

## RESEARCH LETTER

# Improvement in patient-reported “taste” and association with smell in dupilumab-treated patients with severe chronic rhinosinusitis with nasal polyps from the SINUS-24 and SINUS-52 trials

To the Editor,

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a predominantly type 2-mediated inflammatory disease of the nasal cavity and paranasal sinuses.<sup>1</sup> Persistent symptoms of severe CRSwNP include nasal blockage and nasal discharge and olfactory dysfunction, with patients frequently reporting altered sense of smell and taste. In a large, retrospective study of patients with CRSwNP requiring sinus surgery ( $n = 1784$ ), nasal blockage and altered sense of smell and taste (measured using the 22-item Sino-Nasal Outcome Test [SNOT-22]) were the most prevalent ( $\geq 90\%$  of patients) and severe symptoms.<sup>2</sup> These common symptoms are highly burdensome for patients, severely impacting their health-related quality of life (HRQoL).<sup>1,3</sup>

Therapeutic options for patients with CRSwNP are limited, and principally include topical corticosteroids, sinonasal surgery and systemic corticosteroids (SCS). However, such treatments may confer a further increase in disease burden due to short- and long-term adverse events associated with SCS,<sup>4</sup> and a high rate of recurrence post-sinus surgery.<sup>5</sup> Biologic agents targeting the underlying immune-related pathophysiology of CRSwNP are emerging as an effective treatment for CRSwNP. Dupilumab is a fully human VelocImmune<sup>®</sup>-derived monoclonal antibody that binds to interleukin (IL)-4R $\alpha$  to inhibit signalling of both IL-4 and IL-13, which are key and central drivers of type 2 inflammation in multiple diseases.<sup>6</sup>

In the randomized, phase 3 SINUS-24 (NCT02912468) and SINUS-52 (NCT02898454) studies, dupilumab produced rapid and sustained improvements in loss of smell and the University of Pennsylvania Smell Identification Test (UPSIT) compared with placebo.<sup>7</sup> In addition, dupilumab significantly reduced nasal polyp score, nasal congestion and HRQoL compared with placebo, and was generally well tolerated.<sup>8</sup> Given that loss of taste is widely reported in CRSwNP,<sup>9</sup> we determined the effect of dupilumab on patient-reported sense of “taste” and assessed associated changes in sense of “taste” and sense of smell from the pooled SINUS-24 and

SINUS-52 trial populations. Biologic treatment has not previously been reported to impact patient-reported taste in patients with CRSwNP.

Full details of the patient population, methodology and primary and secondary outcomes from the SINUS-24 and SINUS-52 dupilumab phase 3 studies have been published previously.<sup>8</sup> In brief, patients eligible to participate in these studies had bilateral CRSwNP and ongoing symptoms despite intranasal corticosteroid use, had received SCS in the preceding 2 years (this included 74% of patients; mean number of days of SCS use [standard deviation] 33.9 [96.6]) or had previously undergone sinonasal surgery for CRSwNP ( $\geq 1$  prior surgery, 459/724 [63%];  $\geq 3$  prior surgeries, 111/724 [15%]). In SINUS-24, patients were randomized (1:1) to receive dupilumab 300mg subcutaneously (SC) or placebo every 2 weeks (q2w) for 24 weeks. In SINUS-52, patients were randomized (1:1:1) to receive dupilumab 300mg SC q2w for 52 weeks, dupilumab 300mg SC q2w for 24 weeks and then every 4 weeks for the remaining 28 weeks or placebo q2w for 52 weeks.

This post hoc analysis included data for patients who received dupilumab or placebo to Week 24 in SINUS-24 or to Week 52 in SINUS-52. Week 52 data from SINUS-52 are presented for the combined dupilumab q2w groups up to Week 24. Patient-reported sense of “taste” was assessed weekly using a loss-of-taste severity categorical scale (0–3), with a higher score representing greater severity (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms). Sense of smell was measured using the loss-of-smell score (LoS) – reported daily by patients on a scale of 0–3, similar to how patient-reported taste was measured – UPSIT and the SNOT-22 smell/taste item. Analyses were conducted in the intention-to-treat (ITT) population and in an enriched population comprising patients with a loss-of-taste score of  $\geq 1$  (mild and above) at baseline. Mean change in loss-of-taste score from baseline at Week 24 and Week 52 was determined and the least squares (LS) mean differences (95% confidence interval [CI]) for dupilumab versus placebo were calculated. The Spearman’s rank test was used to

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determine the associations between loss-of-taste severity and smell as measured by LoS, UPSIT and the SNOT-22 smell/taste item.

