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Original Article

Effect of Dupilumab in Korean Patients With Uncontrolled Moderate-to-Severe Asthma: A LIBERTY ASTHMA QUEST Sub-analysis

Chin Kook Rhee,[1] **Jung-Won Park**,[2] **Heung-Woo Park**,[3] **You Sook Cho** [4*]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[2]Division of Allergy and Immunology, Department of Internal Medicine, Institute of Allergy, Yonsei University College of Medicine, Seoul, Korea
[3]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, KoreaSeoul National University Medical Research Center, Seoul, Korea
[4]Division of Allergy and Clinical Immunology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

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Correspondence to
You Sook Cho, MD, PhD
Division of Allergy and Clinical Immunology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
Tel: +82-2-3010-3285
Fax: +82-2-3010-6969
Email: yscho@amc.seoul.kr

ORCID iDs
Chin Kook Rhee
https://orcid.org/0000-0003-4533-7937
Jung-Won Park
https://orcid.org/0000-0003-0249-8749
Heung-Woo Park
https://orcid.org/0000-0002-6970-3228
You Sook Cho
https://orcid.org/0000-0001-8767-2667

Trial Registration
ClinicalTrials.gov Identifier: NCT02414854

ABSTRACT

Purpose: To assess the effect of dupilumab on the annualized severe exacerbation rates, change in forced expiratory volume at first second (FEV1), overall asthma control and health-related quality of life in Korean patients from the LIBERTY ASTHMA QUEST study.
Methods: Of the 1,902 patients enrolled in the LIBERTY ASTHMA QUEST study, a phase-3, randomized, double-blind, placebo-controlled, parallel-group study on dupilumab, 74 (4%) were Korean. The patients were randomly assigned to 4 treatment groups (2:2:1:1). The sub-analysis reported herewith was performed with the pooled groups of dupilumab and placebo from the 4 original treatment groups in the LIBERTY ASTHMA QUEST study. The efficacy endpoints were annualized rate of severe exacerbation events during the 52-week study period and changes from baseline in pre-bronchodilator FEV1 in week 12. Asthma control, asthma quality of life and the effect of treatment on the levels of type 2 inflammatory biomarkers were assessed. The safety profile was also evaluated.
Results: In Korean patients, annualized severe exacerbation rates were reduced with dupilumab (n = 49) compared to placebo (n = 25) (0.259 vs 1.942) during the 52-week treatment period. The relative risk reduction with dupilumab was 87% ($P < 0.001$). Improvements in pre-bronchodilator FEV1 (mean difference of 0.24 L, $P = 0.021$) were observed in week 12 in dupilumab-treated patients. Additionally, improvements in asthma control and asthma-related quality of life were observed; the FeNO and serum immunoglobulin E levels were reduced. The incidence of adverse events and serious adverse events was comparable between the dupilumab and placebo group. A total of 11 patients from the dupilumab group reported 63 injection site reactions.
Conclusions: Dupilumab, as an add-on therapy in severe asthma, is efficacious and has an acceptable safety profile in Korean patients.

Trial Registration: ClinicalTrials.gov Identifier: NCT02414854

Keywords: Exacerbation; forced expiratory volume; quality of life; randomized controlled trial; asthma; biological products

Disclosure

Chin Kook Rhee, Heung-Woo Park, You Sook Cho are on advisory panel on Sanofi Aventis Korea Jung-Won Park has no conflict of interest to declare.

Data Sharing Statement

Qualified researchers may request access to patient-level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and data set specifications. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://www.clinicalstudydatarequest.com.

INTRODUCTION

Data from Korean National Health Database and the Cohort for Reality and Evolution of Adult Asthma show an overall prevalence rate of 6.23% in Korean population.[1] Although current treatment strategies for asthma management including inhaled corticosteroid (ICS), long-acting beta-agonist2 (LABA), and short-acting beta-agonist compounds are effective, some patients show inadequately controlled symptoms, repeated asthma exacerbations, or continuous lung function decline.

Despite the existence of several drugs, newer pharmacotherapy options are being developed for better management of asthma. The newer biologics available in Korea for the management of severe asthma are omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab.[2] Among them, dupilumab, an interleukin-4 receptor alpha antagonist was approved for the indication of moderate-to-severe asthma in USA in 2018[3,4] and Korea in 2020[2]. In Korea, dupilumab is approved as an add-on maintenance treatment in patients with uncontrolled type 2 asthma which is defined as follows: severe eosinophilic asthma (blood eosinophil count ≥ 150 cells/μL or fractional exhaled nitric oxide [FeNO] ≥ 25 ppb) or oral corticosteroid dependent asthma.[5]

According to the results of several clinical trials, dupilumab significantly reduces the use of oral corticosteroids by 70% and decreases the levels of inflammatory markers such as FeNO, thymus- and activation-regulated chemokines, eotaxin-3, and immunoglobulin E (IgE).[6,7] Dupilumab enhances lung function and has an acceptable safety profile.[3,4,6-8] In addition, a meta-analysis evaluating the efficacy and safety of dupilumab demonstrates that the addition of dupilumab significantly reduces the risk of severe asthma exacerbations and improves forced expiratory volume in 1 second (FEV1).[9] Another recent meta-analysis of five randomized trials of dupilumab treatment involving 3,369 patients shows significant improvements in FEV1 (standardized mean difference [SMD], 4.29; 95% confidence interval [CI], 2.78–5.81) and asthma quality of life questionnaire (AQLQ) scores (SMD, 4.39; 95% CI, 1.44–7.34). In addition, A significant fall in 5-item asthma control questionnaire (ACQ) scores, morning and evening asthma symptom scores, and severe exacerbation risk (relative risk, 0.73; 95% CI, 0.67–0.79) are observed in dupilumab compared with placebo.[10]

Evidences suggest that using dupilumab as an add-on therapy with other anti-asthma drugs improves the quality of life in patients with severe asthma compared with the standard therapy alone. A multicenter, randomized, double-blind, placebo-controlled, pivotal phase 2b clinical study reports improved lung function and decreased severe exacerbations in patients with uncontrolled persistent asthma when dupilumab was given in addition to ICSs plus LABA therapy.[11]

In the LIBERTY ASTHMA QUEST study, dupilumab significantly decreases exacerbations compared with placebo in patients with severe asthma[12]; however, little is known regarding the effect of dupilumab in Korean patients with severe asthma. The aim of this sub-analysis was to assess the effect of dupilumab on the annualized rate of severe exacerbations and change in FEV1 of the Korean patients. In this sub-analysis of the QUEST study, we report the efficacy and safety of dupilumab and the impact of dupilumab on overall asthma control and health-related quality of life in the Korean population.

