Original Article

Long-Term Safety of Dupilumab in Patients With Moderate-to-Severe Asthma: TRAVERSE Continuation Study

Jorge F. Maspero, MD[a], Anju T. Peters, MD[b], Kenneth R. Chapman, MD[c], Christian Domingo, MD[d], John Stewart, MSc[e], Megan Hardin, MD[f], Jaman Maroni, MD[g], Kelsey Tawo, MD[h], Faisal A. Khokhar, MD[g], Eric Mortensen, MD[g], Elizabeth Laws, PhD[h], Amr Radwan, MD[g], Juby A. Jacob-Nara, MD[h], Yamo Deniz, MD[g], and Paul J. Rowe, MD[h] *Buenos Aires, Argentina; Chicago, Ill; Toronto, ON, Canada; Barcelona, Spain; Montreal, QC, Canada; Cambridge, Mass; Tarrytown, NY; and Bridgewater, NJ*

What is already known about this topic? Efficacy and safety of dupilumab, an mAb blocking type 2 inflammatory cytokines, IL-4/IL-13, has been demonstrated for up to 3 years in adults and adolescents with moderate to severe asthma in previous clinical trials.

What does this article add to our knowledge? The TRAVERSE continuation study extended safety findings up to an additional 3 years in patients with moderate to severe asthma who completed TRAVERSE. Findings were consistent with previous dupilumab asthma studies and the known dupilumab safety profile.

How does this study impact current management guidelines? These findings further support the safety of long-term use of dupilumab in patients with moderate to severe asthma.

BACKGROUND: Previous clinical trials have demonstrated dupilumab efficacy and safety in adults and adolescents with moderate to severe asthma for up to 3 years.

OBJECTIVE: The TRAVERSE continuation study (NCT03620747), a single-arm, open-label study, assessed safety and tolerability of dupilumab 300 mg every 2 weeks up to an additional 144 weeks (~3 years) in patients with moderate to severe asthma who previously completed TRAVERSE (NCT02134028).

METHODS: Primary end points were incidence and event rates per 100 patient-years of treatment-emergent adverse events (TEAEs). Secondary end points included adverse events (AEs) of special interest, serious AEs, and AEs leading to study discontinuation.

RESULTS: A total of 393 patients participated in the TRAVERSE continuation study (cumulative dupilumab exposure, 431.7 patient-years; median treatment duration, 309 days). A total of 29 patients (7.4%) received more than 958 days

[a]Fundación CIDEA, Buenos Aires, Argentina
[b]Northwestern University Feinberg School of Medicine, Chicago, Ill
[c]University of Toronto, Toronto, ON, Canada
[d]Corporació Sanitària Parc Taulí, Sabadell, Autonomous University of Barcelona, Barcelona, Spain
[e]Sanofi, Montreal, QC, Canada
[f]Sanofi, Cambridge, Mass
[g]Regeneron Pharmaceuticals, Inc., Tarrytown, NY
[h]Sanofi, Bridgewater, NJ

This research was sponsored by Sanofi and Regeneron Pharmaceuticals, Inc (ClinicalTrials.gov Identifiers: NCT02134028 and NCT03620747). Medical writing/editorial assistance was provided by Jo Mooij, PhD, and Stephen Horan, MSc, of Excerpta Medica, and was funded by Sanofi and Regeneron Pharmaceuticals, Inc, according to the Good Publication Practice guidelines.

Conflicts of interest: J. F. Maspero has served as a consultant for AstraZeneca and Sanofi; has received speaker fees from GlaxoSmithKline (GSK), Menarini, Novartis, and Uriach; and research grants from Novartis. A. T. Peters has served as a consultant for Optinose, Regeneron Pharmaceuticals, Inc, and Sanofi; and received research support from AstraZeneca, Regeneron Pharmaceuticals, Inc, and Sanofi. K. R. Chapman has received grants and personal fees from AstraZeneca, Boehringer Ingelheim, CSL Behring, Genentech, Grifols, Kamada, Mereo BioPharma, Novartis, Roche, and Sanofi; grants from Amgen, Baxter, and GSK; and personal fees from the CIHR-GlaxoSmithKline Research Chair in Respiratory Health Care Delivery, Merck, and UHN. C. Domingo has received travel and speaker fees from ALK, Allergy Therapeutics, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Esteve, Ferrer Pharma, GSK, HAL Allergy, ImmunoTek, Menarini, Novartis, Pfizer, Sanofi-Aventis, Stallergenes Greer, Takeda, and Teva. J. Stewart, M. Hardin, K. Tawo, E. Laws, J. A. Jacob-Nara, and P. J. Rowe are all employees of Sanofi and may hold stock and/or stock options in the company. J. Maroni, F. A. Khokhar, A. Radwan, and Y. Deniz are employees and shareholders of Regeneron Pharmaceuticals, Inc. E. Mortensen is a previous employee and shareholder of Regeneron Pharmaceuticals, Inc.

Received for publication May 31, 2023; revised November 22, 2023; accepted for publication December 24, 2023.

Available online December 30, 2023.

Corresponding author: Jorge F. Maspero, MD, Fundación CIDEA, Paraguay 2035 3° Cuerpo 2° Subsuelo, (C1121ABE) Ciudad de Buenos Aires, Buenos Aires, Argentina. E-mail: jorge.maspero@fundacioncidea.org.ar.

2213-2198

© 2024 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

https://doi.org/10.1016/j.jaip.2023.12.043

Abbreviations used
100PY- 100 patient-years
AE- adverse event
AESI- adverse event of special interest
COVID-19- coronavirus disease 2019
OCS- oral corticosteroid
PY- patient-year
SAE- serious adverse event
TEAE- treatment-emergent adverse event

of treatment. A total of 214 (54.5%) patients reported at least 1 TEAE (event rate: 171.4); 37 (9.4%) experienced at least 1 treatment-related TEAE, none of which were considered severe; 2 patients reported 6 TEAEs of moderate intensity. A total of 22 (5.6%) patients reported serious AEs (event rate: 6.9). AEs of special interest were reported in 24 patients (6.1%; event rate: 6.0). Five (1.3%) deaths occurred (event rate: 1.2) following serious AEs of coronavirus disease 2019 (COVID-19)—related pneumonia (3 patients), pancreatitis (1 patient), and pulmonary embolism (1 patient). None of the TEAEs leading to death were considered treatment-related. CONCLUSIONS: Dupilumab treatment was well tolerated for up to an additional 3 years. Safety findings were consistent with the known safety profile of dupilumab. These findings further support the long-term use of dupilumab in patients with moderate to severe asthma. **© 2024 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).** **(J Allergy Clin Immunol Pract 2024;12:991-7)**

