The Effect of Dupilumab on Intractable Chronic Rhinosinusitis with Nasal Polyps in Japan

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Objectives/Hypothesis: Dupilumab, which blocks the shared receptor component for interleukin-4 and interleukin-13, reduced polyp size, sinus opacification, and symptom severity, and was well tolerated in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) in the SINUS-52 study (NCT02898454). We assessed dupilumab in patients enrolled at Japanese centers.

Methods: Patients on a background of mometasone furoate nasal spray, received dupilumab 300 mg every 2 weeks (q2w) for 52 weeks (Arm A); dupilumab 300 mg q2w for 24 weeks, followed by every 4 weeks (q4w) for 28 weeks (Arm B); or placebo (Arm C). Co-primary endpoints were week 24 nasal polyp score (NPS), nasal congestion (NC) score, and sinus Lund–Mackay CT (LMK-CT) scores. Symptoms, sense of smell, health-related quality of life, and safety were assessed during the 52-week treatment period.

Results: Of 49 patients enrolled in Japan, 45 completed the study. Week 24 least squares (LS) mean improvement versus placebo were as follows: NPS (Arm A: −3.1, $P < .0001$; Arm B: −2.1, $P = .0011$); NC score (Arm A: −1.2, $P < .0001$; Arm B: −0.9, $P < .0001$); and LMK-CT (Arm A: −5.1, $P = .0005$; Arm B: −2.8, $P = .0425$). The most common treatment-emergent adverse event in dupilumab and placebo-treated patients was nasopharyngitis.

Conclusion: Dupilumab provided rapid, significant, and clinically meaningful improvements for patients with CRSwNP in Japan. Dupilumab was well tolerated, and safety and efficacy were consistent with the overall study population.

Key Words: Chronic rhinosinusitis, nasal polyps, Japanese, efficacy, immunotherapy.

Level of Evidence: 2

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INTRODUCTION

Chronic rhinosinusitis (CRS) is a common condition, affecting up to 12% of the adult population worldwide.[1] It is a heterogeneous disease characterized by inflammation of the nose and paranasal sinuses. Clinically, CRS can be divided into 2 major phenotypes based on the presence or absence of nasal polyps (NP): chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP). Severe NP are small inflammatory lesions predominantly originating from the ethmoid sinus, which frequently co-exist in patients with CRS (CRSwNP).[2] The clinical dichotomization of CRSwNP versus CRSsNP is also reflected at the molecular level with a heterogeneity of inflammation observed in patients with CRSsNP, while type 2 inflammation is predominant in patients with CRSwNP.[3] Patients with severe CRS or CRSwNP often experience a poor quality of life, including increased anxiety, phobias, and depression.[4]

Recommended initial treatments for CRSwNP in Japan are low-dose macrolide therapy and topical corticosteroids, and short courses of systemic steroids when disease worsens, which can help reduce polyp size and improve symptoms.[3,5] Surgery to remove polyps is recommended in patients who do not respond to medical therapy, although post-surgery recurrence of symptoms and polyps is common due to unresolved underlying inflammation.[6] Recurrence is particularly frequent in patients with

comorbid asthma or non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD).[2,7,8]

CRSwNP predominantly displays a type 2 inflammatory signature with interleukin (IL)-4, IL-5, and IL-13 as prominent cytokines.[9] Japanese patients with CRSwNP have been shown to exhibit increased levels of IL-5 and IL-6, particularly in the ethmoid and frontal recess mucosa.[10]

Since the late 1990s, Japan has seen an increase of patients in whom NP have recurred soon after their removal by endoscopic sinus surgery combined with postoperative macrolide therapy.[11] Strong eosinophil-dominant inflammatory cell infiltration was observed in the NP of the patients,[12] and bronchial asthma was a frequent complication. This intractable form of CRSwNP has been described as eosinophilic CRS (ECRS).[13] The Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis Study (JESREC), published in 2015, established diagnostic criteria and severity classification of ECRS in Japan.[2] Other type 2 inflammatory comorbidities are also often seen in patients with CRSwNP, with an estimated 40%–67% of patients with CRSwNP having comorbid asthma, and up to 16% having N-ERD.[2,14,15]

Dupilumab is a fully human VelocImmune®-derived monoclonal antibody[16,17] that blocks the shared receptor component for IL-4 and IL-13, which are key and central drivers of type 2 inflammation in multiple diseases.[18] The SINUS-24 (NCT02912468) and SINUS-52 (NCT02898454) phase 3 studies assessed the efficacy and safety of dupilumab in addition to standard of care in adults with severe CRSwNP over 24- and 52-week study periods, respectively. The combined results of the 2 studies indicated that dupilumab reduced polyp size, sinus opacification, and symptom severity, and was well tolerated across the study population.[19]

In Japan, as of February 2020, dupilumab is approved for the treatment of adults with atopic dermatitis (AD) uncontrolled with existing therapies, and for patients aged ≥12 years with severe or refractory bronchial asthma whose symptoms are inadequately controlled with existing therapies.[20,21] However, as there are data to suggest that the proportion of patients with non-ECRS driven predominantly by T1 and T3 (neutrophilic) inflammation may be higher in Asian populations than Western populations, where ECRS predominates and disease is driven mainly by T2 (eosinophilic) inflammation.[22,23] For this reason, evaluation of the efficacy of dupilumab among the subgroup of Japanese patients with CRSwNP who took part in the SINUS-52 study was undertaken.