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MATERIALS AND METHODS

Study design

The LIBERTY ASTHMA QUEST was a phase-3, randomized, double-blind, placebo-controlled, parallel-group trial (NCT02414854) conducted between May 2015 and November 2017.[12,13] The study included three periods, a 4-week screening period, a 52-week randomized intervention period, and a 12-week post-intervention follow-up period. The study was conducted in accordance with the Declaration of Helsinki, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice guidelines, and applicable regulatory requirements. The study protocol was approved by independent ethics committee or institutional review board at each study site. Written informed consent was obtained from each participant prior to any study-related procedure. Patients younger than 18 years of age provided their assent before participating in this study. Of the 1902 patients enrolled in the LIBERTY ASTHMA QUEST study, 74 (4%) were Korean. Post-hoc analysis of data pertaining to the Korean patients was done with the same clinical parameters as the QUEST study.

Eligibility criteria

Detailed inclusion and exclusion criteria have been published previously.[9,12] Briefly, patients aged ≥ 12 years with a confirmed diagnosis of asthma for ≥ 12 months, based on the guidelines from the National Asthma Education and Prevention Program [14] and the with existing treatment of medium-to-high dose ICS in combination with up to 2 controllers (e.g., LABA, leukotriene receptor antagonists) for at least 3 months; pre-bronchodilator FEV1 ≤ 80% or ≤ 90% of the predicted normal value in those 12 to 17 years of age, respectively; ACQ-5 score ≥ 1.5; reversibility of at least 12% and 200 mL in FEV1 after the administration of 200 to 400 μg albuterol/salbutamol or levalbuterol/levosalbutamol; and at least one hospital admission (e.g. hospitalization or emergency medical care) for worsening of asthma in the previous year or treatment with systemic corticosteroid for at least 3 days were eligible for participation. Patients aged < 12 years, weight < 30 kg, having a history of severe asthma exacerbation within 1-month, smoking history for > 10 years, lung disease other than asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, or Churg-Strauss Syndrome were excluded from the study.

Patient data collection

The data were recorded prospectively at baseline and at the follow-up visits up to 52 weeks (in 2, 4, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 weeks). Post-treatment (12 weeks) patient data was recorded. A baseline visit was conducted before the initiation of treatment and demographic details of the patients, the annualized event rate of severe exacerbation during the 52-week treatment period, change from baseline in pre-bronchodilator FEV1, five item-ACQ-5, AQLQ over time, mean change of type 2 inflammatory biomarkers (eosinophils, FeNO, IgE) from the baseline, adverse events (AEs) and serious adverse events (SAEs) were noted.

Treatment regimen

The patients were randomly (2:2:1:1) assigned to receive a 52-week add-on therapy of subcutaneous dupilumab at a dose of 200 mg (400 mg loading dose) or 300 mg (600 mg loading dose) every 2 weeks as per the local prescribing information or a matched-volume placebo (1.14 mL or 2.00 mL, respectively) for each active dose.

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Endpoints

The prespecified efficacy endpoint included the annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period and change from the baseline in pre-bronchodilator FEV1 in week 12. Patient-reported outcomes, such as ACQ-5 and AQLQ score, were assessed during the 52-week interventional period. The effect of treatment over time on the circulating levels of type 2 inflammation biomarkers (FeNO, serum total IgE, and blood eosinophil counts) was also assessed post hoc, as superior efficacy had been observed in patients with elevated type 2 biomarkers in the overall population of QUEST, previously. The annualized rate of severe exacerbations, pre-bronchodilator FEV1, ACQ-5, and AQLQ score were also assessed post hoc in the subgroups of Korean patients with the baseline eosinophil count ≥ 150 cells/μL or baseline FeNO ≥ 25 ppb. The safety profile was evaluated based on the incidence of treatment-emergent AEs (TEAEs) and SAEs.

Statistical analysis

The safety population included all the patients exposed to study medication, regardless of administered amounts. The intention-to-treat (ITT) population included all patients analyzed according to the randomly allocated treatment groups, regardless of the use of the treatment kit. Details of statistical analysis are published previously.[9,12] Briefly, statistical analysis was performed for the subgroup of Korean patients in the overall ITT population of QUEST Data were analyzed according to the assigned intervention, whether an intervention was received or not. A negative binomial regression model was used to analyze the annualized rate of severe exacerbations. FEV1 and patient-reported outcomes were analyzed using a mixed-effects model. The statistical test was conducted at a 5% significance level.

RESULTS

Patient disposition and demographics

The demographics and clinical characteristics of the Korean patients (n = 74) are presented in **Table 1**. The majority of Korean patients were women (63.5%) and the mean (SD) age was 51.9 (11.6) years. The median number of severe asthma exacerbations in the previous year in patients was 2.0 (range: 1.0–8.0). In total, 64.9% of patients had blood eosinophil count > 150 cells/μL. The baseline median levels of FeNO and blood eosinophil count were 35.0 ppb and 315 cells/μL, respectively.

Severe asthma exacerbation

In the Korean patients, dupilumab reduced the annualized severe exacerbation rates compared with placebo (0.259 vs 1.942) during the 52-week treatment period (**Fig. 1A**); the relative risk reduction with dupilumab vs. placebo in the Korean patients was 87% (P < 0.001). In patients with the baseline eosinophil level ≥ 150 cells/μL, dupilumab reduced the annualized severe exacerbation rates compared with placebo (0.192 vs 3.200) during the 52-week treatment period; the relative risk reduction vs. placebo was 94% (P < 0.001) (**Fig. 1B**). In patients with the baseline eosinophil level < 150 cells/μL, dupilumab slightly reduced the annualized severe exacerbation rates compared with placebo during the 52-week treatment period; however, the difference was not statistically significant (0.344 vs 1.035, P = 0.261).