Key words: *Asthma; Moderate to severe; Long-term; Safety; Adverse events; Dupilumab*

INTRODUCTION

Asthma is a heterogeneous chronic inflammatory disease of the airways characterized by airway hyperresponsiveness, chronic inflammation, acute and chronic bronchoconstriction, airway edema, and mucus plugging. Uncontrolled asthma increases the risk of severe exacerbations and may lead to progressive loss of lung function.[1,2]

Type 2 inflammation, characterized by elevated blood eosinophils or exhaled nitric oxide, is present in more than 70% of patients with severe asthma.[3] Dupilumab, a fully human VelocImmune-derived[4,5] mAb, blocks the shared receptor component for IL-4 and IL-13, key drivers of type 2 inflammation in multiple diseases, thus inhibiting their signaling.[6,7] Dupilumab is approved by the European Medicines Agency and the US Food and Drug Administration for patients with type 2 inflammatory diseases including atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis, and prurigo nodularis.[8,9] However, dupilumab is not commercially available for all indications worldwide or in all European countries.

In the phase 2b (NCT01854047) and phase 3 LIBERTY ASTHMA QUEST (NCT02414854) studies, add-on dupilumab 200 mg and 300 mg every 2 weeks versus placebo reduced annualized rate of severe exacerbations and improved prebronchodilator FEV_1 in patients with non—oral corticosteroid (OCS)-dependent, uncontrolled, moderate to severe asthma.[10,11] In the phase 3 LIBERTY ASTHMA VENTURE study (NCT02528214), add-on dupilumab 300 mg every 2 weeks versus placebo reduced daily OCS dose while reducing the rate of severe exacerbations and improving prebronchodilator FEV_1 in patients with OCS-dependent severe asthma.[12]

Dupilumab was generally well tolerated in these studies. In patients with non—OCS-dependent moderate to severe asthma (phase 2b and QUEST studies), the incidence of adverse events (AEs) was similar across treatment arms (75%-83% of patients receiving dupilumab and 75%-83% on placebo across both studies). Injection-site reactions were somewhat higher in patients on dupilumab (17%-18%) versus placebo (5%-13%)[10,11] Most instances of elevated eosinophil counts were laboratory findings without clinical consequence or associated AEs. In patients with OCS-dependent severe asthma (VENTURE), the incidence of AEs was similar across treatment arms (dupilumab: 62% vs placebo: 64%). Similarly to phase 2b and QUEST, the incidence of injection-site reactions was somewhat higher in the dupilumab treatment arm (9%) than in patients on placebo (4%).[12] A transient increase in median blood eosinophil counts was observed in patients who received dupilumab,[10-12] consistent with the hypothesis that dupilumab, by blocking IL-4/IL-13 signaling, affects eosinophil survival and recruitment to tissues but not their egress from bone marrow, leading to an increased number of circulating blood eosinophils.[7]

TRAVERSE (NCT02134028) was a single-arm, open-label extension study to evaluate the long-term safety and tolerability of dupilumab added on to standard-of-care background controller therapy up to 96 weeks in adult and adolescent patients with moderate to severe asthma who had participated in a previous dupilumab asthma study (phase 2b,[10] phase 3 QUEST,[11] phase 3 VENTURE[12]). Safety findings from TRAVERSE were similar to those from the parent studies and consistent with the known dupilumab safety profile. The efficacy observed in the parent studies was sustained for up to an additional 96 weeks, with a low exacerbation rate and maintenance of lung function improvement.[13] Blood eosinophil counts gradually decreased over the treatment duration up to 96 weeks.[13]

The phase 3b TRAVERSE continuation study (NCT03620747) was an open-label, interventional, outpatient, prospective, multinational, multicenter, noncomparative, single-arm study that evaluated long-term safety in patients with moderate to severe asthma who had previously completed TRAVERSE for a further 3 years.

METHODS

Study design

The phase 3b TRAVERSE continuation study was an open-label, interventional cohort study conducted in 123 study centers in 10 countries (Argentina, Belgium, Canada, France, Germany, Israel, Japan, the Netherlands, South Africa, and the United States), to evaluate the long-term safety of dupilumab in patients with moderate to severe or OCS-dependent severe asthma who had completed the TRAVERSE open-label extension study.[13] The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded

TABLE I. Incidence rates and event rates for AESI over the study

PT*	Patients, n (n of events)	Incidence rate, % (95% CI)	Event rate per 100 PYs (95% CI)
Any class	24 (26)	6.1 (3.91-9.09)	6.0 (4.40-7.99)
Influenza	7 (7)	1.8 (0.72-3.67)	1.6 (0.81-2.78)
COVID-19 pneumonia	3 (4)	0.8 (0.16-2.23)	0.9 (0.35-1.97)
Herpes zoster	3 (3)	0.8 (0.16-2.23)	0.7 (0.23-1.62)
Oral herpes	3 (3)	0.8 (0.16-2.23)	0.7 (0.23-1.62)
COVID-19	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Anaphylactic reaction	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Bronchitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Pneumonia	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Pregnancy	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Respiratory failure	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Urinary tract infection	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Viral upper respiratory tract infection	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)

MedDRA, Medical Dictionary for Regulatory Activities; *PT*, MedDRA Preferred Term.
*Events in this category were reported according to the PTs in MedDRA Version 24.1.

monitoring of patient safety data. Local institutional review boards or ethics committees at each study center oversaw trial conduct and approved all documents for each individual trial center. All patients or their parents/guardians provided written informed consent before participating in the trial. Pediatric patients provided assent according to the Ethics Committee (Institutional Review Board/Independent Ethics Committee)-approved standard practice for pediatric patients at each participating center.

Patients enrolled from parent studies phase 2b,[10] phase 3 QUEST,[11] and phase 3 VENTURE[12] who had completed the TRAVERSE open-label, extension study[13] could volunteer to participate in the TRAVERSE continuation study. Patients were maintained on a background dose of medium- or high-dose inhaled corticosteroids that was stable from TRAVERSE in combination with a second controller (and/or OCSs for those patients from the original parent study VENTURE). Patients requiring a third controller medication were allowed (eg, long-acting β_2-agonist[s], leukotriene receptor antagonist[s], and methylxanthines). Patients were excluded if they were current smokers or had quit smoking within 6 months before enrollment, or had a clinically significant comorbidity or lung disease other than asthma. Patients were also excluded if they had received the following medications in the 3 months before enrollment: anti-IgE therapy, biologic therapy other than dupilumab, systemic immunosuppressants, intravenous immunoglobulin therapy, nonselective β-adrenergic blockers, live/attenuated vaccines, or other investigational drugs.