In this post hoc analysis, we assess the efficacy and safety of dupilumab in a subgroup of patients in the SINUS-52 study (NCT02898454) who were enrolled at study centers in Japan.

METHODS

Study Design

Full details of the phase 3, international, multicenter, randomized, placebo-controlled, double-blind SINUS-52 study have been published previously.[19]

Briefly, all patients enrolled in the trial received 100 µg mometasone furoate nasal spray (MFNS) twice daily in each nostril for a 4-week run-in period and throughout the trial. Following the run-in, patients were randomized 1:1:1 to receive either dupilumab 300 mg every 2 weeks (q2w) for 52 weeks (Arm A); dupilumab 300 mg q2w for 24 weeks and every 4 weeks (q4w) for the subsequent 28 weeks (Arm B); or placebo (Arm C). Patients were then followed up for a period of 12 weeks after end of treatment (MFNS was maintained throughout the follow-up).

Patients were eligible for inclusion in the study if they were ≥18 years of age, had prior treatment with a systemic corticosteroid (SCS) in the past 2 years (or a medical contraindication or intolerance to SCS), or prior NP surgery; bilateral endoscopic NP score (NPS) ≥5 with ≥2 for each nostril; and ≥2 of the following CRS symptoms for ≥8 weeks: nasal congestion (NC)/blockage/obstruction (symptom severity score of 2 or 3), and rhinorrhea or reduction or loss of smell. Full inclusion/exclusion criteria have been published previously.[19]

During the study, rescue treatment with SCS, NP surgery, saline nasal lavage, or systemic antibiotics was permitted at the investigator's discretion.

The study was performed in line with the Declaration of Helsinki and principles of Good Clinical Practice. Written informed consent was obtained from all patients prior to enrollment, and the protocol and its amendments were approved by the appropriate institutional review boards and ethics committees.

Endpoints

The endpoints for this analysis were the same as for the entire study population.[19] The co-primary efficacy endpoints were change from baseline in NPS at week 24 (pooled Arms A + B) versus placebo (Arm C); change from baseline in NC score at week 24 (pooled Arms A + B) versus placebo; and change from baseline in Lund–Mackay computed tomography (LMK-CT) score at week 24 (pooled Arms A + B) versus placebo (Arm C).

Key secondary endpoints were change in 22-item Sino-Nasal Outcomes Test (SNOT-22) score from baseline at week 24, daily loss of smell score, and University of Pennsylvania Smell Identification Test (UPSIT) score for pooled Arms A + B versus placebo; change from baseline at week 52 in NPS, NC score, and SNOT-22 score for Arm A versus placebo; and time to first SCS use and/or surgery. Safety was assessed in terms of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs).

Procedures

CT scans were performed at baseline, week 24, and week 52. UPSIT, SNOT-22, and Visual Analog Scale (VAS) for rhinosinusitis were assessed q4w from week 0 through week 24, and additionally at Weeks 40 and 52. In patients with comorbid asthma, spirometry and 6-item Asthma Control Questionnaire (ACQ-6) were assessed at Weeks 0, 4, 16, 24, 40, and 52. Laboratory tests for biomarkers in blood (eosinophils [EOS], immunoglobulin [Ig]E, thymus and activation-regulated chemokine [TARC], periostin, eotaxin-3), and nasal secretions (eosinophilic cationic protein [ECP], eotaxin-3, IgE) were performed at Weeks 0 and 24, with an additional test for blood biomarkers at week 52.[19]

Statistical Analysis

Efficacy endpoints were assessed as least squares (LS) mean change from baseline. The primary efficacy outcome measures of change from baseline at week 24 in each of the 3 co-primary efficacy endpoints were analyzed using a hybrid method

of the worst-observation carried forward (WOCF) and the multiple imputation (MI).

For patients who underwent surgery for NP or received SCS for any reason, data collected post surgery or post SCS were set to missing, and the worst post-baseline value on or before the time of surgery or SCS use was used to impute the missing week 24 value.

For patients who discontinued treatment without having had surgery or receiving SCS, an MI approach was used to impute missing week 24 values, and data collected after treatment discontinuation for all such patients were included in the analysis.

The imputed data were analyzed by fitting an analysis of covariance (ANCOVA) model with the baseline covariate and factors for treatment, asthma status, prior surgery history, and regions. Statistical inference obtained from all imputed data was combined using Rubin's rule.

Based on the above analysis, results of Asian region as a factor were provided as results of the exploratory subgroup analysis of the Japanese population. Descriptive statistics including number of subjects, mean, standard error (SE), and LS means were provided. In addition, differences in LS means and the corresponding 95% confidence intervals (CIs) were provided along with the corresponding P-values. Differences in biomarkers in blood and nasal secretions were compared qualitatively as mean or median percentage changes from baseline. Safety data are presented as number and percentage of patients reporting each TEAE/SAE.