Similarly, in patients with the baseline FeNO ≥ 25 ppb, dupilumab reduced the annualized severe exacerbation rate vs placebo (0.241 vs. 2.870) during the 52-week treatment period; the relative risk reduction vs placebo was 92% (P ≤ 0.001) (**Fig. 1C**). In patients with the baseline

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Table 1. Demographic and clinical characteristics at baseline (ITT population)

Parameters	1.14 mL/200 mg q2w		2 mL/300 mg q2w		Combined		Total (n = 74)
	Placebo (n = 12)	Dupilumab (n = 24)	Placebo (n = 13)	Dupilumab (n = 25)	Placebo (n = 25)	Dupilumab (n = 49)	
Age (yr)	59.8 (7.8)	46.8 (11.3)	51.6 (8.3)	53.3 (13.0)	55.5 (8.9)	50.1 (12.5)	51.9 (11.6)
Sex							
Women	8 (66.7)	15 (62.5)	9 (69.2)	15 (60.0)	17 (68.0)	30 (61.2)	47 (63.5)
Men	4 (33.3)	9 (37.5)	4 (30.8)	10 (40.0)	8 (32.0)	19 (38.8)	27 (36.5)
BMI (kg/m^2)							
< 25	7 (58.3)	10 (41.7)	8 (61.5)	12 (48.0)	15 (60.0)	22 (44.9)	37 (50.0)
≥ 25 and < 30	4 (33.3)	12 (50.0)	3 (23.1)	8 (32.0)	7 (28.0)	20 (40.8)	27 (36.5)
≥ 30	1 (8.3)	2 (8.3)	2 (15.4)	5 (20.0)	3 (12.0)	7 (14.3)	10 (13.5)
Age at asthma onset (yr)	45.4 (10.2)	35.0 (11.5)	37.1 (14.9)	42.9 (13.0)	41.1 (13.3)	39.0 (12.8)	39.7 (12.9)
Time since the first asthma diagnosis (yr)	14.31 (8.4)	11.92 (8.5)	14.48 (10.6)	10.49 (5.7)	14.40 (9.4)	11.19 (7.2)	12.7 (8.1)
Pre-bronchodilator FEV1 (L)	1.46 (0.4)	1.59 (0.5)	1.30 (0.2)	1.56 (0.4)	1.38 (0.3)	1.57 (0.4)	1.51 (0.4)
Pre-bronchodilator FEV1 percent predicted	63.83 (9.0)	58.96 (12.9)	54.77 (15.1)	62.56 (9.7)	59.12 (13.2)	60.80 (11.4)	60.23 (12.0)
Post-bronchodilator FEV1 (L)	1.80 (0.5)	1.93 (0.6)	1.58 (0.2)	1.94 (0.5)	1.69 (0.4)	1.94 (0.6)	1.85 (0.5)
FEV1 reversibility (%), [median (range)]	23.8 (11.2 to 50.5)	15.4 (2.8 to 97.5)	21.2 (–3.1 to 70.2)	19.7 (2.9 to 81.4)	23.6 (–3.1 to 70.2)	18.8 (2.8 to 97.5)	19.6 (–3.1 to 97.5)
No. of asthma exacerbation experienced in the past year, median (range)	2.0 (1.0 to 3.0)	2.0 (1.0 to 8.0)	2.0 (1.0 to 6.0)	2.0 (1.0 to 4.0)	2.0 (1.0 to 6.0)	2.0 (1.0 to 8.0)	2.0 (1.0 to 8.0)
ICS dose at baseline, mg, median (range)	500.0 (400.0 to 1,250.0)	500.0 (400.0 to 1,300.0)	500.0 (400.0 to 1,300.0)	500.0 (400.0 to 1,500.0)	500.0 (400.0 to 1,300.0)	500.0 (400.0 to 1,500.0)	500.0 (400.0 to 1,500.0)
ICS dose level at baseline							
High	4 (33.3)	6 (25.0)	6 (46.2)	11 (44.0)	10 (40.0)	17 (34.7)	27 (36.5)
Medium	8 (66.7)	18 (75.0)	7 (53.8)	14 (56.0)	15 (60.0)	32 (65.3)	47 (63.5)
Atopic medical condition	8 (66.7)	20 (83.3)	12 (92.3)	21 (84.0)	20 (80.0)	41 (83.7)	61 (82.4)
Atopic dermatitis	-	1 (4.2)	-	-	-	1 (2.0)	1 (1.4)
Allergic conjunctivitis	-	3 (12.5)	2 (15.4)	3 (12.0)	2 (8.0)	6 (12.2)	8 (10.8)
Allergic rhinitis	8 (66.7)	16 (66.7)	10 (76.9)	20 (80.0)	18 (72.0)	36 (73.5)	54 (73.0)
Food allergy	-	3 (12.5)	2 (15.4)	1 (4.0)	2 (8.0)	4 (8.2)	6 (8.1)
Hives	-	1 (4.2)	-	-	-	1 (2.0)	1 (1.4)
IgE (IU/mL), [median (IQR range)]	95.5 (3.0 to 962.0)	160.5 (13.0 to 2,907.0)	257.0 (16.0 to 1,268.0)	300.0 (16.0 to 2,583.0)	210.0 (3.0 to 1,268.0)	223.0 (13.0 to 2,907.0)	218.0 (3.0 to 2,907.0)
Blood eosinophil group (cells/μL)							
< 300	5 (41.7)	12 (50.0)	6 (46.2)	13 (52.0)	11 (44.0)	25 (51.0)	36 (48.6)
≥ 300	7 (58.3)	12 (50.0)	7 (53.8)	12 (48.0)	14 (56.0)	24 (49.0)	38 (51.4)
Blood eosinophil group (cells/μL)							
< 150	5 (41.7)	8 (33.3)	4 (30.8)	9 (36.0)	9 (36.0)	17 (34.7)	26 (35.1)
≥ 150	7 (58.3)	16 (66.7)	9 (69.2)	16 (64.0)	16 (64.0)	32 (65.3)	48 (64.9)
FeNO (ppb)	31.5 (9.0 to 197.0)	37.0 (9.0 to 269.0)	57.0 (12.0 to 127.0)	36.0 (9.0 to 168.0)	34.0 (9.0 to 197.0)	36.0 (9.0 to 269.0)	35.0 (9.0 to 269.0)
FeNO group (ppb)							
< 25	5 (41.7)	10 (41.7)	3 (25.0)	7 (28.0)	8 (33.3)	17 (34.7)	25 (34.2)
≥ 25 and < 50	4 (33.3)	6 (25.0)	2 (16.7)	11 (44.0)	6 (25.0)	17 (34.7)	23 (31.5)
≥ 50	3 (25.0)	8 (33.3)	7 (58.3)	7 (28.0)	10 (41.7)	15 (30.6)	25 (34.2)

Data shown as number (%) or mean (SD), unless otherwise specified.
ITT, intent-to-treat; BMI, body mass index; FEV1, forced expiratory volume at first second; ICS, inhaled corticosteroids; IgE, immunoglobulin E; FeNO, fractional exhaled nitric oxide; SD, standard deviation.