All eligible patients enrolled in the TRAVERSE continuation study received 300 mg dupilumab every 2 weeks administered subcutaneously over a maximum of 144 weeks (~3 years). Patients who had discontinued treatment for 6 or more weeks after TRAVERSE received a 600-mg loading dose at visit 1. For the purpose of this long-term continuation study and to reduce the burden on patients participating in the trial for more than 3 years, a simplified study design was adopted, focusing on long-term clinical safety and late-onset events. Safety monitoring included collection of AEs, serious adverse events (SAEs), and adverse events of special interest (AESIs, as listed in Table I).

Outcomes

The primary safety end point was the incidence rates defined as the percentage of patients reporting any treatment-emergent adverse events (TEAEs) and event rates per 100 patient-years (100 PYs). Secondary end points included incidence and event rates per 100 PYs for AESI over the study, incidence rates for SAE/death over the study, and incidence rates for AEs leading to study discontinuation over the study.

Statistical analysis

Continuous data were summarized using the number of available data (n), mean, SD, median, minimum, and maximum. Categorical and ordinal data were summarized using number and percentage of patients. For categorical variables, patients with missing data were not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data was presented. All safety analyses were performed on the safety population, which is defined as all patients who received at least 1 dose or part of a dose of dupilumab during this study.

The primary end point was analyzed through incidence rates (percentage of patients reporting any TEAEs) and event rates (number of TEAE events per 100 PYs). Incidence rates of TEAEs with corresponding 95% CI by the Clopper-Pearson method were calculated. Event rates per 100 patient-years (PY) of TEAE with corresponding 95% CI (2-sided exact Poisson CIs) were calculated. Incidence rates with corresponding 95% CI (Clopper-Pearson method) and event rates with corresponding 95% CI (exact Poisson method) were presented for AESIs using the same methodology used in the analysis of the primary safety end points. Incidence rates with corresponding 95% CI (Clopper-Pearson method) were presented for SAE/death and for AEs leading to study discontinuation over the study period.

RESULTS

Between August 30, 2018, and February 18, 2022, 393 patients were enrolled at 123 sites; 374 (95.2%) completed study treatment, and 19 (4.8%) discontinued treatment (Figure 1). Of those who participated and were exposed to dupilumab in TRAVERSE and the TRAVERSE continuation study, 60 were patients with non−OCS-dependent moderate to severe asthma from phase 2b (51 dupilumab/dupilumab, 9 placebo/dupilumab), 300 were patients with non−OCS-dependent moderate to severe asthma from QUEST (203 dupilumab/dupilumab, 97 placebo/dupilumab), and 25 were patients with OCS-dependent

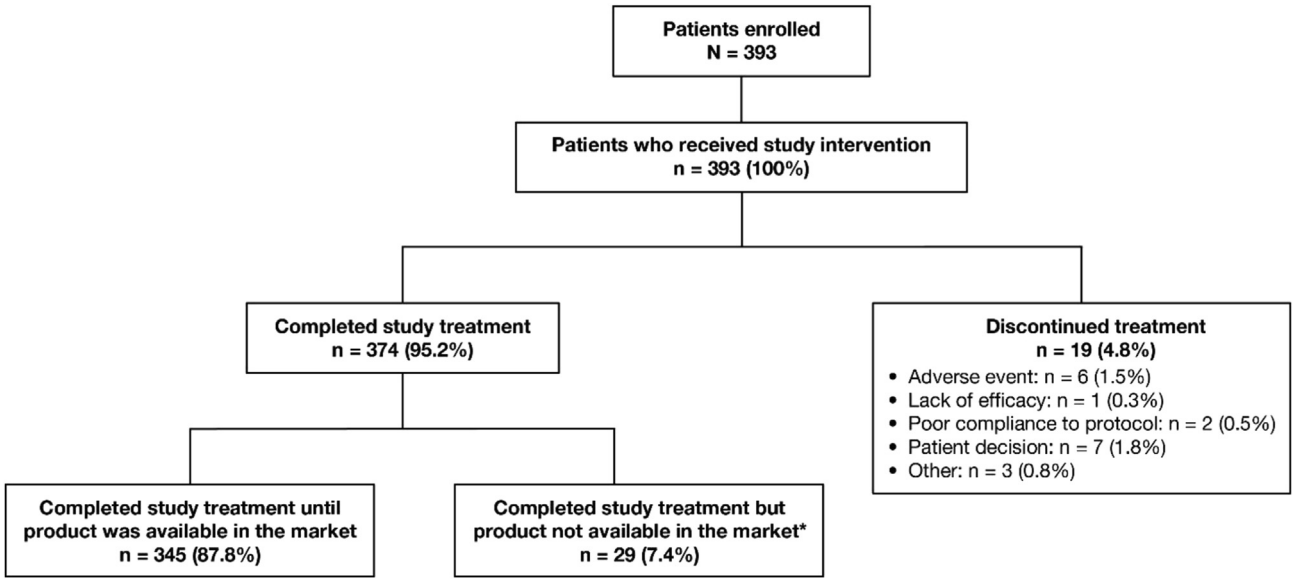

FIGURE 1. Patient disposition. n, number of patients meeting the criterion; N, number of patients in the analysis set. *Confirmed by treatment exposure duration (≥143 weeks). Percentages were calculated using the number of patients enrolled as denominator. No patients from the EXPEDITION study have been included.

TABLE II. Baseline characteristics

Characteristic	N (%)	Mean ± SD
Age (y)	393	52.1 ± 14.2
Sex		
Male	162 (41.2)	—
Female	231 (58.8)	—
Weight (kg)	360	78.82 ± 19.6
BMI (kg/m^2)	353	29.09 ± 6.4
Smoking status		
Never	316 (80.4)	—
Former	77 (19.6)	—
Enrolled within 4 wk of TRAVERSE	54 (13.7)	—
Not enrolled within 4 wk of TRAVERSE	339 (86.3)	—
Race, n (%)		
Caucasian/White	270 (68.7)	—
Black/African American	11 (2.8)	—
Asian/Oriental	105 (26.7)	
American Indian or Alaska Native	1 (0.3)	
Other	6 (1.5)	
Atopic dermatitis	29 (7.4)	—
Nasal polyps	35 (8.9)	—

BMI, Body mass index; *EXPEDITION*, NCT02573233; *SD*, standard deviation. No patients from the EXPEDITION study have been included.

severe asthma from VENTURE (13 dupilumab/dupilumab, 12 placebo/dupilumab). Among the 385 patients in the parent studies, 183 (47.5%) were on medium-dose inhaled corticosteroids and 200 (51.9%) were on high-dose inhaled corticosteroids at the parent study baseline.

