The relationship of sinus opacification, olfaction and dupilumab efficacy in patients with CRSwNP*

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Abstract

Background: Loss of sense of smell is one of the most burdensome symptoms of chronic rhinosinusitis with nasal polyps (CRSwNP) but its relationship to sinus disease on imaging is unclear. Dupilumab improves sense of smell and radiographic severity of sinus disease in patients with CRSwNP. We investigated the relationship of sinus opacification severity and loci to olfactory impairment and dupilumab efficacy in patients with CRSwNP from the SINUS-24/SINUS-52 (NCT02912468/NCT02898454) studies.

Methods: Sinus opacification was evaluated using the Lund-Mackay computed tomography (LMK-CT) score and sense of smell using patient-reported loss of smell (LoS) score, University of Pennsylvania Smell Identification Test (UPSIT) score and the 22-item Sino-Nasal Outcome Test (SNOT-22) smell/taste item.

Results: At baseline, 95% of patients (688/724) had impaired sense of smell and opacification was extensive across all sinuses. Greater olfactory impairment was associated with greater opacification, especially in the ethmoid, sphenoid and frontal sinuses. At Week 24, reductions in LMK-CT total score and ethmoid and sphenoid sinus scores with dupilumab were weakly correlated with improvements in sense of smell assessed by LoS, UPSIT and SNOT-22 smell/taste item. More dupilumab than placebo patients achieved clinically meaningful (≥5-point) improvement in LMK-CT total score at Week 24 and Week 52.

Conclusion: Radiographic disease severity on imaging was associated with smell outcomes in this cohort. Opacification of the ethmoid, sphenoid and frontal sinuses was associated with severe smell loss. These data suggest that dupilumab effects on smell may be partly mediated through reduced sinus inflammation.

Key words: ethmoid sinus, frontal sinus, nasal polyps, smell, sphenoid sinus

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a predominantly type 2-mediated inflammatory disease of the nasal cavity and paranasal sinuses characterised by the presence of 2 or more symptoms of rhinosinusitis (nasal congestion/obstruction [NC], loss of smell, rhinorrhoea, facial pain/headache), presence of nasal polyps on nasal endoscopy and opacification of sinuses in a computed tomography (CT) scan [1, 2]. Nasal polyps are oede-

matous inflammatory lesions that originate from the mucosa of the paranasal sinuses and can obstruct the nasal airway as well as the olfactory cleft. Loss of sense of smell is one of the most troublesome and difficult-to-treat symptoms in patients with CRSwNP [3, 4]. Intranasal corticosteroid sprays are generally used as a first-line treatment in CRSwNP, but evidence regarding efficacy in improving sense of smell is limited [5]. Endoscopic sinus surgery in some cohorts is associated with high rates of recurrence and revision surgery as well as persistent smell loss [6, 7]. Although sinus opacification is a hallmark characteristic of patients with CRSwNP, the association between sinus CT findings and patient symptoms has been conflicting. One prospective study reported a lack of correlation between Lund-Mackay (LMK)-CT scan scores and symptoms or health-related quality of life [8], whereas another study found that incorporation of radiographic characteristics of sinus opacification with LMK-CT scores enhanced the predictive power of patients' subjective symptom severity [9].

Studies indicate that olfactory dysfunction in CRSwNP may be associated with inflammation of the mucosa in the ethmoid sinuses and correlates with opacification of the olfactory cleft [10, 11]. Olfactory dysfunction in CRSwNP appears to be multifactorial and involves a sensory component due to inflammation of the neuroepithelium of the olfactory mucosa, and a conductive component as a result of polyps and inflammatory secretions that impedes odorants from reaching the olfactory epithelium. Loss of smell in CRSwNP correlates with disease severity, has a substantial impact on quality of life and may be the first sign of disease recurrence [12-15].

Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin-4 and -13, which are key and central drivers of type 2 inflammation in multiple diseases including CRSwNP [16-19]. The efficacy and tolerability of dupilumab were established in the randomised, placebo-controlled, phase 3 SINUS-24 (NCT02912468) and SINUS-52 (NCT02898454) studies, in which dupilumab on a background of mometasone furoate nasal spray significantly improved endoscopic, radiologic, clinical and patient-reported outcomes in patients with severe CRSwNP refractory to standard-of-care therapies and was generally well tolerated [20]. Dupilumab treatment also significantly and rapidly improved sense of smell in these patients [20, 21]. In the SINUS studies, dupilumab treatment was associated with significant improvements vs. placebo in sinus opacification as measured by LMK-CT score, with improvements seen across all sinuses regardless of coexisting asthma, non-steroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD) or prior surgery [20]. The inclusion of CT scan assessment in the SINUS studies provides a comprehensive dataset to explore associations between CT findings and other dimensions of CRSwNP disease. Our objectives in the present analysis were to investigate the relationship between sinus disease severity based on LMK-CT score and olfactory impairment at baseline and following treatment in patients with severe CRSwNP from the SINUS trials.