FeNO < 25 ppb, dupilumab did not reduce the annualized severe exacerbation rate vs placebo (0.086 vs 0.452, $P = 0.065$) during the 52-week treatment period.

Pre-bronchodilator FEV1

Pre-bronchodilator FEV1 at week 12 was improved more in the dupilumab-treated patients than the placebo-treated patients (**Fig. 2**). The least-square (LS) mean difference between dupilumab vs placebo was 0.24 L ($P = 0.021$). Dupilumab treatment resulted in significant improvements in pre-bronchodilator FEV1 in patients with the baseline eosinophil count ≥

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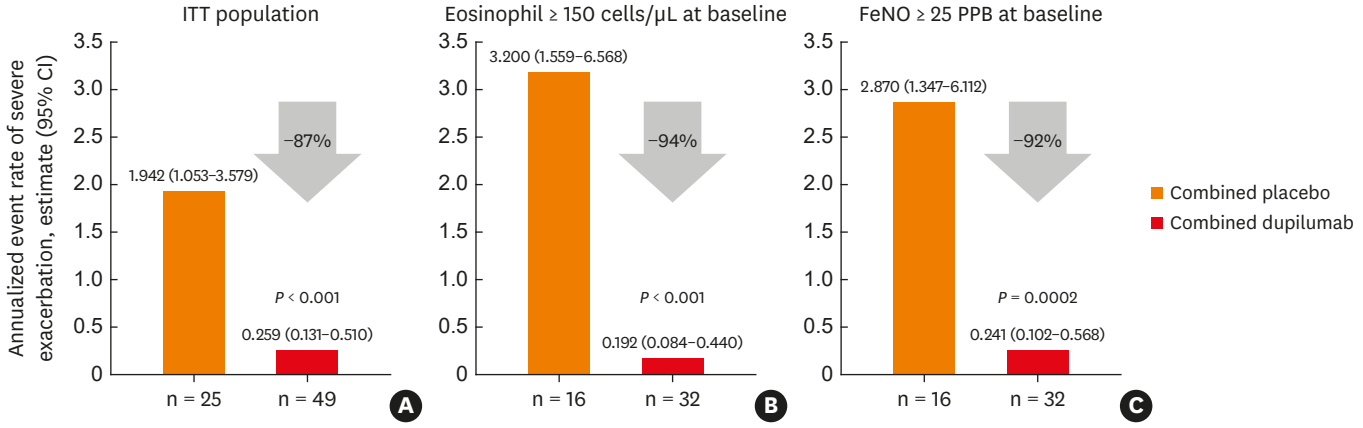

Fig. 1. Reduction of annualized rate of severe exacerbations during the 52-week intervention period in (A) the Korean ITT population, (B) patients with the baseline blood eosinophil ≥ 150 cells/μL, and (C) patients with the baseline FeNO ≥ 25 ppb, for dupilumab vs. placebo.
ITT, intention-to-treat; CI, confidence interval; FeNO, fractional exhaled nitric oxide; ppb, parts per billion.

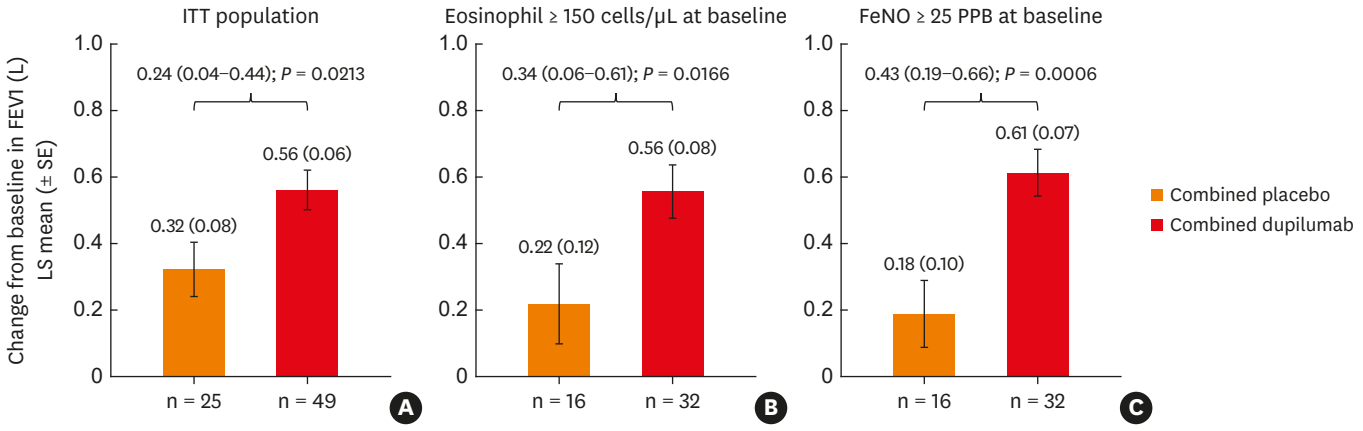

Fig. 2. Magnitude of changes from the baseline in pre-bronchodilator FEV1 in week 12 in (A) the Korean ITT population, (B) patients with the baseline blood eosinophil ≥ 150 cells/μL, and (C) patients with the baseline FeNO ≥ 25 ppb, for dupilumab vs. placebo.
ITT, intention-to-treat; FEV1, forced expiratory volume at first second; LS, least squares; SE, standard error; FeNO, fractional exhaled nitric oxide; ppb, parts per billion.

150 cells/μL (LS mean difference, 0.34 L; $P = 0.017$) and in patients with the baseline FeNO ≥ 25 ppb (LS mean difference, 0.43 L; $P < 0.001$). However, treatment with dupilumab showed no significant improvements compared to placebo in pre-bronchodilator FEV1 in patients with the baseline EOS < 150 cells/μL (LS mean difference, 0.16 L; $P = 0.405$) and in patients with the baseline FeNO < 25 ppb (LS mean difference, −0.01 L; $P = 0.951$).

Pre-bronchodilator FEV1 improved in the first assessment week (week 2) and was sustained throughout the treatment period (**Fig. 3**). Improvements in pre- bronchodilator FEV1 were observed in week 52 in the dupilumab group vs. placebo (LS mean difference, 0.38 L, $P = 0.001$).