Cumulative exposure to dupilumab during the TRAVERSE continuation study was 431.7 PYs. The median study treatment duration was 309 days (range, 25-1047 days). Approximately half the patients enrolled received treatment for 286 days or more, and 29 patients (7.4%) had treatment exposure of more than 958 days. The overall cumulative exposure to dupilumab from the parent study to the TRAVERSE continuation study was 902.3 PYs in the dupilumab/dupilumab group and 393.5 PYs in the placebo/dupilumab group. Cumulative exposure to treatment by parent study is listed in Table E1 in this article's Online Repository at www.jaci-inpractice.org.

Among the 393 patients enrolled, the mean age was 52.1 years at TRAVERSE continuation study baseline (Table II), with most patients (77.9%) aged between 18 and 65 years. There were 8 (2.0%) adolescent patients aged 12 to less than 18 years. More than half the patients (58.8%) were female. Mean weight at baseline was 78.8 ± 19.6 kg, and 136 (38.5%) patients had a body mass index greater than or equal to 30 kg/m^2 at baseline. A total of 77 (19.6%) patients were former smokers (<10 pack-years) at time of enrollment, and 316 (80.4%) patients had never smoked. Fifty-four (13.7%) patients enrolled within 4 weeks after ending the parent study. The time gap off dupilumab treatment between completion of the TRAVERSE study and the start of the TRAVERSE continuation study was mean 393.2 ± 296.9 days. Patients who had received prohibited concomitant treatment within 3 months before enrollment were excluded (see the Methods section).

Overall, 214 (54.5%) patients experienced at least 1 TEAE (740 events) and 37 (9.4%) patients experienced at least 1 TEAE considered treatment-related by the investigator (125 events) (Table III). The most frequently occurring TEAEs were asthma in 54 (13.7%) patients, nasopharyngitis in 33 (8.4%) patients, coronavirus disease 2019 (COVID-19) infection in 25 (6.4%) patients, upper respiratory tract infections in 15 (3.8%) patients, bronchitis in 14 (3.6%) patients, back pain in 13 (3.3%) patients, influenza in 12 (3.1%) patients, arthralgia in 10 (2.5%) patients, injection-site erythema in 10 (2.5%) patients, and headache in 8 (2.0%) patients (Figure 2; see Table E2 in this

TABLE III. TEAE overview and incidence and event rates for TEAE over the study

Category	Patients, n (n of events)	Incidence rate, %	Event rate per 100 PYs
Patients with at least 1 TEAE	214 (740)	54.5	171.4
Patients with at least 1 AESI	24 (26)	6.1	6.0
Patients with at least 1 treatment-related TEAE	37 (125)	9.4	29.0
Patients with at least 1 treatment-emergent SAE	22 (30)	5.6	6.9
Patients with at least 1 TEAE leading to death	5 (5)	1.3	1.2
Patients with at least 1 TEAE leading to definitive treatment discontinuation	5 (5)*	1.3	1.2
Patients with at least 1 TEAE leading to study discontinuation	5 (5)*	1.3	1.2

*One patient who experienced a fatal event of pulmonary embolism was not recorded by the investigator as a TEAE leading to treatment discontinuation or study discontinuation and therefore does not appear in this table.

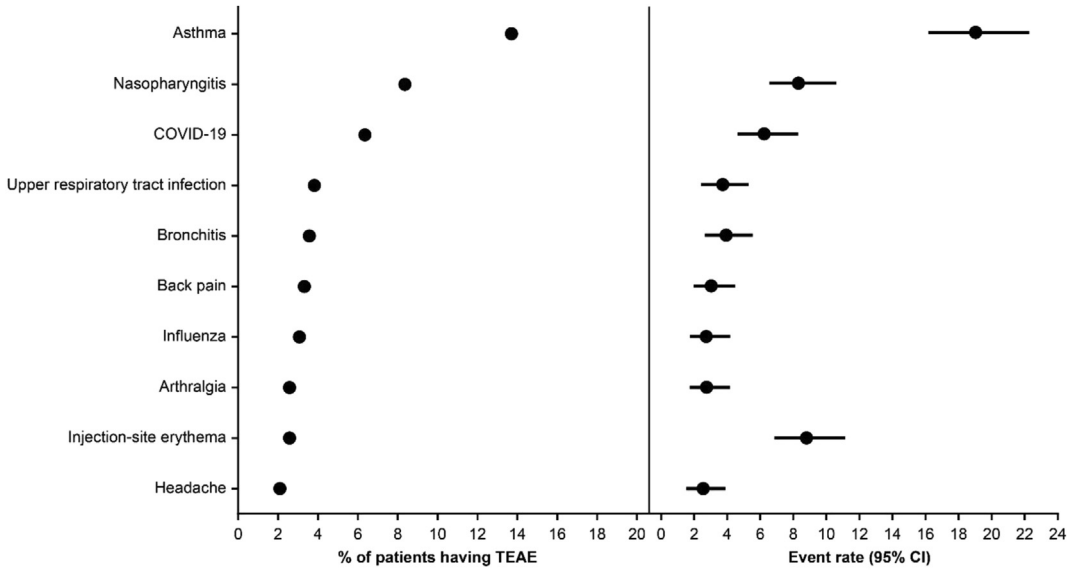

FIGURE 2. The most frequent adverse events and event rates for TEAEs occurring in greater than or equal to 2% of patients. *MedDRA*, Medical Dictionary for Regulatory Activities; *PT*, MedDRA Preferred Term. *By PT, MedDRA Version 24.1. Percentages were calculated using the total number of patients at risk (ie, the safety population) as the denominator. Event rates per 100 PYs and corresponding 95% 2-sided exact Poisson CIs were calculated as number of TEAEs/number of 100 PYs at follow-up.

article's Online Repository at www.jaci-inpractice.org). Of the 37 patients who experienced at least 1 TEAE considered treatment-related, 2 reported 6 TEAEs of moderate intensity. One patient had 2 events of clinically significant decreased platelet counts, 1 event of injection-site erythema, 1 event of decreased neutrophil count, and 1 event of decreased white blood cell count considered clinically significant. Another patient reported 1 event of asthma exacerbation. None of these events led to treatment discontinuation. One patient experienced a moderate TEAE of eosinophilia, which was considered not related to study treatment by the investigator and was fully resolved while on therapy. Among the 214 patients who experienced TEAEs, 2 were adolescents who experienced injection-site induration, neither of which led to death or were considered an SAE or AESI by the investigator.

