Preclinical and Clinical Experience with Dupilumab on the Correlates of Live-Attenuated Vaccines

Michael E. Wechsler, MD, Adelmir Souza-Machado, Professor, Christine Xu, PhD, Xuezhou Mao, PhD, Upender Kapoor, MD, DTCD, Faisal A. Khokhar, MD, John T. O’Malley, MD, PhD, Christopher D. Petro, PhD, Veronica Mas Casullo, MD, Leda P. Mannent, MD, Paul J. Rowe, MD, Juby A. Jacob-Nara, MD, MPH, DHSc, Marcella Ruddy, MD, Elizabeth Laws, PhD, Lisa A. Purcell, PhD, Megan Hardin, MD, MPH

PII: S2772-8293(21)00004-7
DOI: https://doi.org/10.1016/j.jacig.2021.12.003
Reference: JACIG 4
To appear in: Journal of Allergy and Clinical Immunology: Global
Received Date: 8 October 2021
Revised Date: 1 December 2021
Accepted Date: 2 December 2021


This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology.
Preclinical and Clinical Experience with Dupilumab on the Correlates of Live-
Attenuated Vaccines

Michael E. Wechsler, MDa, Adelmir Souza-Machado, Professorb, Christine Xuc, PhD,
Xuezhou Mao, PhDc, Upender Kapoor, MDD, DTCDc, Faisal A. Khokhar, MDd, John T.
O’Malley, MD, PhDd, Christopher D. Petro, PhDd, Veronica Mas Casullo, MDe, Leda P.
Mannent, MDe, Paul J. Rowe, MDe, Juby A. Jacob-Nara, MD, MPH, DHSc, Marcella Ruddy,
MD, Elizabeth Laws, PhDc, Lisa A. Purcell, PhDd, and Megan Hardin, MD, MPH*.

aDivision of Pulmonary, Critical Care and Sleep Medicine, National Jewish Health, Denver,
CO, USA
bUniversidade Federal da Bahia, Salvador, Brazil
cSanofi, Bridgewater, NJ, USA
dRegeneron Pharmaceuticals, Inc., Tarrytown, NY, USA
eSanofi, Cambridge, MA, USA
fSanofi, Chilly-Mazarin, France
*Co-senior authors

Conflicts of interest: M. E. Wechsler reports personal fees from AstraZeneca, Boehringer
Ingelheim, Equillium, Gala Therapeutics, Genentech, Genzyme, Mylan, Novartis, Pulmatrix,
Regeneron Pharmaceuticals, Inc., ResTORbio, Sentien Biotechnologies, Teva; grants and
personal fees from GSK, Sanofi. A. Souza-Machado reports grants from CNPq, GSK,
Sanofi. C. Xu, X. Mao, U. Kapoor, J. T. O’Malley, L. P. Mannent, P. J. Rowe, J. A. Jacob-
Nara, E. Laws, and M. Hardin are employees of Sanofi, and may hold stock and/or stock
options in the company. F. A. Khokhar, C. D. Petro, V. Mas Casullo, and M. Ruddy are
employees and shareholders of Regeneron Pharmaceuticals, Inc. L. A. Purcell is a former
employee and shareholder of Regeneron Pharmaceuticals, Inc.; employee and shareholder
of Vir Biotechnology.
Funding: Research sponsored by Sanofi and Regeneron Pharmaceuticals, Inc.

ClinicalTrials.gov Identifier: NCT02134028. Medical writing and editorial assistance in the development of this manuscript were provided by Jo Mooij, PhD, of Excerpta Medica, and was funded by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc., according to the Good Publication Practice guideline.