Patient characteristics, including loss-of-taste severity score, were balanced across the dupilumab and placebo treatment groups and were consistent with a population with severe CRSwNP in terms of prior nasal polyp surgery, SCS use and time since first diagnosis (Table 1). Overall, patients in both treatment groups had severely impaired sense of “taste” at baseline, with a mean score of 2.09 in the dupilumab group and 2.16 in the placebo group (SINUS-24). Corresponding values in SINUS-52 were 2.16 (dupilumab) and 2.32 (placebo). This included more than half of patients (53.1%) reporting their loss of “taste” at the highest score (3 = severe symptoms). At baseline, a weak correlation was observed between loss-of-taste severity and loss of sense of smell (pooled SINUS-24/52:  $r = .30$ ;  $p < .0001$ ).

In the ITT population, significant improvements in the severity of patient-reported loss of “taste” were seen in patients treated with dupilumab compared with placebo in both SINUS-24 (LS mean difference vs. placebo:  $-0.94$  [95% CI  $-1.14, -0.74$ ];  $p < .0001$ ) and SINUS-52 ( $-0.77$  [ $-0.95, -0.59$ ];  $p < .0001$ ) at Week 24 (Table 2). The beneficial effect of dupilumab was maintained to Week 52 in SINUS-52 (Table 2). Similar significant improvements in the severity of patient-reported loss-of-taste were seen in dupilumab-treated patients in the enriched population at Week 24 (LS mean difference vs. placebo: SINUS-24:  $-0.99$  [95% CI  $-1.21, -0.78$ ];  $p < .0001$ ; SINUS-52,  $-0.80$ , 95% CI  $-0.98, -0.62$ ;  $p < .0001$ ; Table 2). The improvement in loss-of-taste severity induced by dupilumab in this enriched population was rapid and sustained over 24 and 52 weeks (additional data regarding change in taste severity over time can be found here: [https://osf.io/gxyxn/?view\\_only=fb9fb14804264d9c862d2ec0f39d79e1](https://osf.io/gxyxn/?view_only=fb9fb14804264d9c862d2ec0f39d79e1)). A significantly higher proportion of patients receiving dupilumab compared with placebo achieved an improvement in loss-of-taste severity of  $\geq 1$  point at Week 24 in the ITT population (pooled SINUS-24/52: 61.2% vs. 26.2%;  $p < .0001$ ), with this effect maintained at Week 52 (SINUS-52; Table 2). The proportion of patients with an improvement in loss-of-taste severity of

### Key messages

- CRSwNP is associated with nasal symptoms and olfactory dysfunction, which can impact sense of taste.
- Post-hoc analysis showed dupilumab significantly improves patient-reported “taste” versus placebo in patients with severe CRSwNP.
- Improvement in patient-reported “taste” is moderately correlated with improvement in smell outcomes following dupilumab treatment.

$\geq 1$  point was also significantly greater with dupilumab versus placebo in the enriched population at Week 24 (pooled SINUS-24/52: 69.6% vs. 28.3%;  $p < .0001$ ), with this effect maintained at Week 52 (SINUS-52; Table 2). Furthermore, greater proportions of dupilumab-treated patients at 24 and 52 weeks had larger improvements in loss-of-taste severity ( $\geq 2$  and  $\geq 3$  points) than those who received placebo (Table 2). Moderate associations were observed between improvement in loss-of-taste severity and improvements in sense of smell (LoS, SNOT-22 smell/taste item, UPSIT) at Week 24 in the ITT population (pooled SINUS-24/52:  $r = .56, .58$  and  $-.39$ , respectively) and were maintained at Week 52. A weak association was observed with improvement in nasal polyp score (pooled SINUS-24/52:  $r = .26$ ; additional data regarding these correlations can be found here: [https://osf.io/gxyxn/?view\\_only=fb9fb14804264d9c862d2ec0f39d79e1](https://osf.io/gxyxn/?view_only=fb9fb14804264d9c862d2ec0f39d79e1)).