Five patients reported TEAEs that led to treatment discontinuation and study discontinuation: 3 (0.8%) patients with COVID-19 pneumonia, 1 (0.3%) with pancreatitis, and 1 (0.3%) who became pregnant (Table IV). One patient who experienced a fatal AE of pulmonary embolism was not reported by the investigator as having a TEAE leading to treatment discontinuation or study discontinuation (ie, the status of "drug withdrawn," which defined treatment or study discontinuation in the trial, did not apply), and therefore was not included in these categories.

Overall, 22 (5.6%) patients experienced at least 1 SAE (Table V). The exposure-adjusted event rate was 6.9 per 100 PYs. The most commonly reported SAEs were asthma exacerbation (n = 5 [1.0%]) and COVID-19 and COVID-19 pneumonia (both n = 3 [0.8%]). There were 5 (1.3%) patients who experienced an SAE resulting in death: 3 (0.8%) experienced a fatal SAE of pneumonia due to COVID-19, 1 (0.3%) experienced an SAE of pancreatitis leading to death, and 1 experienced an SAE of pulmonary embolism that resulted in death. None of the TEAEs leading to death were considered treatment-related by the investigator.

AESIs were experienced by 24 (6.1%) patients (Table I). The exposure-adjusted event rate was 6.0 per 100 PYs. AESIs that occurred most frequently were influenza (n = 7 [1.8%]), COVID-19 pneumonia (n = 3 [0.8%]), herpes zoster (n = 3 [0.8%]), and oral herpes (n = 3 [0.8%]).

TABLE IV. Incidence and event rates for AE leading to study discontinuation* over the study

SOC PT†	Patients, n (n of events)	Incidence rate, % (95% CI)	Event rate per 100 PYs (95% CI)
Infections and infestations	3 (3)	0.8 (0.16-2.23)	0.7 (0.23-1.62)
COVID-19 pneumonia	3 (3)	0.8 (0.16-2.23)	0.7 (0.23-1.62)
Gastrointestinal disorders	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Pancreatitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Pregnancy, puerperium, and perinatal conditions	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Pregnancy	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)

MedDRA, Medical Dictionary for Regulatory Activities; *PT*, MedDRA Preferred Term; *SOC*, MedDRA System Organ Class.
*One patient who experienced a fatal AE of pulmonary embolism was not recorded by the investigator as a TEAE leading to treatment discontinuation or study discontinuation, and therefore does not appear in this table.
†Events in this category were reported according to the SOCs and PTs in MedDRA Version 24.1.

TABLE V. Incidence and event rates for SAE over the study

SOC PT*	Patients, n (n of events)	Incidence rate, % (95% CI)	Event rate per 100 PYs (95% CI)
Any class	22 (30)	5.6 (3.51-8.48)	6.9 (5.21-9.03)
Infections and infestations	9 (9)	2.3 (1.05-4.35)	2.1 (1.16-3.36)
Bronchitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Pneumonia	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Urinary tract infection	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
COVID-19	3 (3)	0.8 (0.16-2.23)	0.7 (0.23-1.62)
COVID-19 pneumonia	3 (3)	0.8 (0.16-2.23)	0.7 (0.23-1.62)
Immune system disorders	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Anaphylactic reaction	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Nervous system disorders	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Pudendal canal syndrome	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Epilepsy	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Eye disorders	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Cataract	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Cardiac disorders	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Myocardial infarction	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Cardiac failure congestive	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Respiratory, thoracic, and mediastinal disorders	5 (8)	1.3 (0.41-2.97)	1.9 (1.04-3.13)
Asthma	4 (5)	1.0 (0.28-2.61)	1.2 (0.46-2.20)
Pulmonary embolism	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Respiratory failure	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Tracheal stenosis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Gastrointestinal disorders	4 (4)	1.0 (0.28-2.61)	0.9 (0.35-1.97)
Hiatus hernia	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Pancreatitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Enterovesical fistula	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Abdominal pain	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Hepatobiliary disorders	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Cholecystitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Pregnancy, puerperium, and perinatal conditions	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Abortion spontaneous	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
General disorders and administration-site conditions	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Noncardiac chest pain	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)

MedDRA, Medical Dictionary for Regulatory Activities; *PT*, MedDRA Preferred Term; *SOC*, MedDRA System Organ Class.
*Events in this category were reported according to the SOCs and PTs in MedDRA Version 24.1.

DISCUSSION

In this phase 3b, open-label, interventional cohort study designed to evaluate long-term safety of dupilumab in adult and adolescent patients with moderate to severe asthma who had previously completed the TRAVERSE open-label extension study, previous safety findings were extended up to 3 years, for a cumulative dupilumab exposure of 431.7 PYs. Some patients in the study, who were randomized to receive dupilumab during

QUEST and continued to TRAVERSE and the TRAVERSE continuation study, had total durations of exposure of nearly 7 years. Of the 393 patients who were enrolled in this study, 214 (54.5%) experienced at least 1 TEAE, with an event rate of 171.4 per 100 PYs. The proportion of patients reporting TEAEs throughout the TRAVERSE continuation study was lower than that observed in the parent studies, which ranged from 76.3% to 94.7%.[10-13] There were 37 (9.4%) patients who experienced at least 1 TEAE considered treatment-related. None of the treatment-related TEAEs were considered severe, and 2 of these patients reported 6 TEAEs of moderate intensity.

No new patterns in incidence of TEAEs were observed in this study. The most frequent TEAEs were asthma exacerbation in 13.7% of patients, nasopharyngitis in 8.4% of patients, and COVID-19 infection in 6.4% of patients. The most frequently reported SAEs were asthma exacerbation in 1.0% of patients and COVID-19 and COVID-19 pneumonia in 0.8% of patients each. These were similar to the results in the parent studies, in which the most frequently reported TEAEs were nasopharyngitis (17.5%-25.9%), injection-site erythema (2.2%-23.4%), and bronchitis (9.3%-19.0%), and the most frequently reported SAEs were asthma exacerbations (0.5%-3.6%) and pneumonia (0.7%-2.7%).[10-13] Asthma exacerbations and nasopharyngitis are not unexpected in this population of patients with moderate to severe asthma. Early-onset side effects would have been reported during the parent studies. Here, it is of note that the safety profile and tolerability observed during long-term treatment for an additional 3 years in the TRAVERSE continuation study was consistent with that initially observed for up to 3 years throughout the phase 2b, QUEST, VENTURE, and TRAVERSE studies, thus affirming the overall long-term safety and tolerability of dupilumab.