Corresponding author: Michael E. Wechsler, MD, Professor of Medicine and Director of the NJH Cohen Family Asthma Institute

Address: Dept. of Medicine, National Jewish Health, 1400 Jackson St, Denver, CO 80206

Phone: 001-617-285-4987

Email: WechslerM@NJHealth.org or MikeWechsler@gmail.com

Key words: Asthma; Dupilumab; Live-attenuated vaccine; Safety; Immunogenicity; Yellow fever; Mouse model; Influenza vaccine

Abbreviations used

IL- Interleukin

LAIV- Live-attenuated Influenza Vaccine

mAb- Monoclonal antibody

PRNT- Plaque-reduction neutralization titers

q2w- Every 2 weeks

SD- Standard deviation

YFV- Yellow fever vaccine
ABSTRACT

BACKGROUND: Safety and tolerability of live-attenuated vaccines in patients administered dupilumab for moderate-to-severe asthma has not been previously evaluated. During the LIBERTY ASTHMA TRAVERSE open-label extension study (NCT02134028), a yellow fever outbreak in Brazil required vaccination with a live-attenuated vaccine of at-risk individuals.

OBJECTIVE: 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 co-administered 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 pre-vaccination dupilumab concentrations. No vaccine-related adverse events or vaccine hypersensitivity were reported in 36 patients; 1 patient reported non-serious body ache, malaise, and dizziness 7 days after vaccination and fully recovered.

CONCLUSION: The preclinical model suggested that dupilumab does not impact 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, and dupilumab concentrations had no apparent impact on the immunologic response to the vaccine.

ClinicalTrials.gov Identifier: NCT02134028
INTRODUCTION

Dupilumab, a fully human VelocImmune®-derived\textsuperscript{1,2} monoclonal antibody (mAb) blocks the shared receptor component (IL-4R\textalpha) for interleukin-4 and interleukin-13, key and central drivers of type 2 inflammation in multiple diseases.\textsuperscript{3,4} Dupilumab is approved for patients with type 2 inflammatory diseases, including atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyps.\textsuperscript{5-10}

In the spring of 2016, a yellow fever outbreak in Brazil required yellow fever vaccine (YFV) administration for people at-risk of infection. As the possible effect of dupilumab on live-attenuated vaccines has not been studied, at risk patients, who were participating in the ongoing TRAVERSE open-label extension study were instructed to discontinue dupilumab treatment to receive YFV. YFV is a live-attenuated vaccine that is generally represented as safe and well-tolerated and generates a robust and broad adaptive immune response,\textsuperscript{11} which can be evaluated using the plaque reduction neutralization test (PRNT\textsubscript{50}), which quantifies yellow fever neutralizing antibodies and is a measure of protection against infection. Most studies show seroconversion in over 90% of exposed patients. The US Food and Drug Administration approved a log\textsubscript{10} neutralization index $> 0.7$ 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 $\geq 10$ years after vaccination.\textsuperscript{12} Vaccine-related adverse events are typically minor and most commonly include headache, myalgia, low-grade fever, and discomfort at the injection site.\textsuperscript{13} Serious adverse effects with YFV are rare, and include YFV-associated neurotropic disease and YFV-associated viscerotropic disease.\textsuperscript{14}

While non-live vaccination has previously been shown to be unaffected by dupilumab treatment,\textsuperscript{15} the potential impact of dupilumab on live-attenuated vaccines has not previously been evaluated, and immune response to live vaccines following IL-4R\textalpha 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 discontinued 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, 20 female BALB/c mice (approximately 6 weeks old at study start, 5 per treatment group) were administered subcutaneous injections of 25 mg/kg REGN1103 (a dupilumab mouse homolog) or REGN1094 (isotype control) monoclonal antibody every week. 33 µL, equivalent to one-fifth of the human dose of 0.2mL, of the live-attenuated influenza vaccine (FluMist, Live-attenuated Influenza Vaccine [LAIV], MedImmune) or phosphate-buffered saline was co-administered intranasally at Weeks −4 and −2. Animals underwent an influenza virus challenge with 5 × LD₅₀ of H1N1 A/California/07/2009 influenza virus strain administered intranasally at Week 0, and survival was subsequently assessed for 2 weeks (Figure 1). After influenza virus challenge, mice were monitored daily for weight loss and morbidity. Mice that lost 25% or more of starting weight were considered moribund and were euthanized.