RESULTS

Patient Characteristics

Of the 49 patients randomized into SINUS-52 at centers in Japan, 45 completed the study (Supporting Figure 1). Three patients in the placebo group discontinued the study (all due to AEs) and 1 patient in Arm A.

TABLE I.
Baseline Demographics and Clinical Characteristics.

	Placebo (n = 16)	Arm A Dupilumab 300 mg q2w (n = 16)	Arm B Dupilumab 300 mg q2w–q4w (n = 17)
Age, mean (SD), years	55.9 (10.4)	50.5 (10.5)	54.1 (11.8)
Male sex, n (%)	10 (62.5)	12 (75.0)	8 (47.1)
Weight, mean (SD), kg	65.8 (12.6)	71.2 (19.4)	60.9 (10.7)
BMI, mean (SD), kg/m^2	23.4 (3.3)	25.5 (5.4)	23.8 (4.2)
NP duration, mean (SD), years	8.9 (8.6)	9.1 (10.2)	8.1 (8.4)
Age of onset of NP, mean (SD), years	47.1 (13.4)	41.4 (9.6)	46.0 (14.3)
Patients with ≥1 prior surgery, n (%)	11 (68.8)	10 (62.5)	12 (70.6)
Patients with SCS use in the previous 2 years, n (%)	11 (68.8)	10 (62.5)	14 (82.4)
Bilateral endoscopic NPS, mean (SD), range 0–8	5.6 (1.6)	5.6 (1.1)	6.6 (1.2)
LMK-CT score, mean (SD), range 0–24	17.3 (3.0)	19.0 (3.1)	19.7 (3.9)
Total symptom score, mean (SD), range 0–9	6.7 (1.3)	6.5 (1.3)	7.1 (1.3)
Daily NC score, mean (SD), range 0–3	2.2 (0.5)	2.2 (0.5)	2.3 (0.5)
Rhinorrhea score, mean (SD), range 0–3	1.7 (0.7)	1.6 (0.8)	2.0 (0.6)
Loss of smell score, mean (SD), range 0–3	2.7 (0.6)	2.7 (0.5)	2.7 (0.4)
UPSIT score, mean (SD), range 0–40	12.2 (8.4)	13.3 (7.6)	14.2 (8.0)
SNOT-22 total score, mean (SD), range 0–110	45.9 (26.7)	37.7 (15.1)	40.1 (21.2)
VAS for overall rhinosinusitis, mean (SD), range 0–10 cm	7.2 (2.8)	7.8 (1.7)	8.1 (1.5)
NPIF, mean (SD), L/min	80.7 (53.1)	83.0 (40.4)	64.2 (40.4)
Blood eosinophils, mean (SD), Giga/L (reference 0.5 Giga/L)	0.7 (0.8)	0.4 (0.3)	0.6 (0.4)
Total serum IgE, mean (SD), IU/mL (reference 170 IU/mL)	364.4 (349.0)	268.3 (236.4)	292.3 (294.5)
TARC, mean (SD), pg/mL	466.9 (418.7)	365.8 (142.4)	291.0 (219.6)
Periostin, mean (SD), ng/mL	140.3 (68.5)	128.4 (45.0)	141.0 (65.1)
Patients with comorbid type 2 medical history,* n (%)	15 (94.8)	15 (93.8)	14 (82.4)
Patients with comorbid asthma, n (%)	11 (68.8)	8 (50.0)	12 (70.6)
Patients with comorbid N-ERD, n (%)	5 (31.3)	5 (31.3)	4 (23.5)
FEV$_1$ for asthma patients, mean (SD), L	2.3 (0.8)	2.0 (0.5)	2.0 (0.6)
FEV$_1$ for asthma patients, mean (SD), % predicted	78.8 (14.9)	68.4 (11.4)	81.9 (19.2)
ACQ-6 score for asthma patients, mean (SD), range 0–3	1.5 (1.1)	1.0 (0.8)	0.9 (0.75)
Allergic rhinitis history, n (%)	10 (62.5)	12 (75.0)	12 (70.6)

*Includes AD, allergic conjunctivitis, allergic rhinitis (seasonal or perennial), eosinophilic esophagitis, hives, food allergy, and asthma/N-ERD.

ACQ-6 = 6-item Asthma Control Questionnaire; AD = atopic dermatitis; BMI = body mass index; FEV$_1$ = forced expiratory volume in 1 second; IU = international units; LMK-CT = Lund–Mackay computed tomography; NC = nasal congestion; N-ERD = NSAID-exacerbated respiratory disease; NP = nasal polyp; NPIF = nasal peak inspiratory flow; NPS = nasal polyp score; q2w = every 2 weeks; q4w = every 4 weeks; SCS = systemic corticosteroids; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcomes Test; TARC = thymus and activation-regulated chemokine; UPSIT = University of Pennsylvania Smell Identification Test; VAS = Visual Analog Scale.

Baseline demographics were broadly balanced across the 3 treatment arms, although a higher percentage of patients in Arm B had used SCS in the previous 2 years (82.4%, compared with 62.5% and 68.8% in Arms A and C, respectively) (Table I).