Materials and methods

Study design and patients

Details of the study design and patient eligibility for the SINUS-24 and SINUS-52 trials were published previously [20]. Briefly, in both studies eligible patients had severe CRSwNP defined as endoscopic bilateral nasal polyps score (NPS) ≥5 (out of maximum possible score of 8) and ≥2 in each nasal cavity, and ≥2 of the following symptoms for ≥8 weeks: NC/blockage/obstruction with moderate or severe symptom severity (score 2 or 3 out of maximum possible score of 3) and a weekly average severity of >1 at the time of randomisation, and either loss of smell or rhinorrhoea (anterior/posterior). There were no inclusion criteria based on LMK-CT or loss of sense of smell scores. Patients were randomised to dupilumab 300 mg or placebo every 2 weeks (q2w) for 24 weeks in SINUS-24 and to dupilumab 300 mg q2w for 52 weeks, dupilumab q2w for 24 weeks and then every 4 weeks for the remaining 28 weeks, or placebo q2w for 52 weeks in SINUS-52.

Ethics

The SINUS-24 and SINUS-52 studies were conducted according to the Declaration of Helsinki principles. All patients provided signed written informed consent prior to study participation. Institutional review boards and independent ethics committees reviewed and approved the protocols, informed consent forms and patient information before study initiation.

Outcome measures

Sinus opacification was assessed using the LMK-CT score. Change from baseline in LMK-CT score to Week 24 was a pre-specified secondary endpoint in the SINUS studies. CT scans were performed at baseline in both studies and at Week 24 (SINUS-24) and Weeks 24 and 52 (SINUS-52). All sinus CT images underwent blinded, independent, central review for LMK scoring. LMK-CT staging involves scoring 6 bilateral areas of sinus opacification from 0 to 2 (0 = no abnormality; 1 = partial opacification; 2 = total opacification), for a possible range of total score from 0 to 24 [22]. LMK-CT scores were also assessed for all sinuses individually and for the ostiomeatal complex (score of 0 or 2 only).

Loss of smell was assessed using daily loss of smell (LoS) score recorded by patients using an eDiary (score 0–3 [0 = none; 1 = mild; 2 = moderate; 3 = severe]) [20, 23, 24], and at study clinic visits using the University of Pennsylvania Smell Identification Test [25, 26] (UPSIT; score 0–40 [anosmia: ≤18; severe microsmia: 19–25; moderate microsmia: 26–30 in women and 26–29 in men; mild microsmia: 31–34 in women and 30–33 in men; normosmia: >34 in women and >33 in men]) and the 22-item Sino-Nasal

Table 1. Baseline demographics and disease characteristics (pooled SINUS-24 and SINUS-52 ITT).

	Placebo q2w (n=286)	Dupilumab 300 mg q2w [a] (n=438)
Age, mean (SD), years	51.28 (12.90)	51.47 (12.79)
Male sex, n (%)	165 (57.7)	272 (62.1)
Time since NP first diagnosis, mean (SD), years	10.83 (9.01)	11.12 (9.73)
Patients with ≥1 prior NP surgery, n (%)	187 (65.4)	272 (62.1)
Time since most recent NP surgery, mean (SD), years	7.06 (6.33)	7.22 (6.52)
Patients with SCS use in the previous 2 years, n (%)	209 (73.1)	329 (75.1)
Bilateral endoscopic NPS, mean (SD), (range 0-8)*	5.91 (1.26)	6.00 (1.24)
LMK-CT score, mean (SD), (range 0-24)*	18.53 (4.10)	18.26 (4.03)
Maxillary (L/R)	1.27 (0.46)/1.30 (0.47)	1.26 (0.45)/1.27 (0.45)
Anterior ethmoid (L/R)	1.62 (0.50)/1.63 (0.48)	1.59 (0.51)/1.62 (0.50)
Posterior ethmoid (L/R)	1.52 (0.52)/1.53 (0.52)	1.50 (0.52)/1.50 (0.52)
Sphenoid (L/R)	1.34 (0.57)/1.39 (0.56)	1.30 (0.58)/1.34 (0.58)
Frontal (L/R)	1.57 (0.58)/1.58 (0.56)	1.53 (0.59)/1.54 (0.59)
Ostiomeatal complex (L/R)	1.91 (0.42)/1.87 (0.49)	1.92 (0.39)/1.89 (0.46)
NC score, mean (SD), (range 0-3)*	2.41 (0.54)	2.39 (0.60)
UPSIT score, mean (SD), (range 0-40)†	14.09 (8.30)	13.90 (8.16)
LoS score, mean (SD), (range 0-3)*	2.72 (0.52)	2.74 (0.54)
TSS, mean (SD), (range 0-9)*	7.18 (1.39)	7.14 (1.45)
VAS for overall rhinosinusitis, mean (SD), (range 0-10 cm)*	7.97 (2.14)	7.82 (2.02)
SNOT-22 total score, mean (SD), (range 0-110)*	52.27 (21.11)	50.05 (20.33)
Patients with asthma, n (%)	170 (59.4)	258 (58.9)
Patients with NSAID-ERD, n (%)	82 (28.7)	122 (27.9)

[a] All patients from the 2 studies randomised to dupilumab 300 mg q2w dosing – Arm A over the 52-week treatment period and Arm B (first 24 weeks q2w) of SINUS-52, and the dupilumab arm of SINUS-24. * Higher scores indicate greater disease severity. † Higher scores indicate lower disease severity. ITT: intention-to-treat; LMK-CT: Lund-Mackay computed tomography; LoS: loss of smell; L/R: left/right; NC: nasal congestion/obstruction; NP: nasal polyps; NPS: nasal polyps score; NSAID-ERD: non-steroidal anti-inflammatory drug-exacerbated respiratory disease; q2w: every 2 weeks; SCS: systemic corticosteroid; SD: standard deviation; SNOT-22: 22-item Sino-Nasal Outcome Test; TSS: Total Symptom Score; UPSIT: University of Pennsylvania Smell Identification Test; VAS: visual analogue scale.