Clinical study design

Study participants were participating in LIBERTY ASTHMA TRAVERSE (NCT02134028) at the time of yellow fever vaccination. TRAVERSE was a multinational, multicenter, single-arm, open-label extension study evaluating subcutaneous dupilumab 300 mg every 2 weeks (q2w) up to 2 years in patients with moderate-to-severe or oral corticosteroid–dependent severe asthma who previously completed the EXPEDITION (NCT02573233), phase 2b (NCT01854047), QUEST (NCT02414854), or VENTURE (NCT02528214) studies. Patients included in the current analysis were previously enrolled in QUEST or VENTURE and had
received either dupilumab (QUEST: 200 mg or 300 mg q2w for 52 weeks; VENTURE: 300 mg q2w for 24 weeks) or placebo in these studies.

The study design and methods of the TRAVERSE clinical trial have been reported elsewhere. TRAVERSE was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guideline, and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of 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/guardians, provided written informed consent before participating in the trial.

Patients and yellow fever vaccination

The patient population consisted of patients in the TRAVERSE study living in the outbreak-affected areas in Brazil who 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 prior to vaccine receipt, and the need for additional blood sampling for drug pharmacokinetics and immunogenicity assessments, and pre- and post-vaccination antibody titers. Patients had discontinued dupilumab treatment for at least 7 days prior to YFV administration. A single dose of YFV (YF-17D, Stamaril™) was administered in line with local practice guidelines. Blood samples for determination of dupilumab concentrations were collected on or before the vaccination, and 28 to 54 days after vaccination, and required additional patient consent. The amount of blood drawn during the study was 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 to −70 °C.
Clinical outcomes

**Dupilumab serum concentrations**

Concentrations of functional dupilumab in serum were assessed using a validated ELISA method (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) with dupilumab as the assay standard and IL-4Rα as capture reagent. Concentrations of dupilumab with one or two unoccupied binding sites were measured. The lower limit of quantification was 0.078 mg/L. Dupilumab concentrations were anticipated to have reached steady state (time at which dupilumab intake is equal to dupilumab elimination from the body resulting in consistent dupilumab concentrations) in asthma patients by Week 24 of the parent study. For the purpose of this evaluation, mean therapeutic concentrations of dupilumab for patients with asthma were considered to be 37.4 mg/L (Data not shown).

**Plaque reduction neutralization titers**

The humoral immune response to YFV was determined 28 to 42 days after vaccination using a PRNT assay (performed externally by Q2 solutions: Clinical Laboratory Services, LLC) that calculated the reciprocal dilution neutralizing 50% of the virus (PRNT$_{50}$). Seroprotection was defined as a PRNT$_{50}$ of $>1:10$.%

**IgG measurements**

Yellow fever–specific antibody responses were measured through a modified multiplexed Luminex® immunoassay using a Luminex FLEXMAP 3D® and associated xPONENT® software, as described previously. Luminex assays provide a semi-quantitative measurement; they are not Good Laboratory Practice (GLP) 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, yellow fever NS1 protein; The Native Antigen Company) and irrelevant proteins (Fel D 1, Vero lysate, Tetanus Toxoid; List Biologicals) as internal negative controls were coupled to fluorescent-barcoded MagPlex® microspheres (Luminex Corporation). 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 PE-conjugated anti-human IgG1 (Clone HP6001; Southern Biotech), anti-human IgG2 (Clone 31-7-4; Southern Biotech), anti-human IgG3 (Clone HP6050; Southern Biotech), anti-human IgG4 (Clone HP6025; abcam), 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, standard deviation [SD], frequency, and proportion) were used to analyze dupilumab serum concentrations in the mouse model. Kaplan–Meier analysis was performed to analyze survival upon 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 manuscript for publication. The report was written by an independent medical writing company, 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 co-administration of a live-attenuated influenza vaccine and the REGN1103 dupilumab surrogate, one out of 5 (20%) of the unvaccinated animals survived after influenza challenge, whereas there was 100% survival during the 2 weeks post-influenza challenge in all vaccinated animals, irrespective of whether they were administered REGN1103 or isotype control (Figure 2). These results suggest that IL-4Rα blockade had no impact on post-challenge survival of mice immunized with the live-attenuated influenza vaccine.