Baseline clinical characteristics were generally balanced across the treatment arms and indicated that enrolled patients had severe CRSwNP (Table I). Across the treatment groups, 50.0%–70.6% of patients had comorbid asthma, and 23.5%–31.3% had comorbid N-ERD.
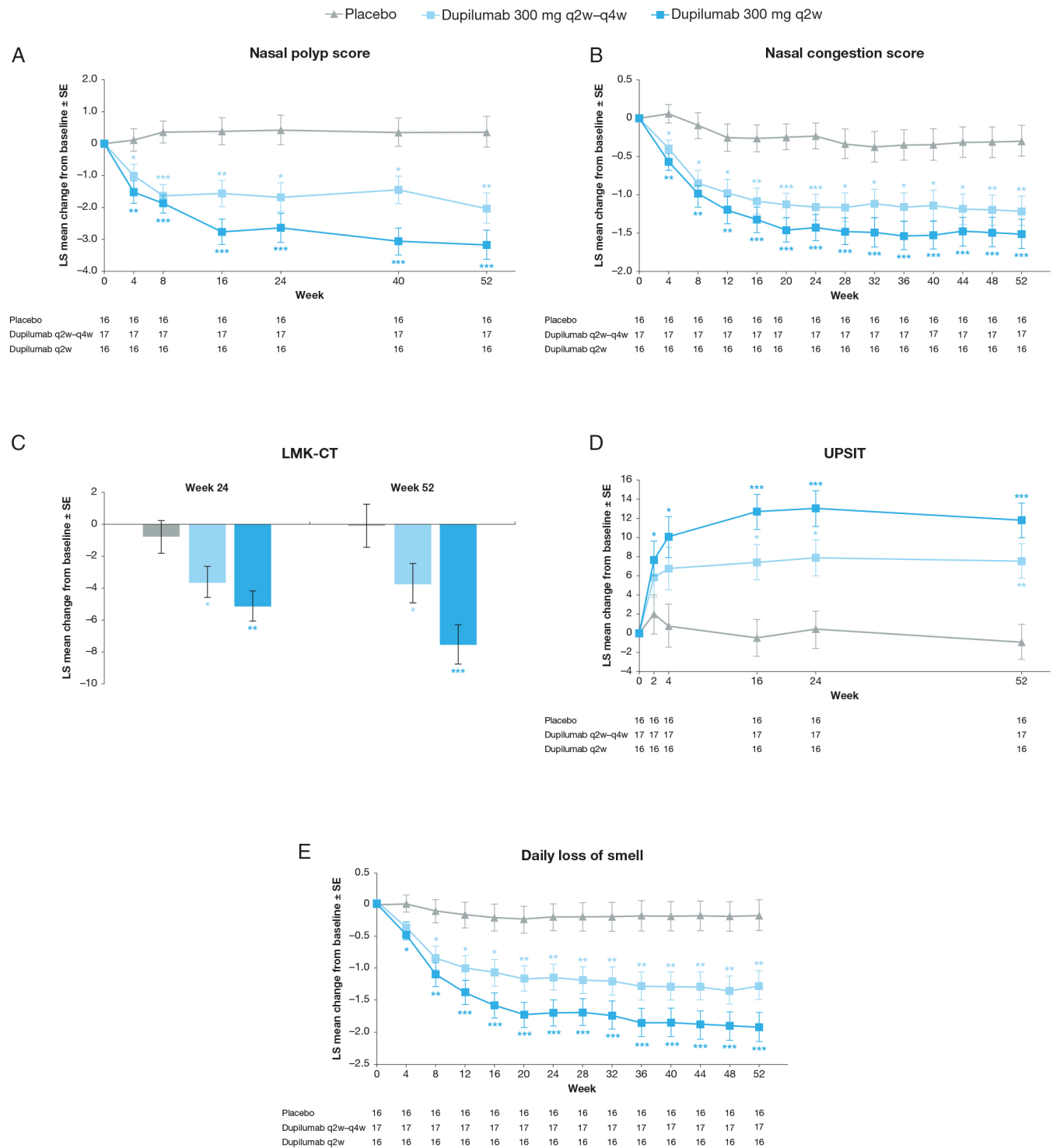
*p < .05, **p < .001, ***p < .0001

Fig. 1. LS mean change from baseline in: (A) nasal polyp score, (B) nasal congestion score, (C) LMK-CT, (D) UPSIT, and (E) daily loss of smell score. LMK-CT = Lund–Mackay computed tomography; LS = least squares; q2w = every 2 weeks; q4w = every 4 weeks; SE = standard error; UPSIT = University of Pennsylvania Smell Identification Test.

Baseline demographics and disease characteristics were similar to the overall study population, with the exception of body mass index, which was lower in the Japan subgroup. Mean baseline (standard deviation [SD]) blood eosinophil levels were high across the overall population (0.43 [0.35] Giga/L) and the Japanese subpopulation (0.54 [0.51] Giga/L).