Asthma control

Patients in the dupilumab showed greater improvements in ACQ-5 scores than patients in the placebo group throughout the treatment period (**Fig. 4A**). In patients with the baseline EOS ≥ 150 cells/μL, LS mean differences in ACQ-5 score were statistically significant ($P < 0.001$) in weeks 2, 20, 24, 40, 44, and 48 for dupilumab compared with placebo (**Fig. 4B**). In patients

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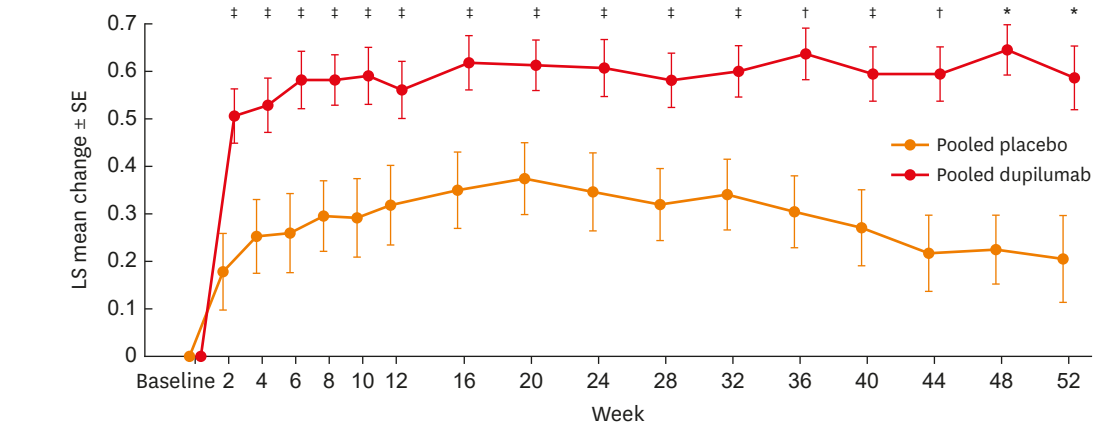
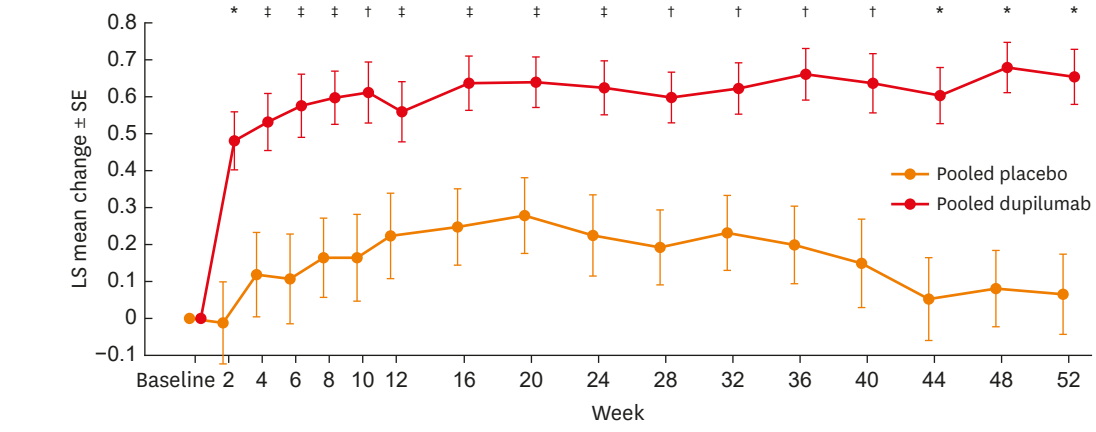


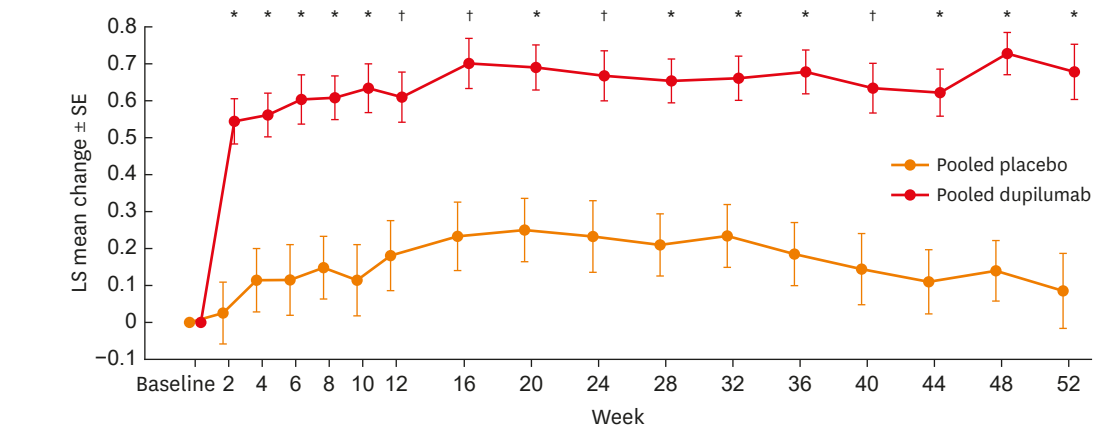
	Baseline	2	4	6	8	10	12	16	20	24	28	32	36	40	44	48	52
Pooled placebo	25	25	25	25	25	25	25	25	22	23	24	24	24	24	24	24	17
Pooled dupilumab	49	48	47	49	49	48	48	49	49	47	47	44	46	45	46	46	31

A



	Baseline	2	4	6	8	10	12	16	20	24	28	32	36	40	44	48	52
Pooled placebo	16	16	16	16	16	16	16	16	13	14	15	15	15	15	15	15	11
Pooled dupilumab	32	31	31	32	32	31	31	32	32	31	30	28	30	29	31	30	20

B



	Baseline	2	4	6	8	10	12	16	20	24	28	32	36	40	44	48	52
Pooled placebo	16	16	16	16	16	16	16	16	14	14	15	15	15	15	15	15	12
Pooled dupilumab	32	32	31	32	32	31	31	32	32	31	31	30	30	29	31	30	22

C

Fig. 3. Changes from the baseline in pre-bronchodilator FEV1 during the 52-week intervention period in (A) the Korean ITT population, (B) patients with the baseline blood eosinophil ≥ 150 cells/μL, and (C) patients with the baseline FeNO ≥ 25 ppb for both dupilumab doses vs. both placebos combined.
LS, least squares; SE, standard error; FEV1, forced expiratory volume in 1 second; FeNO, fractional exhaled nitric oxide; ITT, intention-to-treat.
*$P \leq 0.0001$; †$P \leq 0.001$; ‡$P \leq 0.05$.