Loss of taste is widely reported in CRSwNP and is suggested to be associated with loss of smell.<sup>9</sup> In this post hoc analysis of the SINUS-24 and SINUS-52 studies, dupilumab was associated with greater improvements in the severity of patient-reported loss-of-taste, compared with placebo, in patients with CRSwNP. The significant benefit of dupilumab on patient-reported “taste” versus placebo was also evident when the analysis excluded patients not reporting any loss of “taste” (enriched population) at baseline. Improvement in “taste” with dupilumab was moderately

TABLE 1 Demographics and baseline characteristics of patients with CRSwNP with loss-of-taste severity score  $>0$  (mild and above, enriched population)

Pooled SINUS-24/SINUS-52	Placebo (n = 265)	Dupilumab 300 mg q2w (n = 385)	All (n = 650)
Age, mean (SD), years	51.07 (12.80)	51.49 (12.98)	51.32 (12.90)
Male sex, n (%)	152 (57.4)	236 (61.3)	388 (59.7)
Prior surgery for NP and/or SCS use during previous 2 years, n (%)	259 (97.7)	376 (97.7)	635 (97.7)
Prior surgery for NP, n (%)	174 (65.7)	238 (61.8)	412 (63.4)
Time since first diagnosis of NP, mean (SD), years	10.93 (9.02)	10.81 (9.22)	10.86 (9.13)
Loss-of-taste severity score, n (%)			
1	39 (14.7)	65 (16.9)	104 (16.0)
2	84 (31.7)	117 (30.4)	201 (30.9)
3	142 (53.6)	203 (52.7)	345 (53.1)

Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; NP, nasal polyps; q2w, every 2 weeks; SCS, systemic corticosteroids; SD, standard deviation.

correlated with the improvement seen in smell outcomes (as measured by LoS, UPSIT and SNOT-22). The association with improvement in nasal polyp score was weak, potentially suggesting less direct influence on taste than the change in smell outcomes. This may relate to differences between retronasal and orthonasal olfaction. Rapid improvement in smell with dupilumab has previously been observed.<sup>7</sup> Rapid improvement in taste was also observed here with dupilumab treatment, with an improvement compared with placebo occurring by Week 4. The association between improvement in patient-reported "taste" and smell is of particular

interest given that loss of smell has been shown to correlate with disease severity in CRSwNP and to have a detrimental impact on HRQoL.<sup>3</sup> Data on taste from CRSwNP dupilumab trials have not been presented previously and, to our knowledge, dupilumab is the first biologic treatment to demonstrate improved patient-reported loss of "taste" in severe CRSwNP. Some of the observed taste improvement may be due to dupilumab's beneficial effect on smell, although a full understanding of the mechanism of taste improvement is not known, especially as taste buds and olfactory receptors are anatomically distinct. One potential limitation of this analysis

**TABLE 2** Change in patient-reported "taste" and proportion of patients achieving  $\geq 1$ -,  $\geq 2$ -, and  $\geq 3$ -point improvement with dupilumab versus placebo at Weeks 24 and 52

Population <sup>a</sup> (n placebo/dupilumab)	Change from baseline LS mean (SE)		LS mean difference (95% CI) versus placebo <sup>b</sup>	p value
	Placebo	Dupilumab		
<b>Week 24</b>				
SINUS-24 ITT (133/143)	-0.17 (0.08)	-1.11 (0.08)	-0.94 (-1.14, -0.74)	<.0001
SINUS-24 enriched <sup>c</sup> (121/123)	-0.26 (0.09)	-1.25 (0.08)	-0.99 (-1.21, -0.78)	<.0001
SINUS-52 ITT (153/295)	-0.36 (0.08)	-1.13 (0.06)	-0.77 (-0.95, -0.59)	<.0001
SINUS-52 enriched <sup>c</sup> (144/262)	-0.46 (0.08)	-1.26 (0.07)	-0.80 (-0.98, -0.62)	<.0001
<b>Week 52</b>				
SINUS-52 ITT (153/150) <sup>d</sup>	-0.24 (0.08)	-1.17 (0.09)	-0.93 (-1.14, -0.71)	<.0001
Population (n placebo/dupilumab)	Placebo	Dupilumab	Risk difference (95% CI)	p value <sup>e</sup>
<b>% achieving <math>\geq 1</math>-point improvement</b>				
<b>Week 24</b>				
Pooled SINUS-24/SINUS-52 enriched <sup>c</sup> (265/385)	28.3	69.6	41.3 (34.20, 48.42)	<.0001
<b>Week 52</b>				
SINUS-52 enriched <sup>c</sup> (144/262)	23.6	70.6	47.0 (38.14, 55.86)	<.0001
<b>% achieving <math>\geq 2</math>-point improvement</b>				
<b>Week 24</b>				
Pooled SINUS-24 & SINUS-52 enriched <sup>c</sup> (265/385)	8.7	37.4	28.7 (22.82, 34.63)	<.0001
<b>Week 52</b>				
SINUS-52 enriched <sup>c</sup> (144/262)	7.6	45.0	37.4 (29.98, 44.82)	<.0001
<b>% achieving <math>\geq 3</math>-point improvement</b>				
<b>Week 24</b>				
Pooled SINUS-24 & SINUS-52 enriched <sup>c</sup> (265/385)	0.8	8.6	7.8 (4.83, 10.80)	<.0001
<b>Week 52</b>				
SINUS-52 enriched <sup>c</sup> (144/262)	2.8	13.4	10.6 (5.66, 15.50)	.0015

Abbreviations: CI, confidence interval; ITT, intention-to-treat; LS, least squares; NSAID-ERD, non-steroidal anti-inflammatory drug-exacerbated respiratory disease; SE, standard error.