Efficacy Assessment

Significantly greater improvements in NPS (Fig. 1A), NC score (Fig. 1B), and sinus opacification LMK-CT score (Fig. 1C) were observed at all timepoints in patients who received dupilumab 300 mg (Arms A and B) compared with placebo (Arm C). The greatest changes from baseline were seen in Arm A ($P < .001$ at all timepoints compared with placebo).

Similar trends were seen for the secondary endpoints. Significant differences in change from baseline at week 24 and week 52 were observed in both dupilumab treatment arms, when compared with placebo, across a range of secondary efficacy outcomes (Table II). Patients in both dupilumab treatment arms had significant improvements in NPS (LS mean change Arm A: −3.1 [95% CI: −4.3, −1.8], $P < .0001$; Arm B: −2.1 [95% CI: −3.4, −0.8], $P = .0011$) and VAS for overall rhinosinusitis (Arm A: −4.2 [95% CI: −6.1, −2.3], $P < .0001$; Arm B: −2.7 [95% CI: −4.7, −0.8], $P = .0051$) by week 24.

The greatest improvements in UPSIT and daily loss of smell scores were observed in the first few weeks of the study, and remained significantly different to placebo through week 52 (Fig. 1D–E). In patients with comorbid asthma, significant improvements in forced expiratory volume in 1 second (FEV_1) (LS mean: 0.34 [95% CI: 0.05, 0.63]; $P = .0234$) and ACQ-6 score (LS mean: −1.45 [95%

TABLE II.
LS Mean Change in Efficacy Outcomes from Baseline at Week 24 and Week 52.

LS Mean Change from Baseline (SE)	Placebo (n = 16)	Arm A Dupilumab 300 mg q2w (n = 16)	LS Mean Difference (95% CI)	Arm B Dupilumab 300 mg q2w–q4w (n = 17)	LS Mean Difference (95% CI)
Week 24					
Bilateral endoscopic NPS, range 0–8	0.4 (0.5)	−2.6 (0.5)	−3.1 (−4.3, −1.8)	−1.7 (0.5)	−2.1 (−3.4, −0.8)
			$P < .0001$		$P = .0011$
Daily NC score, range 0–3	−0.2 (0.2)	−1.4 (0.2)	−1.2 (−1.7, −0.7)	−1.2 (0.2)	−0.9 (−1.4, −0.5)
			$P < .0001$		$P < .0001$
Lund–Mackay CT score, range 0–24	−0.8 (1.0)	−5.9 (1.0)	−5.1 (−8.2, −2.0)	−3.6 (1.0)	−2.8 (−5.9, 0.3)
			$P = .0005$		$P = .0425$
Total symptom score, range 0–9	−0.7 (0.4)	−4.1 (0.4)	−3.4 (−4.5, −2.4)	−3.2 (0.4)	−2.5 (−3.6, −1.4)
			$P < .0001$		$P < .0001$
Loss of smell score, range 0–3	−0.2 (0.2)	−1.7 (0.2)	−1.5 (−2.0, −1.0)	−1.1 (0.2)	−0.9 (−1.5, −0.4)
			$P < .0001$		$P = .0005$
UPSIT score, range 0–40	0.3 (2.0)	13.0 (1.9)	12.7 (7.5, 17.9)	7.9 (1.9)	7.6 (2.4, 12.7)
			$P < .0001$		$P = .0038$
SNOT-22 total score, range 0–110	−10.1 (3.7)	−26.2 (3.5)	−16.1 (−25.8, −6.5)	−21.4 (3.5)	−11.4 (−20.8, −1.9)
			$P = .0011$		$P = .0186$
VAS for overall rhinosinusitis, range 0–10 cm	−1.2 (0.8)	−5.4 (0.7)	−4.2 (−6.1, −2.3)	−3.9 (0.7)	−2.7 (−4.7, −0.8)
			$P < .0001$		$P = .0051$
Week 52					
Bilateral endoscopic NPS, range 0–8	0.4 (0.5)	−3.2 (0.5)	−3.5 (−4.8, −2.3)	−2.0 (0.5)	−2.4 (−3.7, −1.1)
			$P < .0001$		$P = .0002$
Daily NC score, range 0–3	−0.3 (0.2)	−1.5 (0.2)	−1.2 (−1.7, −0.7) $P < .0001$	−1.2 (0.2)	−0.9 (−1.4, −0.4)
					$P = .0005$
Lund–Mackay CT score, range 0–24	−0.1 (1.3)	−7.6 (1.2)	−7.5 (−10.9, −4.0)	−3.7 (1.2)	−3.6 (−7.1, −0.2)
			$P < .0001$		$P = .0371$
Total symptom score, range 0–9	−0.7 (0.5)	−4.7 (0.5)	−4.0 (−5.3, −2.6)	−3.5 (0.5)	−2.8 (−4.1, −1.5)
			$P < .0001$		$P < .0001$
Loss of smell score, range 0–3	−0.2 (0.2)	−1.9 (0.2)	−1.8 (−2.4, −1.1)	−1.3 (0.2)	−1.1 (−1.7, −0.5)
			$P < .0001$		$P = .0004$
UPSIT score, range 0–40	−1.0 (1.9)	11.8 (1.8)	12.7 (7.8, 17.7)	7.5 (1.8)	8.5 (3.6, 13.4)
			$P < .0001$		$P = .0006$
SNOT-22 total score, range 0–110	−7.2 (3.9)	−26.1 (3.6)	−18.9 (−29.1, −8.8)	−18.7 (3.6)	−11.5 (−21.4, −1.6)
			$P = .0002$		$P = .0227$
VAS for overall rhinosinusitis, range 0–10 cm	−0.1 (0.9)	−5.3 (0.8)	−5.2 (−7.5, −3.0)	−3.1 (0.8)	−3.0 (−5.2, −0.8)
			$P < .0001$		$P = .0077$