Outcome Test (SNOT-22) smell/taste item (score 0–5 [0 = No problem, 1 = Very mild problem, 2 = Mild or slight problem, 3 = Moderate problem, 4 = Severe problem and 5 = Problem as bad as it can be]). LoS score was the average of the prior 7 days for the baseline score, and prior 28 days for monthly post-baseline scores. UPSIT was assessed at baseline in both studies and at Weeks 2, 8, 16 and 24 (SINUS-24) or Weeks 2, 4, 16, 24 and 52 (SINUS-52). SNOT-22 was assessed at baseline in both studies and at Weeks 8, 16 and 24 (SINUS-24) or Weeks 4, 8, 16, 24, 40 and 52 (SINUS-52).

Scoring of NPS was performed centrally by masked review of the video recordings of standardised bilateral nasal endoscopies obtained at baseline and Weeks 8, 16 and 24 (SINUS-24) or Weeks 4, 8, 16, 24, 40 and 52 (SINUS-52). Polyps in the left and right nostril were scored according to size and location on a scale of 0–4 (0 = no polyps; 1 = small polyps; 2 = moderately sized polyps; 3 = large polyps; 4 = large polyps causing complete obstruction), with NPS reported as a sum score for both nostrils (range 0–8). NC (range 0–3) was recorded daily by patients using an eDiary. NC score was the average of the prior 7 days for the baseline score, and prior 28 days for monthly post-baseline scores.

Statistical analyses

Efficacy was analysed using pooled data from the SINUS-24 and SINUS-52 intention-to-treat (ITT) populations for the Week 24 analyses and data from the SINUS-52 ITT population for the Week 52 analyses. The analysis combined all patients from the 2 studies randomised to dupilumab 300 mg q2w dosing – Arm A over the 52-week treatment period and Arm B (first 24 weeks q2w) of SINUS-52, and the dupilumab arm of SINUS-24. For the placebo group, the placebo arms of both SINUS-24 up to Week 24 and SINUS-52 up to Week 52 were combined. Efficacy analyses were also conducted in subgroups of patients with or without prior sino-nasal surgery and/or use of systemic cortico-