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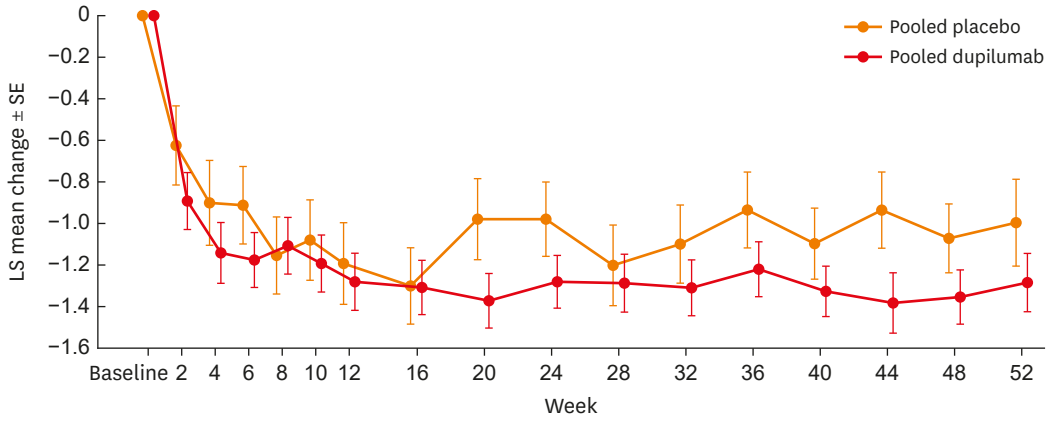
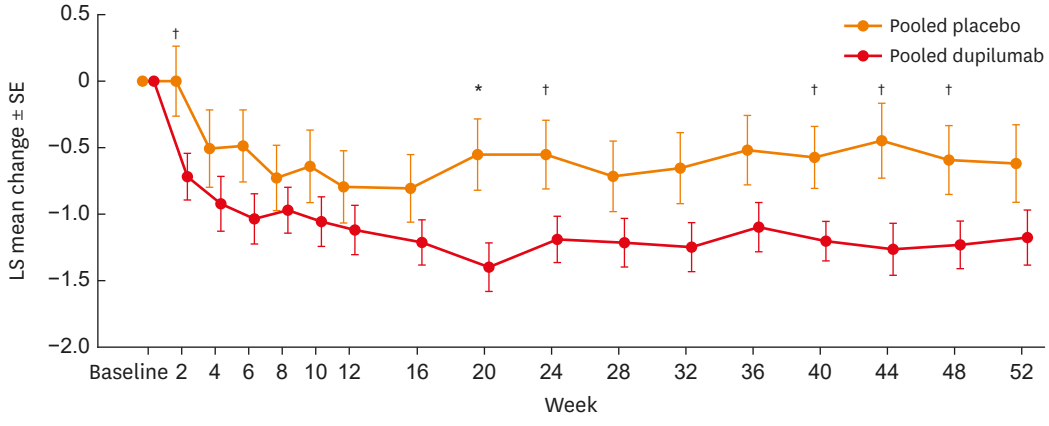


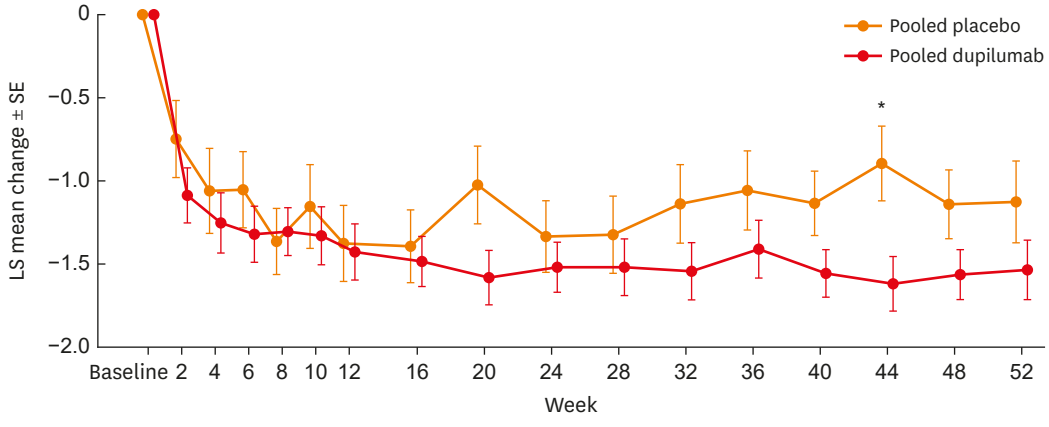
	Baseline	2	4	6	8	10	12	16	20	24	28	32	36	40	44	48	52
Pooled placebo	25	23	25	25	25	25	25	25	22	23	24	24	24	24	24	24	17
Pooled dupilumab	49	48	46	49	49	47	48	49	49	47	46	45	43	44	45	44	31

A



	Baseline	2	4	6	8	10	12	16	20	24	28	32	36	40	44	48	52
Pooled placebo	16	14	16	16	16	16	16	16	13	14	15	15	15	15	15	15	11
Pooled dupilumab	32	31	31	32	32	31	31	32	32	31	30	29	27	28	30	28	20

B



	Baseline	2	4	6	8	10	12	16	20	24	28	32	36	40	44	48	52
Pooled placebo	16	14	16	16	16	16	16	16	14	14	15	15	15	15	15	15	12
Pooled dupilumab	32	32	31	32	32	31	31	32	32	31	30	30	27	28	30	29	22

C

Fig. 4. Changes from the baseline in total asthma control (ACQ-5) scores during the 52-week intervention period in (A) the Korean ITT population, (B) patients with the baseline blood eosinophil ≥ 150 cells/μL, and (C) patients with the baseline FeNO ≥ 25 ppb for both dupilumab doses vs. both placebos combined.
LS, least squares; SE, standard error; ACQ-5, 5-item asthma control questionnaire; ITT, intention-to-treat; FeNO, fractional exhaled nitric oxide.
*P < 0.001; †P < 0.05 vs. matched placebo.

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with the baseline FeNO ≥ 25 ppb, LS mean differences in ACQ-5 score were statistically significant ($P < 0.001$) in week 44 for dupilumab compared with placebo (**Fig. 4C**).