CI = confidence interval; CT = computed tomography; LS = least squares; NC = nasal congestion; NPS = nasal polyp score; q2w = every 2 weeks; q4w = every 4 weeks; SNOT-22 = 22-item Sino-Nasal Outcomes Test; UPSIT = University of Pennsylvania Smell Identification Test; VAS = Visual Analog Scale.

Treatment Emergent Adverse Events.

	Placebo (n = 16)	Dupilumab	
		Arm A 300 mg q2w (n = 16)	Arm B 300 mg q2w–q4w (n = 17)
TEAEs			
Patients with any TEAE, n (%)	14 (87.5)	13 (81.3)	17 (100)
Patients with any treatment emergent SAE, n (%)	2 (12.5)	0	0
Patients with any TEAE leading to death, n (%)	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation, n (%)	3 (18.8)	0	0
TEAEs by Primary System Organ Class and MedDRA Preferred Term that occurred at a frequency of ≥2 cases in any treatment group, n (%)			
Any class	14 (87.5)	13 (81.3)	17 (100)
Infections and infestations	11 (68.8)	9 (56.3)	14 (82.4)
Nasopharyngitis	5 (31.3)	6 (37.5)	9 (52.9)
Pharyngitis	1 (6.3)	3 (18.8)	1 (5.9)
Influenza	0	2 (12.5)	2 (11.8)
Bronchitis	2 (12.5)	0	1 (5.9)
Periodontitis	2 (12.5)	0	1 (5.9)
Nervous system disorders	2 (12.5)	1 (6.3)	2 (11.8)
Eye disorders	1 (6.3)	1 (6.3)	2 (11.8)
Vascular disorders	0	0	2 (11.8)
Hypertension	0	0	2 (11.8)
Respiratory, thoracic, and mediastinal disorders	8 (50.0)	4 (25.0)	6 (35.3)
Epistaxis	3 (18.8)	2 (12.5)	0
Nasal polyps	2 (12.5)	1 (6.3)	0
Asthma	2 (12.5)	0	4 (23.5)
Gastrointestinal disorders	4 (25.0)	3 (18.8)	8 (47.1)
Abdominal discomfort	0	1 (6.3)	2 (11.8)
Gastritis	0	0	2 (11.8)
Gastroesophageal reflux disease	0	0	2 (11.8)
Skin and subcutaneous tissue disorders	3 (18.8)	4 (25.0)	2 (11.8)
Asteatosis	0	2 (12.5)	0
Musculoskeletal and connective tissue disorders	2 (12.5)	1 (6.3)	2 (11.8)
General disorders and administration-site conditions	1 (6.3)	4 (25.0)	2 (11.8)
Injection-site reactions	0	3 (18.8)	0
Injury, poisoning, and procedural complications	2 (12.5)	2 (12.5)	3 (17.6)

MedDRA = Medical Dictionary for Regulatory Activities; q2w = every 2 weeks; q4w = every 4 weeks; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

CI: −2.09, −0.82]; $P < .0001$) were observed by week 24 for the 2 dupilumab treatment arms combined compared with placebo (Supporting Table 1).

The proportion of patients and time to first SCS use and/or NP surgery was analyzed using the Cox proportional hazards model and log rank test stratified by asthma status, prior surgery history, and regions, by considering the first SCS rescue use or surgery (actual or planned) for NP as the event. After 52 weeks, 9.1% of patients treated with dupilumab required SCS use or NP surgery compared with 31.3% of patients treated with placebo (Supporting Figure 2). By week 52, negative median percentage changes in blood biomarkers (eosinophils, total IgE, TARC, and periostin) were observed in both the dupilumab treatment arms (Supporting Table 2 and Supporting Figure 3).

Smaller decreases were seen in the placebo group, except for periostin, which had increased by week 52.

Safety

Most patients in the Japan subgroup experienced at least 1 TEAE (Table III). In the placebo arm, 2 patients reported a treatment-emergent SAE, and 3 had TEAEs leading to treatment discontinuation. No patients in either of the dupilumab arms experienced SAEs or TEAEs leading to study or treatment withdrawal.