Only 1 case each of treatment-emergent SAE—cataract (Medical Dictionary for Regulatory Activities Preferred Term) under the Medical Dictionary for Regulatory Activities System Organ Class "eye disorders" and anaphylactic reaction (Medical Dictionary for Regulatory Activities Preferred Term)—was observed; both were considered to be not related to the study drug by the investigators, and no action was taken regarding the study medication. No cases of eosinophilic granulomatosis with polyangiitis or eosinophilic pneumonia were observed. SAEs of cardiac disorders were reported in 2 (0.5%) patients (myocardial infarction and cardiac failure congestive) for an event rate of 0.5 per 100 PYs. No cardiovascular deaths were observed.

Limitations of this study were largely related to study design. The TRAVERSE continuation study was a single-arm, open-label continuation study of the TRAVERSE single-arm, open-label extension study. There was no evaluation of efficacy and no comparison arm included in the study. Data on antidrug antibodies or immunogenicity were not collected, to minimize burden on patients. Only those who had completed both the original parent study (phase 2b, phase 3 QUEST, or phase 3 VENTURE) and the extension study (TRAVERSE) were eligible to participate, potentially contributing to bias in the study population, because those who received and responded to dupilumab in the parent study may have been more likely to continue to the TRAVERSE and TRAVERSE continuation studies than those who received placebo. Only a small proportion of patients who participated in TRAVERSE were eligible to enroll in the continuation study due to the wide commercial availability of dupilumab in the participants' countries (ie, patients from only those countries where dupilumab was not already commercially available could enroll in TRAVERSE continuation). In addition, patients would receive treatment only until dupilumab became commercially available or for a maximum of 144 weeks after starting treatment (whichever came first); the commercial availability of dupilumab reduced the duration of treatment to less than 144 weeks in all countries except South Africa. In addition, this study was conducted during the COVID-19 pandemic, which impacted the ability of some patients to complete or attend study visits on time. However, this did not notably impact the ability to monitor patient safety during the trial.

CONCLUSIONS

In a population of 393 patients with moderate to severe asthma who participated in the open-label TRAVERSE continuation study for up to an additional 3 years after completion of TRAVERSE, safety findings were consistent with the known safety profile of dupilumab. These results further support the long-term use of dupilumab in this patient population.

REFERENCES

1. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. N Engl J Med 1998;339:1194-200.
2. Haselkorn T, Fish JE, Zeiger RS, Szefler SJ, Miller DP, Chipps BE, et al. Consistently very poorly controlled asthma, as defined by the impairment domain of the Expert Panel Report 3 guidelines, increases risk for future severe asthma exacerbations in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. J Allergy Clin Immunol 2009;124:895-902.e1-4.
3. Fahy JV. Type 2 inflammation in asthma–present in most, absent in many. Nat Rev Immunol 2015;15:57-65.
4. Macdonald LE, Karow M, Stevens S, Auerbach W, Poueymirou WT, Yasenchack J, et al. Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes. Proc Natl Acad Sci U S A 2014;111:5147-52.
5. Murphy AJ, Macdonald LE, Stevens S, Karow M, Dore AT, Pobursky K, et al. Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice. Proc Natl Acad Sci U S A 2014;111:5153-8.
6. Gandhi NA, Pirozzi G, Graham NMH. Commonality of the IL-4/IL-13 pathway in atopic diseases. Expert Rev Clin Immunol 2017;13:425-37.
7. Le Floc'h A, Allinne J, Nagashima K, Scott G, Birchard D, Asrat S, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4Rα antibody, is required to broadly inhibit type 2 inflammation. Allergy 2020;75:1188-204.
8. European Medicines Agency. DUPIXENT® (dupilumab). Summary of product characteristics. Accessed April 26, 2023. https://www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf
9. US Food and Drug Administration. DUPIXENT® (dupilumab). Highlights of prescribing information. Accessed April 26, 2023. https://www.regeneron.com/sites/default/files/Dupixent_FPI.pdf
10. Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet 2016;388:31-44.
11. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med 2018;378:2486-96.
12. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med 2018;378:2475-85.
13. Wechsler ME, Ford LB, Maspero JF, Pavord ID, Papi A, Bourdin A, et al. Long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma (TRAVERSE): an open-label extension study. Lancet Respir Med 2022;10:11-25.

ONLINE REPOSITORY

TABLE E1. Cumulative exposure to dupilumab treatment per study

n (PYs)	Placebo/dupilumab (N = 118)	Dupilumab/dupilumab (N = 267)
Overall cumulative exposure		
Parent study to TRAVERSE continuation*	118 (393.5)	267 (902.3)
Parent study†		
Phase 2b	9 (4.1)	51 (23.4)
QUEST	97 (96.3)	203 (201.8)
VENTURE	12 (5.6)	13 (6.0)
TRAVERSE‡	118 (157.0)	267 (373.7)
Phase 2b	9 (16.6)	51 (94.0)
QUEST	97 (125.7)	203 (265.8)
VENTURE	12 (14.8)	13 (13.9)
TRAVERSE continuation§	118 (130.4)	267 (297.4)
Phase 2b	9 (7.1)	51 (43.8)
QUEST	97 (104.9)	203 (234.7)
VENTURE	12 (18.4)	13 (18.9)

EXPEDITION, NCT02573233.
Placebo/dupilumab, patients from placebo arm of the parent study; dupilumab/dupilumab, patients from the dupilumab arm of the parent study.
No patients from the EXPEDITION study have been included.
*Treatment duration of the parent study, TRAVERSE, and TRAVERSE continuation–derived cumulative exposure.
†Treatment duration of the respective parent study-derived cumulative exposure.
‡Treatment duration of only TRAVERSE-derived cumulative exposure.
§Treatment duration of only TRAVERSE continuation–derived cumulative exposure.

