab surrogate with a live attenuated influenza vaccine. We then evaluated safety and immunogenicity of the YFV in a *post hoc* analysis of a population of dupilumab-treated patients with moderate-to-severe asthma who participated in the LIBERTY ASTHMA TRAVERSE open-label extension clinical trial.

There was no apparent impact on the ability to mount an immune response to live attenuated virus. Of the 37 patients who discontinued dupilumab treatment and were then exposed to YFV, all demonstrated postvaccine yellow fever-neutralizing antibody titers consistent with seroprotection.<sup>20</sup> In all 37 patients, an anti-yellow fever antibody response to various yellow fever antigens was observed in a pattern consistent with an appropriate T<sub>H</sub>1 cell-driven response. These data indicate that dupilumab does not inhibit the production of seroprotective yellow fever-neutralizing antibody titers. In the 13 patients with therapeutic dupilumab concentrations in their serum at the time of vaccination, the vaccine-induced neutralizing antibody response appeared to be independent of prevaccination dupilumab concentrations. All but 1 of these patients showed a boosting of neutralizing antibody titers to yellow fever, and the patient not showing a postvaccination increase in titers was already seropositive before vaccination.

The live attenuated YFV was well tolerated by all exposed patients. Of the 37 patients who received the vaccine, 1 reported a nonserious adverse event of "vaccination complication" (body pain, feeling of malaise, and dizziness), which has been reported in up to 30% of patients following YFV administration.<sup>21</sup> The patient fully recovered within 2 weeks. The 2 patients who were seroprotected before vaccination did not respond to the vaccine inasmuch as their levels of neutralizing antibodies to yellow fever remained stable with no boosting response; however, both patients remained seroprotected after vaccination. Although uncommon, a similar lack of response to YFV in previously seroprotected patients was also observed by Campi-Azevedo et al.<sup>22</sup>

This was a *post hoc* analysis conducted in a convenience sample of patients who were exposed to YFV. Because of the emergent nature of the event, there was some variability in the timing of data collection, and not all pharmacokinetic samples or PRNTs were collected at the same time. Prevaccination neutralizing titers were obtained for 23 patients, and 10 of these patients were seropositive before the YFV administration, suggesting potential prior exposure to virus or previous vaccination. Although there was no placebo arm with which to compare the effect of YFV, the safety and efficacy of this vaccine has been well

described in the literature.<sup>21,23</sup> Although this may limit interpretation of the findings, the overall results suggest that live attenuated vaccines may have acceptable safety and are effective in the setting of dupilumab administration, thus supporting further dedicated study.

In this analysis, we found that the immune response to YFV in all patients was sufficient to be considered immunoprotective, but the study does not allow us to extrapolate this to a potential impact on other live attenuated vaccines or to make more general conclusions regarding immune responses in individuals who have steady-state serum levels of dupilumab at the time of administration of the YFV, as all of the patients had discontinued dupilumab treatment before vaccination.

In conclusion, our clinical data suggest that in the setting of therapeutic serum levels of dupilumab, the live attenuated YFV was effective, demonstrated no safety concerns, and appeared to be well tolerated. Further studies are warranted to investigate the safety, tolerability, and humoral immune response to live attenuated vaccines among patients being treated with dupilumab.

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