Changes in IgG isotypes IgG1, IgG2, and IgG3 titers in response to vaccination were similar irrespective of whether or not mice had received REGN1103 or isotype control, whereas the variability in IgA titer appeared higher in mice receiving control rather than REGN1103 (see Figure E1 in this article’s Online Repository at https://jaci-global.org). Co-administration of REGN1103 and live-attenuated influenza had little effect on mice bodyweight whereas unvaccinated mice administered REGN1103 lost more than 25% of their body weight by Day 5 post-infection (see Figure E2 in this article’s Online Repository at https://jaci-global.org).

Clinical study data: baseline patient characteristics

This analysis includes 37 patients who participated in TRAVERSE and received YFV. Of these, 33 were rolled over from the QUEST study and four were rolled over from the VENTURE study. Baseline characteristics were comparable to the overall TRAVERSE non-oral corticosteroid-dependent population. Mean (SD) patient age was 46.5 (12.0) years (range 24 to 68), and 32.4% were male (Table I).
Dupilumab serum concentrations pre- and post-yellow fever vaccination

Prior to 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 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 YFV. The mean (SD) duration between pre-vaccine sampling of dupilumab concentration and YFV was 4.3 (6.4) days, range 0 to 25 days, while the mean duration of post-vaccine dupilumab concentration sampling was 35.2 (6.4) days, range 28 to 54 days. The mean (SD) interval between the last dose of dupilumab and YFV administration was 22.3 (11.9) days (range 7-51 days). The mean (SD) interval between the last dupilumab administration and the pre-vaccination sampling of serum dupilumab concentrations was 18.4 (8.5) days (range 7-44 days). The mean (SD) pre-vaccination serum dupilumab concentration was 59.5 (±36.7) mg/L (see Table E1 in this article’s Online Repository at https://jaci-global.org ). The mean (SD) interval between the last dupilumab administration and the post-vaccination serum sample was 57.5 (8.8) days (range 39-79 days), and the mean (SD) post-vaccination serum dupilumab concentration had decreased to 13.7 (±15.3) mg/L (see Table E1 in this article’s Online Repository at https://jaci-global.org ).

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. All 37 patients had seroprotective levels of anti-yellow fever antibodies based on their post-vaccination PRNT50 (PRNT50 > 1:10; mean titer 1:7699 ± 10951, Figure 3). Pre-vaccination PRNT50 were available for 23 of 37 patients (Table II). After YFV administration, PRNT50 increased in 21 (91.3%) of these 23 patients and remained stable in
two patients (8.7%) (Figure 3). Of note, the two patients for whom PRNT$_{50}$ did not increase had seroprotective values prior to vaccine administration.

Of the 23 patients for whom pre- and post-vaccination PRNT$_{50}$ were available, dupilumab serum concentrations on the day of vaccination were available for 15 patients. Both in the population of 15 patients with same-day data available and in the remaining eight patients, the vaccine-induced neutralizing antibody response appeared independent of pre-vaccination dupilumab concentrations (Figure 4). The mean pre-vaccination dupilumab concentration in the subgroup of 15 patients with same-day dupilumab serum concentrations was 76.4 mg/L. Thirteen (86.7%) of the 15 patients 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 median fold change from pre- to post-yellow fever vaccination of 1.2 for YFV lysate (0.9-1.4, 25th and 75th quartile), 1.4 for yellow fever envelope protein (1.1-2.1) and 7.3 for yellow fever NS1 (3.5-19.7). There was no observed increase in irrelevant antigens, for example 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 IgG4 concentrations (see Figure E3 in this article’s Online Repository at https://jaci-global.org).