Asthma-related quality of life

In the Korean patients, improvements in AQLQ scores were comparable between the dupilumab and placebo groups (LS mean [standard error, SE], 0.77 [0.14] vs 0.62 [0.20]; $P = 0.551$) (**Fig. 5A**). Similarly, in patients with the baseline EOS ≥ 150 cells/μL, there was no significant difference between the dupilumab and placebo groups (LS mean [SE], 0.76 [0.18] vs 0.18 [0.27]; $P = 0.06$) (**Fig. 5B**) and those with the baseline FeNO ≥ 25 ppb (LS mean [SE], 1.04 [0.17] vs 0.60 [0.24]; $P = 0.131$) (**Fig. 5C**).

Biomarker of type 2 inflammation

During the 52-week treatment period, EOS (median [95% CI], 0.505 [0.240–0.650] vs 0.210 [0.130–0.370] cells/μL); FeNO (median [95% CI], 46.0 [20.0–70.0] vs 20.0 [14.0–24.0] ppb) and serum IgE (median [95% CI], 156.0 [68.0–348.0] vs 44.5 [28.0–83.0] IU/mL) levels were more reduced in the patients receiving dupilumab compared with placebo (**Supplementary Fig. S1**). Especially, decreases of FeNO and serum IgE were significant and consistent in the dupilumab group through the 52-week period.

AE and SAE

No death occurred in any group during the study period. Incidences of TEAEs (88.0% vs 89.8%) and treatment-emergent SAEs (12.0% vs 10.2%) were comparable between the dupilumab and placebo group. Four patients (8.2%) in the dupilumab group had AEs leading to permanent treatment discontinuations (**Table 2**).

A total of 11 patients (22.4%) in the dupilumab group reported treatment-emergent injection site reaction events, while no patient in the placebo group reported injection site reaction. Overall, 24 (38.1%) injection site reactions lasted more than 72 hours.

Table 2. Summary of treatment-emergent adverse events (safety population)

Events	Placebo (n = 25)	Dupilumab (n = 49)
TEAE	22 (88.0)	44 (89.8)
Treatment emergent SAE	3 (12.0)	5 (10.2)
TEAE leading to a permanent treatment discontinuation	-	4 (8.2)
Injection site reactions		
TEAE	-	11 (22.4)
TEAE related to IMP reported by investigator	-	11 (22.4)
Patients with ISR (n = 11)		
1 episode	-	2 (18.2)
2 episodes	-	1 (9.1)
3 episodes	-	2 (18.2)
≥ 4 episodes	-	6 (54.5)
ISRs duration (hour) (n = 63)		
< 24	-	24 (38.1)
≥ 24 and < 72	-	15 (23.8)
≥ 72	-	24 (38.1)

Data shown as number (%).
TEAE, treatment-emergent adverse events; SAE, serious adverse event; IMP, investigational medicinal product; ISR, injection site reaction.

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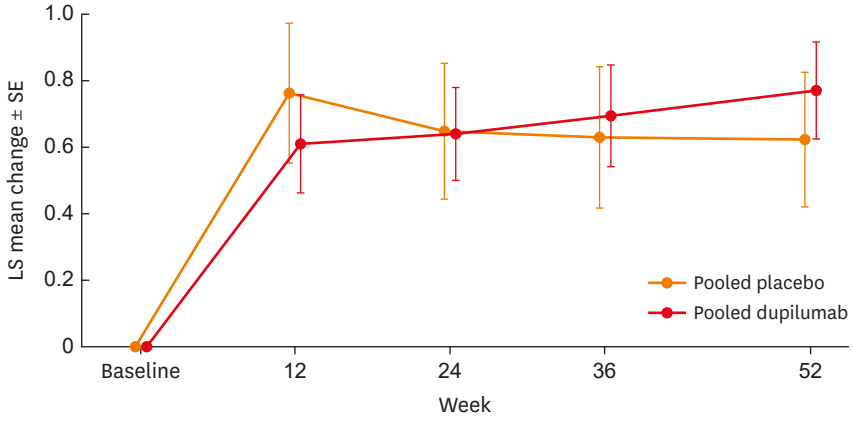
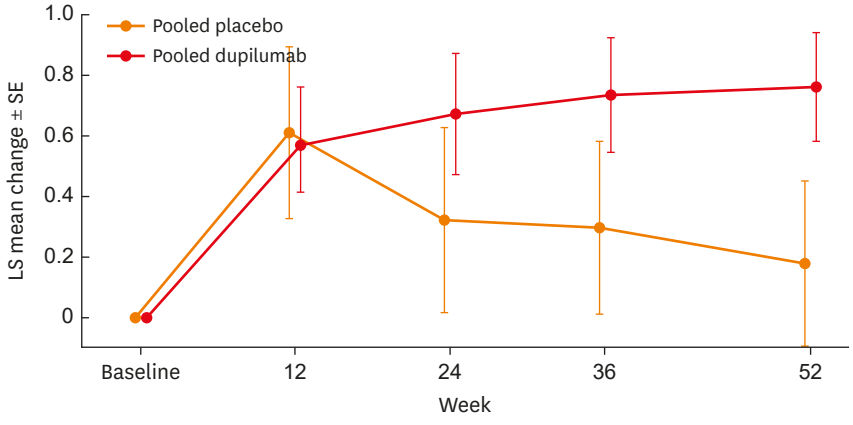


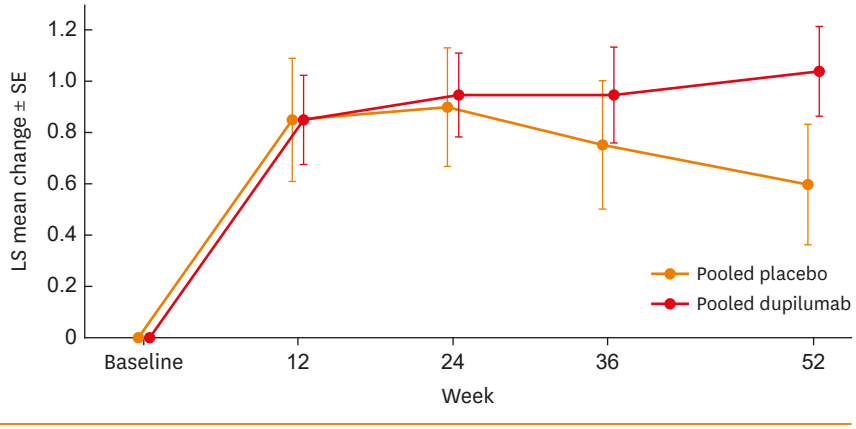
Pooled placebo	23	23	21	22	17
Pooled dupilumab	48	47	48	43	33

A



Pooled placebo	15	15	13	14	11
Pooled dupilumab	32	31	32	28	23

B



Pooled placebo	16	16	14	15	13
Pooled dupilumab	32	31	32	28	25

C

Fig. 5. Changes from the baseline in asthma-related quality of life (AQLQ) scores during the 52-week intervention period in (A) the Korean ITT population, (B) Patients with the baseline blood eosinophil ≥ 150 cells/μL, and (C) Patients with the baseline FeNO ≥ 25 ppb for both dupilumab doses vs. both placebos combined.
LS, least squares; SE, standard error; AQLQ(S), Standardized Asthma Quality of Life Questionnaire; ITT, intention-to-treat; FeNO, fractional exhaled nitric oxide.