Across all arms, the most common TEAEs were infections and infestations (Arm A: 56.3%; Arm B: 82.4%; placebo: 68.8%), followed by respiratory, throracic, and mediastinal disorders (Arm A: 25.0%; Arm B: 35.3%;

placebo: 50.0%). The most frequent TEAE by MedDRA Preferred Term in the dupilumab treatment arms as well as in the placebo arm was nasopharyngitis (Arm A: 37.5%; Arm B: 52.9%; placebo 31.3%) (Table III). The reported TEAEs were in line with those reported by the study population as a whole.[19]

DISCUSSION

Overall, treatment with dupilumab 300 mg q2w added to daily MFNS significantly improved endoscopic measures (NPS, LMK-CT scan score), clinical and patient-reported symptoms (NC, UPSIT score, daily loss-of-smell score, total symptom score), and health-related quality of life outcomes (SNOT-22 symptoms) in Japanese patients with CRSwNP.

Results were comparable with the overall intention-to-treat population, and the study met all three co-primary endpoints. Treatment effects were noted as early as week 4 and were maintained throughout the 52-week study period. TEAEs were also similar to those reported by the overall study population, indicating no ethnicity/race differences in safety profiles.[19]

As demonstrated in this analysis, and in the study population as a whole, dupilumab rapidly and persistently reduced symptoms of CRSwNP and reduced the requirement for SCS or sinonasal surgery, compared with placebo.

The improvements were clinically meaningful across all aspects of disease, and the effects were reflected in reduced polyp size and sinus disease, and in relief of major symptoms of CRSwNP (nasal congestion, loss of smell, and rhinorrhea). Impairment of the sense of smell is one of the most troublesome symptoms for patients with CRSwNP and has a substantial effect on health-related quality of life.

The magnitude of the additional reductions in NP size and sinus disease observed from week 24 to week 52 in SINUS-52 was greater in patients who had received dupilumab q2w for the duration of the study than in those who switched to dupilumab q4w after week 24. A similar trend was observed in the overall SINUS-52 study population as previously reported and the magnitude of the observed improvements was numerically higher in patients who continued q2w dosing than among those who switched to a q4w dose regimen. However, given the small number of patients included in the current analysis, additional real-world experience either in the clinical practice setting or through a disease registry study will be required to support the most appropriate long-term management, including dosing regimen, for Japanese patients with CRSwNP. Patients in the placebo group obtained no meaningful improvements in polyp size, CT scan score, or sense of smell.

Decreases were observed in TARC, periostin, total IgE, and blood eosinophil biomarkers in dupilumab patients, indicating a direct impact on the underlying inflammation.[24] Although these changes cannot be described as statistically significant, these data would suggest that TARC and periostin may be the best among the tested biomarkers for indicating disease improvement in patients treated with dupilumab.

The previous phase 2 study in CRSwNP indicated a substantial positive impact of add-on dupulimab on patient-reported outcomes and quality of life measures. A 16-week, randomized, controlled study of dupilumab 300 mg weekly compared with placebo demonstrated significant improvements in 5-item Asthma Control Questionnaire, 5-dimension EuroQoL questionnaire (EQ-5D), and in 5 Short-Form 36-item questionnaire (SF-36) domains (general health, physical functioning, role-physical, social functioning, and vitality).[25]

Furthermore, in the SINUS-52 study, improvement in the upper airway disease was associated with an improvement in lung function and asthma control. In a post hoc analysis of the phase 3 LIBERTY ASTHMA QUEST study, patients receiving dupilumab 200 mg or 300 mg q2w with self-reported CRS had significant improvements in Asthma Quality of Life Questionnaire (AQLQ) scores by week 12 which were maintained through week 52.[26] While not directly assessed in this analysis, reduction of symptom burden is key in improving quality of life in these patients.

A limitation of this analysis is the relatively small population of the subgroup of patients in Japan. Additionally, the study did not allow for a comparison to be made with patients who were not receiving MFNS. Furthermore, given the duration of the study, long-term effects beyond 1 year were not assessed. In SINUS-24, treatment effects diminished after dupilumab discontinuation, whereas in SINUS-52, treatment effects continued to improve up to week 52, underscoring the need for continued suppression of type 2 inflammation for sustained disease control.

However, the underlying strength of this analysis is that it provided a specific assessment of the efficacy and safety of dupilumab in Japanese patients; this facilitated an evaluation of potential race-related pharmacokinetic or pharmacodynamic differences in this patient population. No notable pharmacokinetic differences between non-Japanese and Japanese patients were observed, with only a slightly higher serum concentration of dupilumab likely as a consequence of the tendency toward a lower body weight in the latter group (data not shown).

When classified according to the JESREC algorithm, the proportion of patients with ECRS versus non-ECRS disease at baseline was comparable between the Japanese subgroup (81.6%; n = 40/49 and 18.4%; n = 9/49, respectively) and the overall SINUS-52 study cohort (83.3%; n = 365/438 and 16.7%; n = 73/438, respectively). Evaluation of the efficacy of dupilumab among patients with ECRS and non-ECRS disease as defined by the JESREC criteria is an important clinical question. Further evaluation of the efficacy and safety of dupilumab in patients with ECRS and non-ECRS with NP will be required.

In conclusion, this subgroup analysis showed that dupilumab provided rapid, significant, and clinically meaningful improvements, broadly, across all the outcome measures for CRSwNP disease in Japanese patients. Dupilumab was well tolerated and its safety and efficacy were consistent with the overall study population.