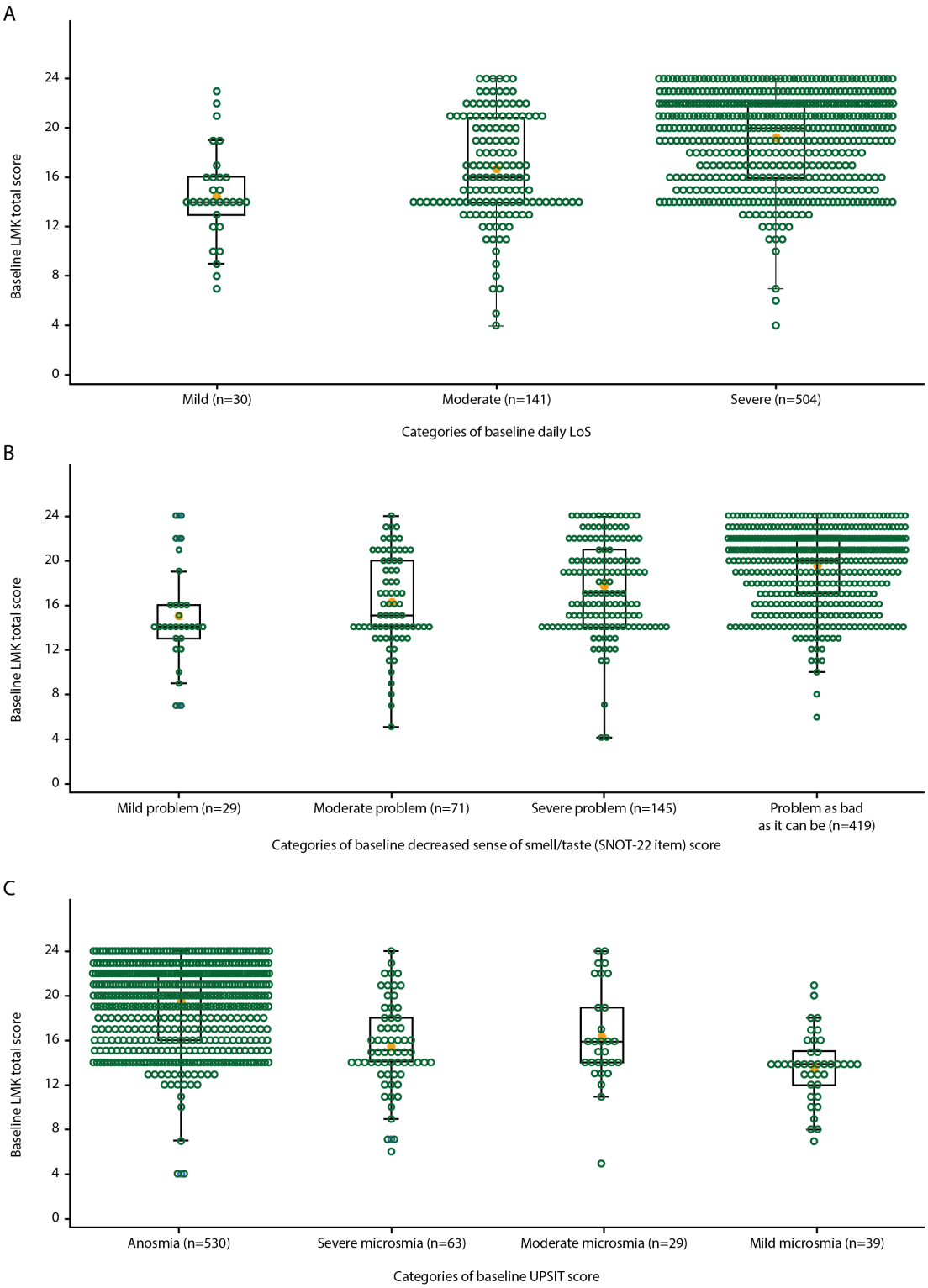
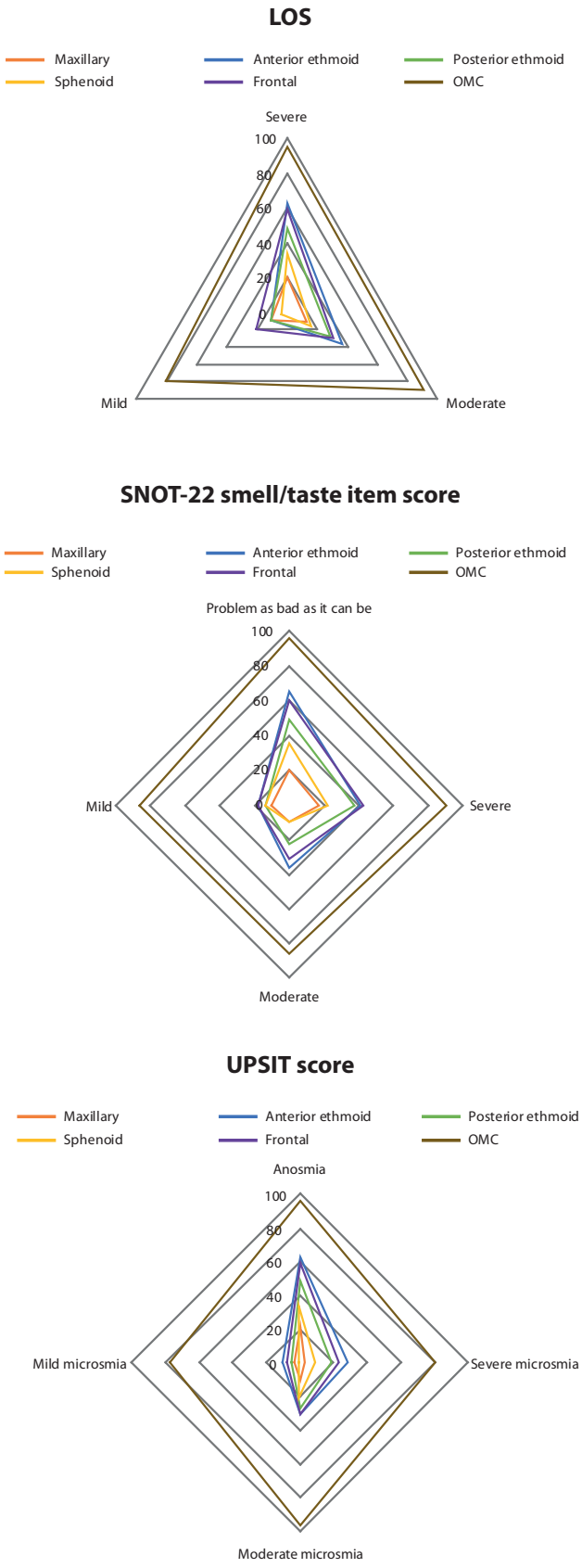


Figure 1. Baseline total LMK-CT score vs. baseline (A) LoS, (B) SNOT-22 smell/taste item score and (C) UPSIT score in patients with impaired smell at baseline (pooled studies). Baseline total LMK-CT scores (range 0–24) vs. baseline loss of smell scores in the pooled (SINUS-24/52) population with impaired smell at baseline (n=688). Patients with impaired smell at baseline defined as those who did not have "None" for LoS, "Normosmia" for UPSIT and "No problem" for SNOT-22 smell/taste item. Open green circles represent individual patient data. The horizontal line represents the median value, the boxes represent the interquartile range and the whiskers extend to the last value within 1.5 × interquartile range. The mean is represented by the orange dot. p-values were derived from the Kruskal–Wallis test for comparing all the groups together. LMK: Lund-Mackay; LMK-CT: LMK-computed tomography; LoS: loss of smell; q2w: every 2 weeks; SNOT-22: 22-item Sino-Nasal Outcome Test; UPSIT: University of Pennsylvania Smell Identification Test.



steroids (SCS).