_Safety_

Out of the 37 patients administered the YFV, one patient reported a vaccine-related adverse event. The patient reported body ache, malaise, and dizziness that was non-serious and resolved within 2 weeks. There were no reports of vaccine hypersensitivity. During a mean (SD) follow-up period of 186.6 (72.3) days after vaccination (range 98-553), to the sponsor’s knowledge, there were no cases of yellow fever among the 37 patients assessed.
This manuscript 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-4Rα blockade potentially impacts the safety, tolerability and efficacy of live-attenuated vaccines. While 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 post-vaccination and contributes to generating robust long-term immunity.\

In a mouse model, survival after an influenza virus challenge was not affected when animals were co-administered 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. Among the 37 patients who discontinued dupilumab treatment and were then exposed to YFV, all demonstrated post-vaccine yellow fever neutralizing antibody titers consistent with seroprotection. In all 37 patients, anti-yellow fever antibody response to various yellow fever antigens was observed, in a pattern consistent with an appropriate Th1-driven response. These data indicate that dupilumab does not appear to inhibit the production of seroprotective yellow fever neutralizing antibody titers. Among the 13 patients with therapeutic dupilumab concentrations in serum at the time of vaccination, the vaccine-induced neutralizing antibody response appeared to be independent of pre-vaccination dupilumab concentrations. All but one of these patients showed a boosting of neutralizing antibody titers to yellow fever, and the patient not showing a post-vaccination increase in titers was already seropositive prior to vaccination.

The live-attenuated YFV was well tolerated by all exposed patients. Of the 37 patients who received the vaccine, one patient reported a non-serious 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. The patient fully recovered within 2 weeks.
Two patients who were seroprotected pre-vaccination did not respond to the vaccine inasmuch as neutralizing antibodies to yellow fever remained stable with no boosting response; however, both patients remained seroprotected post-vaccination. While uncommon, a similar lack of response to YFV in previously sero-protected patients was also observed by Campi-Azevedo et al.23

This was a post hoc analysis conducted in a convenience sample of patients who were exposed to YFV. Due to 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. Pre-vaccination 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.22,24 While this may limit interpretation of the findings, the overall results suggest that live-attenuated vaccines may have acceptable safety and effective in the setting of dupilumab administration and support 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 on immune responses in individuals who have steady-state serum levels of dupilumab at the time of the YFV as all patients had discontinued dupilumab prior to 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 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.
CONTRIBUTORS

In the preclinical study LAP contributed to the conception and design of the study. CDP acquired data and performed the statistical analyses.

In the clinical study MH, LM, EL, MR, NA, CX, XM, JO, MW, and LAP contributed to the conception and design of the study. LAP and CDP contributed to the in vitro assays design and acquisition of data for the YFV clinical samples. CX acquired data and performed the statistical analyses.

All authors participated in the interpretation of the data, provided critical feedback and final approval for submission, and took responsibility for the accuracy, completeness, and protocol adherence of data and analyses. All investigators had confidentiality agreements with the sponsors.
REFERENCES