TABLE E2. Proportion of patients reporting any TEAE and event rates per 100 PYs in the TRAVERSE continuation study

System organ class PT	Patients, n (n of events)	Incidence rate, % (95% CI)	Event rate per 100 PYs (95% CI)
Infections and infestations	130 (221)	33.1 (27.64-39.28)	51.2 (46.44-56.28)
Bronchitis bacterial	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
External ear cellulitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Furuncle	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Helicobacter infection	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Fungal skin infection	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Oral candidiasis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Tinea versicolor	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Acute sinusitis	3 (4)	0.8 (0.16-2.23)	0.9 (0.35-1.97)
Bronchitis	14 (17)	3.6 (1.95-5.98)	3.9 (2.66-5.56)
Conjunctivitis	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Cystitis	3 (4)	0.8 (0.16-2.23)	0.9 (0.35-1.97)
Ear infection	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Eye infection	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Gastroenteritis	7 (8)	1.8 (0.72-3.67)	1.9 (1.04-3.13)
Hordeolum	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Infected bite	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Laryngitis	3 (3)	0.8 (0.16-2.23)	0.7 (0.23-1.62)
Laryngopharyngitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Lower respiratory tract infection	5 (5)	1.3 (0.41-2.97)	1.2 (0.46-2.20)
Myringitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Nasal vestibulitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Nasopharyngitis	33 (36)	8.4 (5.78-11.79)	8.3 (6.49-10.54)
Otitis externa	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Otitis media chronic	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Pharyngitis	5 (6)	1.3 (0.41-2.97)	1.4 (0.69-2.55)
Pharyngotonsillitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Pneumonia	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Respiratory tract infection	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Rhinitis	5 (7)	1.3 (0.41-2.97)	1.6 (0.81-2.78)
Sinusitis	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Subcutaneous abscess	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Tonsillitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Tooth infection	3 (3)	0.8 (0.16-2.23)	0.7 (0.23-1.62)
Tracheobronchitis	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Upper respiratory tract infection	15 (16)	3.8 (2.14-6.30)	3.7 (2.43-5.33)
Urinary tract infection	7 (7)	1.8 (0.72-3.67)	1.6 (0.81-2.78)
Wound infection	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Bronchitis viral	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
COVID-19	25 (27)	6.4 (4.12-9.39)	6.3 (4.63-8.22)
COVID-19 pneumonia	3 (4)	0.8 (0.16-2.23)	0.9 (0.35-1.97)
Conjunctivitis viral	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Gastroenteritis viral	7 (7)	1.8 (0.72-3.67)	1.6 (0.81-2.78)
Herpes zoster	4 (4)	1.0 (0.28-2.61)	0.9 (0.35-1.97)
Influenza	12 (12)	3.1 (1.58-5.33)	2.8 (1.74-4.17)
Laryngitis viral	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Oral herpes	3 (3)	0.8 (0.16-2.23)	0.7 (0.23-1.62)
Oral viral infection	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Suspected COVID-19	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Viral infection	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Viral pharyngitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Viral rhinitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Viral upper respiratory tract infection	4 (5)	1.0 (0.28-2.61)	1.2 (0.46-2.20)

(continued)

TABLE E2. *(Continued)*

System organ class PT	Patients, n (n of events)	Incidence rate, % (95% CI)	Event rate per 100 PYs (95% CI)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	4 (5)	1.0 (0.28-2.61)	1.2 (0.46-2.20)
Melanocytic naevus	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Seborrheic keratosis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Skin papilloma	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Gallbladder adenoma	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Squamous cell carcinoma	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Blood and lymphatic system disorders	6 (6)	1.5 (0.56-3.32)	1.4 (0.69-2.55)
Anemia	3 (3)	0.8 (0.16-2.23)	0.7 (0.23-1.62)
Iron deficiency anemia	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Polycythemia	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Eosinophilia	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Immune system disorders	3 (3)	0.8 (0.16-2.23)	0.7 (0.23-1.62)
Anaphylactic reaction	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Seasonal allergy	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Metabolism and nutrition disorders	4 (5)	1.0 (0.28-2.61)	1.2 (0.46-2.20)
Decreased appetite	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Diabetes mellitus	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Hypercholesterolemia	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Psychiatric disorders	7 (7)	1.8 (0.72-3.67)	1.6 (0.81-2.78)
Attention deficit/hyperactivity disorder	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Depression	3 (3)	0.8 (0.16-2.23)	0.7 (0.23-1.62)
Insomnia	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Middle insomnia	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Nervous system disorders	19 (27)	4.8 (2.91-7.55)	6.3 (4.63-8.22)
Carotid artery stenosis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Cerebral hematoma	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Headache	8 (11)	2.0 (0.88-4.01)	2.5 (1.51-3.94)
Migraine	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Tension headache	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Dizziness	3 (3)	0.8 (0.16-2.23)	0.7 (0.23-1.62)
Paresthesia	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Posttraumatic neuralgia	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Presyncope	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Neuropathy peripheral	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Pudenal canal syndrome	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Epilepsy	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Cervicobrachial syndrome	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Radiculopathy	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Sciatica	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Eye disorders	10 (19)	2.5 (1.22-4.68)	4.4 (3.01-6.14)
Cataract	1 (3)	0.3 (0.01-1.42)	0.7 (0.23-1.62)
Dry eye	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Chalazion	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Conjunctivitis allergic	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Eye discharge	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Eye inflammation	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Eye pruritus	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Iritis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Ear and labyrinth disorders	2 (3)	0.5 (0.06-1.84)	0.7 (0.23-1.62)
Vertigo	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Vertigo positional	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Cardiac disorders	4 (4)	1.0 (0.28-2.61)	0.9 (0.35-1.97)
Atrial fibrillation	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)

(continued)

TABLE E2. *(Continued)*

System organ class PT	Patients, n (n of events)	Incidence rate, % (95% CI)	Event rate per 100 PYs (95% CI)
Palpitations	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Myocardial infarction	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Cardiac failure congestive	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Vascular disorders	6 (6)	1.5 (0.56-3.32)	1.4 (0.69-2.55)
Hypertension	6 (6)	1.5 (0.56-3.32)	1.4 (0.69-2.55)
Respiratory, thoracic, and mediastinal disorders	72 (121)	18.3 (14.33-23.07)	28.0 (24.55-31.85)
Asthma	54 (82)	13.7 (10.32-17.93)	19.0 (16.10-22.24)
Asthmatic crisis	3 (4)	0.8 (0.16-2.23)	0.9 (0.35-1.97)
Bronchospasm	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Eosinophilic bronchitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Pulmonary embolism	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Cough	4 (4)	1.0 (0.28-2.61)	0.9 (0.35-1.97)
Dyspnea	4 (5)	1.0 (0.28-2.61)	1.2 (0.46-2.20)
Hyperventilation	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Productive cough	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Respiratory failure	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Dysphonia	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Hiccups	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Oropharyngeal pain	5 (5)	1.3 (0.41-2.97)	1.2 (0.46-2.20)
Rhinorrhea	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Laryngeal edema	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Rhinitis allergic	7 (8)	1.8 (0.72-3.67)	1.9 (1.04-3.13)
Tracheal stenosis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Gastrointestinal disorders	26 (50)	6.6 (4.32-9.69)	11.6 (9.38-14.13)
Hiatus hernia	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Toothache	5 (5)	1.3 (0.41-2.97)	1.2 (0.46-2.20)
Pancreatitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Enterovesical fistula	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Duodenitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Gastritis	7 (10)	1.8 (0.72-3.67)	2.3 (1.39-3.71)
Diarrhea	4 (4)	1.0 (0.28-2.61)	0.9 (0.35-1.97)
Gastroesophageal reflux disease	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Abdominal distension	3 (3)	0.8 (0.16-2.23)	0.7 (0.23-1.62)
Abdominal pain	5 (5)	1.3 (0.41-2.97)	1.2 (0.46-2.20)
Abdominal pain upper	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Dysphagia	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Nausea	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Vomiting	3 (10)	0.8 (0.16-2.23)	2.3 (1.39-3.71)
Dry mouth	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Glossitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Glossodynia	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Hepatobiliary disorders	3 (4)	0.8 (0.16-2.23)	0.9 (0.35-1.97)
Cholecystitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Hepatic function abnormal	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Hepatic steatosis	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Skin and subcutaneous tissue disorders	25 (31)	6.4 (4.12-9.39)	7.2 (5.44-9.26)
Angioedema	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Urticaria	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Actinic keratosis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Dermatitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Dermatitis allergic	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Dermatitis contact	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Dry skin	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)