Correlations between baseline sinus LMK-CT scores and baseline smell scores in the subgroup of patients with impaired smell at baseline (defined as those without "None" for baseline LoS, "Normosmia" for baseline UPSIT and "No problem" for baseline SNOT-22 decreased sense of smell/taste item) were computed using the Spearman correlation coefficient. Kruskal Wallis p-values compared median LMK-CT scores across loss of smell severity categories. Correlations between changes from baseline at Week 24 in LMK-CT score and changes from baseline at Week 24 in LoS, UPSIT, SNOT-22 smell/taste item, NPS and NC in the ITT population were assessed using Spearman correlation.

Least squares mean changes and percentage changes from baseline for the ITT population were derived using an analysis of covariance model with the change from baseline in LMK-CT score as the response variable and the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history and regions as covariates. For the pooled analyses, the study was added as an additional covariate. Data collected after treatment discontinuation were included. Data post SCS or sinus surgery were set to missing and imputed by worst observation carried forward; other missing data were imputed by multiple imputation.

Responder analyses evaluated the proportion of patients in the ITT population who achieved improvements meeting or exceeding the minimum clinically important difference for LMK-CT score (improvement of ≥5 points from baseline [23] to Weeks 24 and 52). Clinically meaningful difference was defined as a score change in a clinical measure, experienced by an individual patient over a predetermined time period that has been demonstrated in the target population to have a significant treatment benefit [27]. The proportion of patients achieving a response was compared between dupilumab and placebo in the ITT population and separately in each subgroup using a Mantel-Haenszel test performed on the association between the responder status

Figure 2. Percentage of patients with complete sinus opacification by sinus and baseline loss of smell severity, measured by LoS, UPSIT score and SNOT-22 smell/taste item score category in patients with impaired smell at baseline (pooled studies). Patients with impaired smell at baseline (n=688) were defined as those who did not have "None" for LoS, "Normosmia" for UPSIT and "No problem" for SNOT-22 smell/taste item. Sinus opacification was measured by LMK-CT using the LMK staging system (0–2). Percentage of patients with score of 2 (total opacification) for each sinus are presented. LMK: Lund-Mackay; LMK-CT: LMK-computed tomography; LoS: loss of smell; OMC: ostiomeatal complex; SNOT-22: 22-item Sino-Nasal Outcome Test; UPSIT: University of Pennsylvania Smell Identification Test.

Table 2. Associations between change from baseline in LMK-CT score and change from baseline in sense of smell and other clinical endpoints with dupilumab at Week 24 (pooled ITT).

		Spearman correlation coefficient (95% CI)			
	n	Δ LMK-CT total	Δ LMK-CT anterior ethmoid	Δ LMK-CT posterior ethmoid	Δ LMK-CT sphenoid
Δ LoS score	418	0.377 (0.292, 0.457)*	0.368 (0.282, 0.448)*	0.334 (0.246, 0.417)*	0.332 (0.244, 0.415)*
Δ SNOT-22 smell/taste item	406	0.300 (0.208, 0.386)*	0.297 (0.206, 0.384)*	0.236 (0.142, 0.326)*	0.294 (0.203, 0.381)*
Δ UPSIT	406	–0.321 (–0.406, –0.231)*	–0.313 (–0.398, –0.222)*	–0.257 (–0.345, –0.163)*	–0.261 (–0.349, –0.168)*
Δ NPS	408	0.456 (0.376, 0.530)*	0.367 (0.280, 0.448)*	0.401 (0.316, 0.479)*	0.341 (0.252, 0.424)*
Δ NC	418	0.334 (0.246, 0.416)*	0.316 (0.227, 0.399)*	0.295 (0.204, 0.380)*	0.250 (0.158, 0.338)*

Analyses are for patients in the pooled ITT population treated with dupilumab 300 mg every 2 weeks (all patients from the 2 studies randomised to dupilumab 300 mg q2w dosing – Arm A over the 52-week treatment period and Arm B [first 24 weeks q2w] of SINUS-52, and the dupilumab arm of SINUS-24). Δ denotes change from baseline at Week 24. *p<0.0001. CI: confidence interval; ITT: intention-to-treat; LMK-CT: Lund-Mackay computed tomography; LoS: loss of smell; NC: nasal congestion/obstruction; NPS: nasal polyps score; SNOT-22: 22-item Sino-Nasal Outcome Test; UPSIT: University of Pennsylvania Smell Identification Test.

and treatment group, stratified by asthma/NSAID-ERD status, prior surgery history, region and, for the pooled analyses, the study as covariates. Odds ratios (ORs) with 95% confidence intervals (CIs) were computed. Patients who underwent or had planned surgery for nasal polyps or received SCS were considered as non-responders for time points after using SCS or surgery.