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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients from QUEST</th>
<th>Patients from VENTURE</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo/Dupilumab</td>
<td>Dupilumab/Dupilumab</td>
<td>Placebo/Dupilumab</td>
</tr>
<tr>
<td></td>
<td>(n = 11)</td>
<td>(n = 22)</td>
<td>(n = 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>48.1 (11.3)</td>
<td>44.9 (11.8)</td>
<td>47.0 (17.1)</td>
</tr>
<tr>
<td>Min : Max</td>
<td>30 : 65</td>
<td>24 : 68</td>
<td>33 : 66</td>
</tr>
<tr>
<td>Male (%)</td>
<td>5 (45.5)</td>
<td>5 (22.7)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Dupilumab serum concentration at last visit before yellow fever</td>
<td>56.4 (41.0)</td>
<td>58.0 (35.8)</td>
<td>85.6 (33.2)</td>
</tr>
<tr>
<td>Min : Max</td>
<td>0.039 : 112</td>
<td>0.039 : 127</td>
<td>59.4 : 123</td>
</tr>
<tr>
<td>Race</td>
<td>Caucasian/White, n (%)</td>
<td>5 (45.5)</td>
<td>14 (63.6)</td>
</tr>
<tr>
<td></td>
<td>Black/of African descent, n (%)</td>
<td>3 (27.3)</td>
<td>5 (22.7)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Other, n (%)</td>
<td>Hispanic, n (%)</td>
<td>Not Hispanic, n (%)</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------</td>
<td>-----------------</td>
<td>--------------------</td>
</tr>
<tr>
<td></td>
<td>3 (27.3)</td>
<td>7 (63.6)</td>
<td>4 (36.4)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td>3 (13.6)</td>
<td>17 (77.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 baseline aeroallergen</td>
<td>specific-IgE ≥ 0.035</td>
<td>IU/mL,</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*BMI*, body mass index; *IgE*, immunoglobulin E; *IU*, international units; *NA*, not applicable; *NC*, not calculated; *SD*, standard deviation.
Table II. Serum dupilumab concentrations and vaccine seroprotection in the study patient populations

<table>
<thead>
<tr>
<th>N</th>
<th>Pre-vaccination</th>
<th>Post-vaccination</th>
<th>Serum dupilumab concentration mg/L, mean (SD)</th>
<th>Patients with seroprotection (PRNT$_{50}$ &gt;1:10), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td></td>
<td>Pre-vaccination</td>
<td>Post-vaccination</td>
</tr>
<tr>
<td>37*</td>
<td>35 (94.5)</td>
<td>37 (100)</td>
<td>59.5 (36.1)</td>
<td>13.7 (15.3)</td>
</tr>
<tr>
<td>23†</td>
<td>23</td>
<td>23</td>
<td>61.0 (37.2)</td>
<td>12.5 (15.0)</td>
</tr>
</tbody>
</table>

N/A, not available; PRNT$_{50}$, plaque-reduction neutralization titers; SD, standard deviation.

*All patients who discontinued dupilumab and received the yellow fever vaccination for whom post-vaccination serum dupilumab concentrations and plaque-reduction neutralization titers were available.

†Patient subgroup excluding patients with missing pre-vaccination PRNT$_{50}$.
147–7–14
–35

Virus challenge
(H1_CA09; i.n.)

Isotype control, or REGN1103; s.c. (25 mg/kg)

Monitor for survival

PBS, or LAIV (i.n.) vaccine

Isotype control, or REGN1103; s.c. (25 mg/kg)

Harvest splenocytes, serum

Isotype control, or REGN1103; s.c. (25 mg/kg)

Isotype control, or REGN1103; s.c. (25 mg/kg)

Isotype control, or REGN1103; s.c. (25 mg/kg)
Unvaccinated, uninfected
REGN1103 (α-mIL4Ra mlgG1), unvaccinated
REGN1103 (α-mIL4Ra mlgG1), FluMist
REGN1094 (mlgG1 control), FluMist
REGN1094 (mlgG1 control), unvaccinated
REGN1103 (α-mIL4Ra mlgG1), unvaccinated
- Pre-vaccination PK collected before YFV administration
- Pre-vaccination PK collected at the same day of YFV administration

**Graph:**
- **Y-axis:** PRNT$_{50}$ increase (post-titer/pre-titer)
- **X-axis:** Pre-vaccination dupilumab concentration (mg/L)

The graph shows a scatter plot with two types of data points:
- Black filled circles represent pre-vaccination PK collected before YFV administration.
- White open circles represent pre-vaccination PK collected at the same day of YFV administration.