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DISCUSSION

A significant reduction of the annualized severe exacerbation rates and a significant improvement in lung function with the acceptable safety in severe asthma patients on the 52-week dupilumab treatment in Korea are the key findings of the current study.

Although results of the QUEST study indicate the potential efficacy of dupilumab for the severe asthma, there might be variability across different ethnic backgrounds. Thus, a sub-analysis of each ethnic group must be needed to predict the response to dupilumab and to provide a practical guideline in the real-world clinic. Recently, Tohda et al.[15] have published a sub- analysis of the Japanese population from the QUEST study. The current analysis shows that the baseline characteristics of Korean patients were similar to those of the overall QUEST population[12] and the sub-population of Japanese patients.[15] The only exception was body mass index which was lower in Japanese patients compared with Korean patients. Interestingly, even though the baseline characteristics were similar, the baseline EOS (520 vs 360 cells/μL), FeNO (51.25 vs 34.97 ppb), and IgE (415.7 vs 432.0 IU/mL) of Korean patients were higher than all the patients participating in the original QUEST study.

In terms of the efficacy of dupilumab, the magnitude of a reduction of severe exacerbations and improvements of FEV1 in Korean patients was much higher than that noted in the original QUEST phase 3 study. These variabilities in dupilumab efficacy might come from differences in ethnicity and/or compliance to the treatment. A greater improvement in the incidence of severe exacerbation rates was noted in the dupilumab-treated Korean patients than the dupilumab-treated Japanese patients (relative risk reduction, 87% vs 62%).[15] Similarly, in patients with the baseline FeNO ≥ 25 ppb, the relative risk reduction was 92% in the dupilumab-treated Korean patients vs. 81% in the dupilumab-treated Japanese patients.[15] Pre-bronchodilator FEV1 improved rapidly in the dupilumab-treated patients compared with the placebo-treated patients. Improvements in pre-bronchodilator FEV1 were observed with dupilumab by the first assessment week (week 2) and sustained throughout the 52-week treatment period. Moreover, LS mean differences in pre-bronchodilator FEV1 in week 12 seemed to be greater in Korean patients than the overall QUEST population. LS mean differences in pre-bronchodilator FEV1 in week 12 were 0.14 L for the 200 mg once every 2 weeks and 0.13 L for 300 mg once every 2 weeks doses, respectively (both $P < 0.001$) in all QUEST population, whereas 0.32 L ($P = 0.021$) and 0.18 L ($P < 0.001$) in Korean patients.

In the Korean patients with asthma, dupilumab improved ACQ-5 scores throughout the treatment period, but AQLQ scores were comparable between the dupilumab and placebo groups. LS mean difference in the ACQ-5 score was statistically significant. These results were also comparable with that of the original QUEST study.[12]

With a regard to the effect on type 2 high inflammatory asthma, dupilumab reduced FeNO and IgE levels in line with the previous reports.[7,15] In this analysis, reductions in the risk of severe exacerbations and improvements in pre-bronchodilator FEV1 were even more greater in type 2 asthma patients characterized by the elevated baseline blood EOS ≥ 150 cells/μL and FeNO ≥ 25 ppb, which was similar with the original QUEST study[12] and the sub-analysis of the QUEST in Japan.[15] A recently published expert opinion from the Korean Academy of Asthma, Allergy and Clinical Immunology, indicates that dupilumab is an effective and approved treatment option for patients with severe eosinophilic asthma aged 12 years.[16]

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Dupilumab is a safe drug in general. An acceptable safety profile was observed with respiratory tract infections and injection-site reactions was the most common AEs.[11] In the VENTURE study aiming a reduction in oral glucocorticoid dose, Rabe et al.[7]showeddecreases in the rate of severe exacerbations and improvements in FEV1, and also observed that injection site reactions were more common in the dupilumab-treated patients compared with the placebo-treated patients (9% vs 4%). In another randomized controlled trial evaluating the efficacy and safety of dupilumab in patients with persistent, moderate-to-severe asthma, elevated EOS, nasopharyngitis, nausea, and headache were reported along with injection site reaction events.[8] In this analysis, AEs leading to permanent treatment discontinuations were noted in 8.2% of patients and there were no deaths. In addition, treatment-emergent injection site reaction events were noted in 11 dupilumab-treated patients, but none in the placebo-treated patients. These findings are in accordance with other studies.[11,12]

Dupilumab has been studied for other indications including atopic dermatitis,[17] and chronic rhinosinusitis with nasal polyps.[18] A *post hoc* analysis of data from the pivotal, phase 2b study demonstrates that dupilumab significantly improves allergic rhinitis-associated nasal symptoms in patients with uncontrolled asthma and comorbid perennial allergic rhinitis.[19] In this analysis, the effect of dupilumab on other diseases was not assessed. However, considering that no variability was observed according to ethnicity observed in Korean patients with asthma in this study, it is conceivable to expect that the effect of dupilumab on the other type 2 high inflammatory diseases of the Korean patients may be similar to other studies.

Although this is the first prospective randomized, double-blind, placebo-controlled study of dupilumab in the Korean patients with uncontrolled type 2 asthma, a small sample size and *post hoc* nature of some analyses are limitations. Hence, future studies on the efficacy and safety of dupilumab should be conducted in a larger Korean population to confirm the findings of the present analysis.

In conclusion, this *posthoc* analysis of the Korean subgroup in the QUEST study indicates the substantial efficacy and acceptable safety of dupilumab as an add-on therapy in severe asthma for a period of over one year. The study demonstrates a significant decrease in severe exacerbations and enhanced FEV1 in dupilumab-treated versus placebo-treated Korean patients, suggesting no negative impact of Korean ethnicity on the efficacy of dupilumab.

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SUPPLEMENTARY MATERIAL

Supplementary Fig. S1

Change in type 2 inflammatory biomarkers ([A] eosinophil, [B] FeNO, [C] IgE).

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