Results

Baseline analyses: sinus opacification and association with loss of smell severity

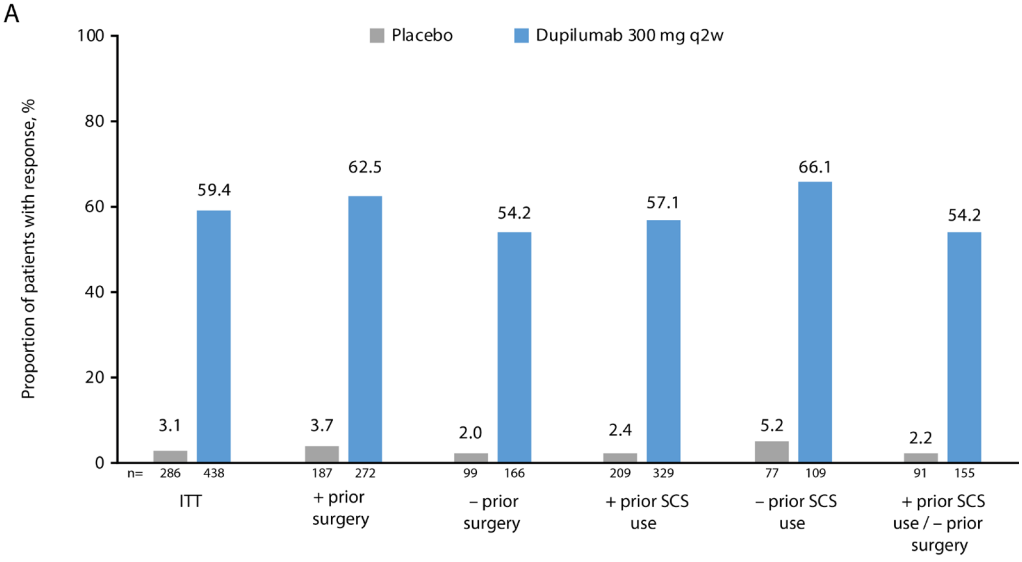
Baseline demographics and disease characteristics were similar between the placebo and dupilumab groups (Table 1). The mean total LMK-CT score was 18.53 in the placebo group and 18.26 in the dupilumab group (out of a maximum possible score of 24), with mean scores for each of the left/right paranasal sinuses ranging from 1.3 to 1.9 (maximum 2), consistent with almost complete sinus opacification. Almost all patients (688/724, 95.0%) had impaired smell, with the majority of these patients showing severe loss of smell across all 3 measures: 72.5% by LoS ("Severe"), 59.5% by SNOT-22 ("Problem as bad as it can be") and 76.1% by UPSIT ("Anosmia").

Among patients with impaired smell at baseline, sinus opacification was highest in those with the most severe loss of smell (Figure 1). Median LMK-CT total scores showed increased opacification with increasing loss of smell severity measured by LoS, SNOT-22 smell/taste item, and UPSIT (all p<0.0001). Spearman correlation coefficients for the relationships between LMK-CT total score and LoS, SNOT-22 smell/taste item, and UPSIT at baseline were 0.311, 0.313, and –0.348, respectively, indicating weak correlations (Figure S1). In addition, complete opacification of paranasal sinuses was more frequently associated with severe than mild loss of smell at baseline (Figure 2). The proportion of patients with complete opacification of the anterior ethmoid sinus was 62.3%, 64.7% and 62.5% for those with severe loss of smell at baseline as assessed by LoS, SNOT-22 smell/taste item and UPSIT, respectively, compared with 10.0%, 17.2% and 10.3% for patients with mild loss of smell at baseline (all p<0.0001). The corresponding proportions for the posterior ethmoid sinus were 47.8%/49.2%/48.9% vs. 10.0%/13.8%/5.1% (all p<0.0001) and the proportions for the sphenoid sinus were 33.3%/34.8%/33.4% vs. 3.3%/13.8%/0.0% (p<0.0001, p=0.002, and p-value not estimable, respectively).

Associations between changes in LMK-CT scores and changes in sense of smell and other clinical endpoints

The change from baseline in LMK-CT total score at Week 24 with dupilumab showed weak correlation with the changes from baseline in all three measures of sense of smell (LoS, SNOT-22 smell/taste item and UPSIT; Spearman correlation coefficients were 0.377, 0.300 and –0.321, respectively [Table 2 and Figure S2]). Similar correlations were found between changes in sense of smell scores and changes in LMK-CT scores for the anterior ethmoid, posterior ethmoid and sphenoid sinuses (Table 2). In addition, changes in LMK-CT total score and ethmoid and sphenoid sinus scores at Week 24 were weakly to moderately correlated with changes in the two coprimary endpoints of the SINUS studies, NPS (Spearman correlation coefficients 0.341 to 0.456) and NC (0.250 to 0.334) (Table 2 and Figure S2). Associati-

A



Odds ratio vs. placebo (95% confidence interval)*					
56.8 (26.3, 122.4)	51.2 (21.3, 123.3)	72.5 (15.1, 348.2)	60.5 (22.7, 161.1)	63.5 (15.3, 262.4)	64.3 (13.5, 306.8)