BIBLIOGRAPHY

1. de Conde AS, Soler ZM. Chronic rhinosinusitis: epidemiology and burden of disease. *Am J Rhinol Allergy* 2016;30:134–139.
2. Tokunaga T, Sakashita M, Haruna T, et al. Novel scoring system and algorithm for classifying chronic rhinosinusitis: the JESREC study. *Allergy* 2015;70:995–1003.
3. Peters AT, Spector S, Hsu J, et al. Diagnosis and management of rhinosinusitis: a practice parameter update. *Ann Allergy Asthma Immunol* 2014;113:347–385.
4. Chung JH, Lee YJ, Kang TW, et al. Altered quality of life and psychological health (SCL-90-R) in patients with chronic rhinosinusitis with nasal polyps. *Ann Otol Rhinol Laryngol* 2015;124:663–670.
5. Rudmik L, Schlosser RJ, Smith TL, Soler ZM. Impact of topical nasal steroid therapy on symptoms of nasal polyposis: a meta-analysis. *Laryngoscope* 2012;122:1431–1437.
6. DeConde AS, Mace JC, Levy JM, Rudmik L, Alt JA, Smith TL. Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. *Laryngoscope* 2017;127:550–555.
7. Young J, Frenkiel S, Tewfik MA, Mouadeb DA. Long-term outcome analysis of endoscopic sinus surgery for chronic sinusitis. *Am J Rhinol* 2007;21:743–747.
8. Veloso-Teles R, Cerejeira R. Edoscopic sinus surgery for chronic rhinosinusitis with nasal polyps: clinical outcome and predictive factors of recurrence. *Am J Rhinol Allergy* 2017;31:56–62.
9. Han JK. Subclassification of chronic rhinosinusitis. *Laryngoscope* 2013;123: S15–S27.
10. Kubota K, Takeno S, Taruya T, Sasaki A, Ishino T, Hirakawa K. IL-5 and IL-6 are increased in the frontal recess of eosinophilic chronic rhinosinusitis patients. *J Otolaryngol Head Neck Surg* 2017;46:36.
11. Haruna S, Nakanishi M, Otori N, Moriyama H. Histopathological features of nasal polyps with asthma association: an immunohistochemical study. *Am J Rhinol* 2004;18:165–172.
12. Nakayama T, Yoshikawa M, Asaka D, et al. Mucosal eosinophilia and recurrence of nasal polyps – new classification of chronic rhinosinusitis. *Rhinology* 2011;49:392–396.
13. Fujieda S, Imoto Y, Kato Y, et al. Eosinophilic chronic rhinosinusitis. *Allergol Int* 2019;68:403–412.
14. Stevens WW, Peters AT, Hirsch AG, Nordberg CM, Schwartz BS, Mercer DG. Clinical characteristics of patients with chronic rhinosinusitis with nasal polyps, asthma, and aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract* 2017;5:1061–1070.
15. Hakansson K, Thomsen SF, Konge L, Mortensen J, Backer V, von Buchwald C. A comparative and descriptive study of asthma in chronic rhinosinusitis with nasal polyps. *Am J Rhinol Allergy* 2014;28: 383–387.
16. Murphy AJ, Macdonald LE, Stevens S, 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;111:5153–5158.
17. Macdonald LE, Karow M, Stevens S, et al. Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes. *Proc Natl Acad Sci U S A* 2014;111:5147–5152.
18. Gandhi NA, Pirozzi G, Graham NMH. Commonality of the IL-4/IL-13 pathway in atopic diseases. *Expert Rev Clin Immunol* 2017;13:425–437.
19. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet* 2019;394:1638–1650.
20. Matsunaga K, Katoh N, Fujieda S, Izuhara K, Oishi K. Dupilumab: basic aspects and applications to allergic diseases. *Allergol Int* 2020 (in press;69: 187–196.
21. DUPIXENT® (dupilumab). Japan PMDA. Available at: http://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/780069_4490405G1024_1_04. Accessed March 2020.
22. Kim YH. Establishing a therapeutic strategy targeting NF-ΚB in Asian patients with chronic rhinosinusitis with nasal polyps. *Allergy Asthma Immunol Res* 2019;11:757–759.
23. Zhang Y, Gevaert E, Lou H, et al. Chronic rhinosinusitis in Asia. *J Allergy Clin Immunol* 2017;140:1230–1239.
24. Jonstam K, Swanson BN, Mannent LP, et al. Dupilumab reduces local type 2 pro-inflammatory biomarkers in chronic rhinosinusitis with nasal polyposis. *Allergy* 2019;74:743–752.
25. Bachert C, Hellings PW, Mullol J, et al. Dupilumab improves patient-reported outcomes in patients with chronic rhinosinusitis with nasal polyps and comorbid asthma. *J Allergy Clin Immunol Pract* 2019;7: 2447–2449.
26. Maspero JF, Katelaris CH, Busse WW, et al. Dupilumab efficacy in uncontrolled, moderate-to-severe asthma with self-reported chronic rhinosinusitis. *J Allergy Clin Immunol Pract* 2020;8:527–539.