(continued)

TABLE E2. *(Continued)*

System organ class PT	Patients, n (n of events)	Incidence rate, % (95% CI)	Event rate per 100 PYs (95% CI)
Eczema	6 (7)	1.5 (0.56-3.32)	1.6 (0.81-2.78)
Erythema	6 (8)	1.5 (0.56-3.32)	1.9 (1.04-3.13)
Hand dermatitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Pruritus	2 (3)	0.5 (0.06-1.84)	0.7 (0.23-1.62)
Rash	2 (3)	0.5 (0.06-1.84)	0.7 (0.23-1.62)
Skin hyperpigmentation	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Alopecia	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Musculoskeletal and connective tissue disorder	42 (53)	10.7 (7.70-14.45)	12.3 (9.96-14.94)
Pain in jaw	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Arthralgia	10 (12)	2.5 (1.22-4.68)	2.8 (1.74-4.17)
Arthritis	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Hemarthrosis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Joint effusion	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Joint swelling	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Osteoarthritis	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Rotator cuff syndrome	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Muscle spasms	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Muscular weakness	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Myalgia	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Intervertebral disc protrusion	1 (2)	0.3 (0.01-1.42)	0.5 (0.12-1.27)
Back pain	13 (13)	3.3 (1.76-5.66)	3.0 (1.97-4.52)
Chest wall hematoma	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Musculoskeletal chest pain	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Musculoskeletal pain	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Musculoskeletal stiffness	3 (3)	0.8 (0.16-2.23)	0.7 (0.23-1.62)
Neck pain	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Pain in extremity	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Bursitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Tendonitis	1 (2)	0.3 (0.01-1.42)	0.5 (0.12-1.27)
Tenosynovitis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Trigger finger	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Renal and urinary disorders	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Urinary retention	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Nephrolithiasis	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Pregnancy, puerperium, and perinatal conditions	1 (2)	0.3 (0.01-1.42)	0.5 (0.12-1.27)
Abortions and stillbirth	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Pregnancy	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Reproductive system and breast disorders	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Vaginal hemorrhage	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Congenital, familial, and genetic disorders	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Sucrase-isomaltase deficiency	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
General disorders and administration-site conditions	33 (113)	8.4 (5.78-11.79)	26.2 (22.81-29.88)
Injection-site bruising	3 (4)	0.8 (0.16-2.23)	0.9 (0.35-1.97)
Injection-site erythema	10 (38)	2.5 (1.22-4.68)	8.8 (6.83-11.12)
Injection-site hematoma	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Injection-site induration	2 (3)	0.5 (0.06-1.84)	0.7 (0.23-1.62)
Injection-site edema	1 (3)	0.3 (0.01-1.42)	0.7 (0.23-1.62)
Injection-site pain	5 (36)	1.3 (0.41-2.97)	8.3 (6.49-10.54)
Injection-site pruritus	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Injection-site reaction	3 (9)	0.8 (0.16-2.23)	2.1 (1.16-3.36)
Injection-site swelling	2 (4)	0.5 (0.06-1.84)	0.9 (0.35-1.97)

(continued)

TABLE E2. *(Continued)*

System organ class PT	Patients, n (n of events)	Incidence rate, % (95% CI)	Event rate per 100 PYs (95% CI)
Pyrexia	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Asthenia	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Chest discomfort	3 (3)	0.8 (0.16-2.23)	0.7 (0.23-1.62)
Fatigue	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Influenza-like illness	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Noncardiac chest pain	3 (3)	0.8 (0.16-2.23)	0.7 (0.23-1.62)
Peripheral swelling	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Calcinosis	1 (2)	0.3 (0.01-1.42)	0.5 (0.12-1.27)
Investigations	7 (10)	1.8 (0.72-3.67)	2.3 (1.39-3.71)
Eosinophil count increased	3 (3)	0.8 (0.16-2.23)	0.7 (0.23-1.62)
Neutrophil count decreased	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
White blood cell count decreased	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
White blood cell count increased	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Intraocular pressure increased	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Injury, poisoning, and procedural complications	33 (46)	8.4 (5.78-11.79)	10.7 (8.57-13.09)
Facial bones fracture	1 (3)	0.3 (0.01-1.42)	0.7 (0.23-1.62)
Foot fracture	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Hand fracture	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Joint dislocation	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Joint injury	4 (4)	1.0 (0.28-2.61)	0.9 (0.35-1.97)
Meniscus injury	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Animal bite	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Fall	3 (4)	0.8 (0.16-2.23)	0.9 (0.35-1.97)
Head injury	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Ligament sprain	6 (6)	1.5 (0.56-3.32)	1.4 (0.69-2.55)
Limb injury	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Skin laceration	4 (4)	1.0 (0.28-2.61)	0.9 (0.35-1.97)
Skin wound	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Tendon rupture	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)
Wound	2 (4)	0.5 (0.06-1.84)	0.9 (0.35-1.97)
Accidental overdose	5 (6)	1.3 (0.41-2.97)	1.4 (0.69-2.55)
Overdose	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Incarcerated incisional hernia	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Procedural pain	1 (1)	0.3 (0.01-1.42)	0.2 (0.00-0.93)
Vaccination complication	2 (2)	0.5 (0.06-1.84)	0.5 (0.12-1.27)