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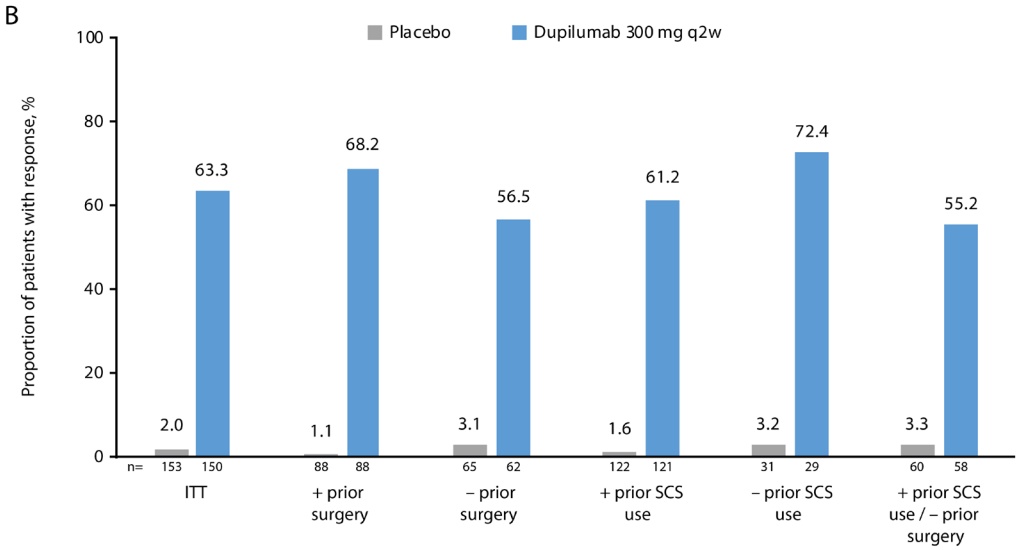

Odds ratio vs. placebo (95% confidence interval)*					
67.5 (21.4, 212.6)	170.2 (23.0, 1261.8)	33.3 (7.9, 140.2)	68.8 (17.6, 268.2)	42.8 (6.1, 301.6)	30.1 (7.1, 127.5)

Figure 3. Responder rate for clinically meaningful improvement in LMK-CT total score from baseline at (A) Week 24 (pooled ITT) and (B) Week 52 (SINUS-52 ITT). Responders defined as patients with improvement in LMK-CT total score of ≥5 points (see Methods) [23]. Patients indicated for surgery or received SCS and missing data considered non-responders. For patients who discontinued treatment without using SCS or surgery, data collected off-treatment were used to determine responder status. Odds ratios vs. placebo were derived using Mantel-Haenszel estimator. *p<0.0001 vs. placebo. ITT: intention-to-treat; LMK-CT: Lund-Mackay computed tomography; q2w: every 2 weeks; SCS: systemic corticosteroid.

ons between changes in LMK-CT scores and changes in sense of smell and other clinical endpoints were similar at Week 52.

Dupilumab effect on sinus opacification

A significantly greater proportion of dupilumab-treated patients achieved the clinically meaningful response threshold for change in LMK-CT total score (defined as improvement ≥5 points) at Weeks 24 and 52 than those treated with placebo. In the pooled ITT population, 59.4% of patients in the dupilumab group were responders at Week 24, compared with 3.1% in the placebo group (Figure 3; OR 56.8; 95% CI 26.3, 122.4; p<0.0001). The responder rate at Week 52 in patients treated with dupilumab 300 mg q2w in SINUS-52 was 63.3% vs. 2.0% with placebo (OR 67.5; 95% CI 21.4, 212.6; p<0.0001). The dupilumab treatment effect was broadly similar in the subgroups of patients with prior history of SCS use and/or surgery (Figure 3). An illustration of sinus CT scan images for a patient who responded to dupilumab with a change from baseline exceeding the clinically meaningful threshold at Week 24 is shown in Figure S3. Greater proportions of dupilumab-treated than placebo-treated patients showed complete resolution of sinus opacification (LMK-CT total score = 0) across the majority of individual sinus components at Weeks 24 and 52 (Figure S4). The changes in distribution of opacification (normal/partial/fully occluded) in individual sinuses with dupilumab vs. placebo were statistically significant (p<0.05) in patients demonstrating severe smell impairment (LoS = severe; UPSIT = anosmia; and SNOT-22 smell/taste item = problem as bad as it can be) at Weeks 24 and 52. Within the other categories of smell impairment, comparisons between dupilumab and placebo were not universally statistically significant (Figure S4).

Discussion

This comprehensive analysis of patients with CRSwNP in the SINUS-24 and SINUS-52 trials demonstrates that patients had a significant burden of sinus disease at baseline, with almost complete opacification of all paranasal sinuses bilaterally. Higher LMK-CT scores at baseline were associated with greater severity of smell loss.

The association between sinus disease and impaired olfaction in chronic rhinosinusitis remains controversial, with some studies suggesting that olfactory cleft involvement rather than paranasal opacification may be more important in loss of smell [28, 29]. However, other studies have reported that both olfactory cleft and sinus opacification are correlated with smell loss [10] and are predictive of smell recovery after surgery for nasal polyposis [30]. Our study did not include analysis of olfactory cleft opacification. It has been suggested that disease localised in the ethmoid and sphenoid sinuses might play a greater role in olfactory impairment than the maxillary and frontal sinuses [11]. Our findings, that patients with severe loss of smell had greater opacification in the ethmoid and sphenoid sinuses than those with less severe smell impairment, support this concept. Moreover, among the patients in our analysis with severe loss of smell, more than 60% had complete opacification of the anterior ethmoid sinus, with lower proportions for the posterior ethmoid (48%) and sphenoid (33%). These findings suggest that inflammatory involvement of the anterior ethmoid sinuses may play an important role in olfactory impairment in patients with severe CRSwNP.