<sup>a</sup>Patients with missing values were recorded as non-responders. In the pooled SINUS-24 & SINUS-52 ITT population, for placebo  $n = 83/203$  for imputed/observed data and for dupilumab  $n = 62/376$ ; in the SINUS-52 ITT population,  $n = 77/76$  and  $n = 54/241$ , respectively. "Observed" includes observed events and observed non-responder. "Imputed" only includes imputed non-responder; no events are imputed.

<sup>b</sup>Each of the imputed complete data were analysed by fitting an analysis of variance model with the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history and regions as covariates.

<sup>c</sup>Enriched population includes patients with loss-of-taste severity  $>0$  at baseline.

<sup>d</sup>Dupilumab 300mg q2w treatment arm only.

<sup>e</sup>p values derived by Cochran–Mantel–Haenszel test stratified by study, asthma/NSAID-ERD status, prior surgery history and region.

is the use of a subjective, patient-reported scale to assess changes in taste severity. In addition, data were not collected using an objective taste test during SINUS-24 and SINUS-52; results here demonstrate a beneficial effect of dupilumab compared with placebo on patient-reported “taste.”

In conclusion, our analysis shows that in patients with severe CRSwNP, dupilumab treatment improved patient-reported “taste” versus placebo. Moderate associations between “taste” and smell outcomes are consistent with the known role played by smell in patient-reported “taste.” These data provide further evidence to support the wide-ranging beneficial effect of dupilumab on the signs and symptoms of severe CRSwNP.

## AUTHOR CONTRIBUTIONS

All authors provided critical review and revision and final approval of the publication and accept accountability for the accuracy and integrity of the content. ATP contributed to the study concept or design, acquired data and provided interpretation/analysis of the data. ZMS, RCK, EH, JFM, LC, SF and APL provided data interpretation/analysis. HZ, SN, AHK, SS, JAJ-N, PR and YD contributed to the study concept or design and provided data interpretation/analysis.

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Regeneron Pharmaceuticals Inc; Sanofi.

## CONFLICT OF INTEREST

A.T. Peters: Regeneron Pharmaceuticals, Inc., Sanofi—advisory board member; AstraZeneca—research support and advisory board member; Optinose—consultant and research support. Z.M. Soler: Lyra, Novartis, Olympus, Optinose—advisory board and/or consultant; Healthy Humming—Medical Director. R.C. Kern: Genentech, GlaxoSmithKline, Lyra, Sanofi/Regeneron Pharmaceuticals, Inc.,—consultant. E. Heffler: AstraZeneca, Boehringer Ingelheim, Circassia, GlaxoSmithKline, Nestlé Purina, Novartis, Sanofi Genzyme, Teva, Valeas—research grants. J.F. Maspero: AstraZeneca, Novartis, Sanofi—research grants, speaker fees, and advisory boards; Boehringer Ingelheim—speaker fees and advisory boards; GlaxoSmithKline—research grants and advisory boards; Menarini, Uriach—speaker fees; MSD—advisory boards. L. Crampette: Medtronic, Novartis, Zambon—speaker fees; ALK, AstraZeneca, Sanofi Genzyme—advisory board member. S. Fujieda: AstraZeneca, GlaxoSmithKline, Kyowa Hakkō Kirin, Sanofi—advisory board member; Kyorin, Mitsubishi Tanabe Pharma, Taiho Pharma—speaker fees. A.P. Lane: Sanofi—advisory board member. H. Zhang, S. Nash, S. Siddiqui, Y. Deniz: Regeneron Pharmaceuticals, Inc.—employees, may hold stock and/or stock options in the company. A.H. Khan,

J.A. Jacob-Nara, P. Rowe: Sanofi—employees, may hold stock and/or stock options in the company.

## DATA AVAILABILITY STATEMENT

Qualified researchers may request access to patient-level data and related study documents including clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan and dataset 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>.

## ETHICAL APPROVAL

The local institutional review board or ethics committee at each study centre oversaw trial conduct and documentation. All patients provided written informed consent before participating in the trial.

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