Loss of sense of smell is a prominent symptom frequently reported by patients with CRSwNP as well as one of the most important symptoms affecting their overall quality of life [3, 4]. The majority of patients in the SINUS studies had severe loss of smell at baseline, as assessed using 3 different measures for olfactory dysfunction. The association between degree of smell impairment and LMK-CT scores suggests that loss of smell could serve as a marker of sinus involvement and disease severity in patients with CRSwNP. Previous analyses of the SINUS study population have shown that loss of smell is associated with other symptoms of disease. In one recent analysis, patients with baseline anosmia (UPSIT score <19) had worse CRSwNP symptoms (as measured using Total Symptom Score) than patients who did not have baseline anosmia [21]. Another analysis showed that improvements in nasal congestion and health-related quality of life (as measured using SNOT-22) with dupilumab were greater in patients with better olfactory outcomes by UPSIT at Weeks 24 and 52 [31].

The improvements in LMK-CT score of the ethmoid and sphenoid sinuses with dupilumab were weakly correlated with the improvements in sense of smell and other outcomes (Spearman correlation coefficients 0.24 to 0.40). While this suggests that reduced opacification of the ethmoid and sphenoid sinuses was associated with improvements in patient-reported outcomes such as sense of smell and nasal congestion, and also with improvements in olfactory function and nasal polyp score, the low strength of the correlations indicates that other factors are also involved. The sparse assessment schedule for LMK-CT (baseline and Week 24 in both studies, and additionally at Week 52 in SINUS-52) contrasts with the early and frequent assessment of smell. While this assessment schedule provides a good picture of the rapid onset of smell recovery with dupilumab, evident by Day 3 [21], it does not provide information on the onset of LMK-CT reduction before 24 weeks. The phase 2 study of dupilumab in CRSwNP reported significant improvement in LMK-CT score vs. placebo at Week 16 [32], but studies employing earlier LMK-CT assessments would be required to investigate the time course of LMK-CT reduction before 16 weeks. Reduction of sinus opacification may play a role in smell improvement, although other mechanisms, such as type 2 inflammation [33], may be involved and will require further study.

Thresholds for defining clinically meaningful change within individual patients with CRSwNP for LMK-CT score, using data from the SINUS-24 and SINUS-52 trials, have been recently estimated

[23]. Using the responder definition of improvement of ≥5 points in total LMK-CT score determined by Han et al. [23], our results showed that a significantly greater proportion of patients treated with dupilumab vs. placebo achieved a clinically meaningful improvement in LMK-CT total score at Week 24, and at Week 52. In addition, the proportion of dupilumab-treated patients achieving the ≥5-point threshold of improvement was similar in subgroups of patients considered difficult to treat, namely those with prior sinus surgery and/or SCS use.

Conclusion

Sinus opacification (particularly anterior ethmoid opacification) was highest in patients with severe impairment of smell, as measured by UPSIT, LoS score and SNOT-22 smell/taste item. Severely impaired smell at baseline was associated with increased LMK-CT scores for ethmoid and sphenoid sinuses in this cohort and can potentially serve as one of the markers of objective CRSwNP disease severity. In practice, assessment of sense of smell may serve as a simple method to identify patients with high burden of disease including sinus opacification.

Abbreviations

CI: confidence interval; CRSwNP: chronic rhinosinusitis with nasal polyps; CT: computed tomography; ITT: intention-to-treat; LMK-CT: Lund-Mackay computed tomography; LoS: loss of smell; NC: nasal congestion/obstruction; NPS: nasal polyps score; NSAID-ERD: non-steroidal anti-inflammatory drug-exacerbated respiratory disease; OR: odds ratio; q2w: every 2 weeks; SCS: systemic corticosteroids; SNOT-22: 22-item Sino-Nasal Outcome Test; UPSIT: University of Pennsylvania Smell Identification Test

Authorship contribution

SEL, CB, GG and SHC were involved in data acquisition; AP conducted the data analysis; all authors were involved in the interpretation of the data, provided critical feedback during development of the manuscript, approved the final version of the manuscript for submission and agree to be accountable for all aspects of the work.

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Conflict of interest

Lee SE: AstraZeneca, GlaxoSmithKline, Regeneron Pharmaceuticals Inc., Sanofi – clinical trial funding; AstraZeneca, Genentech, GlaxoSmithKline, Novartis, Regeneron Pharmaceuticals Inc., Sanofi – advisory board member. Amin N, Siddiqui S: Regeneron Pharmaceuticals Inc. – former employees, may hold stock and/or stock options. Mannent LP, Praestgaard A, Khan AH, Jacob-Nara JA: Sanofi – employees and may hold stock and/or stock options in the company. Bachert C: ALK-Abelló A/S, AstraZeneca, GlaxoSmithKline, Mylan, Novartis, Sanofi, Stallergenes Greer – advisory board member, speaker fees. Gross G: ALK-Abelló A/S, Sanofi – speaker; Merck, Novartis, Sanofi – research grants. Cho SH: Regeneron Pharmaceuticals Inc., Sanofi – research grants. Nash S, Kamat S: Regeneron Pharmaceuticals Inc. – employees and may hold stock and/or stock options in the company.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

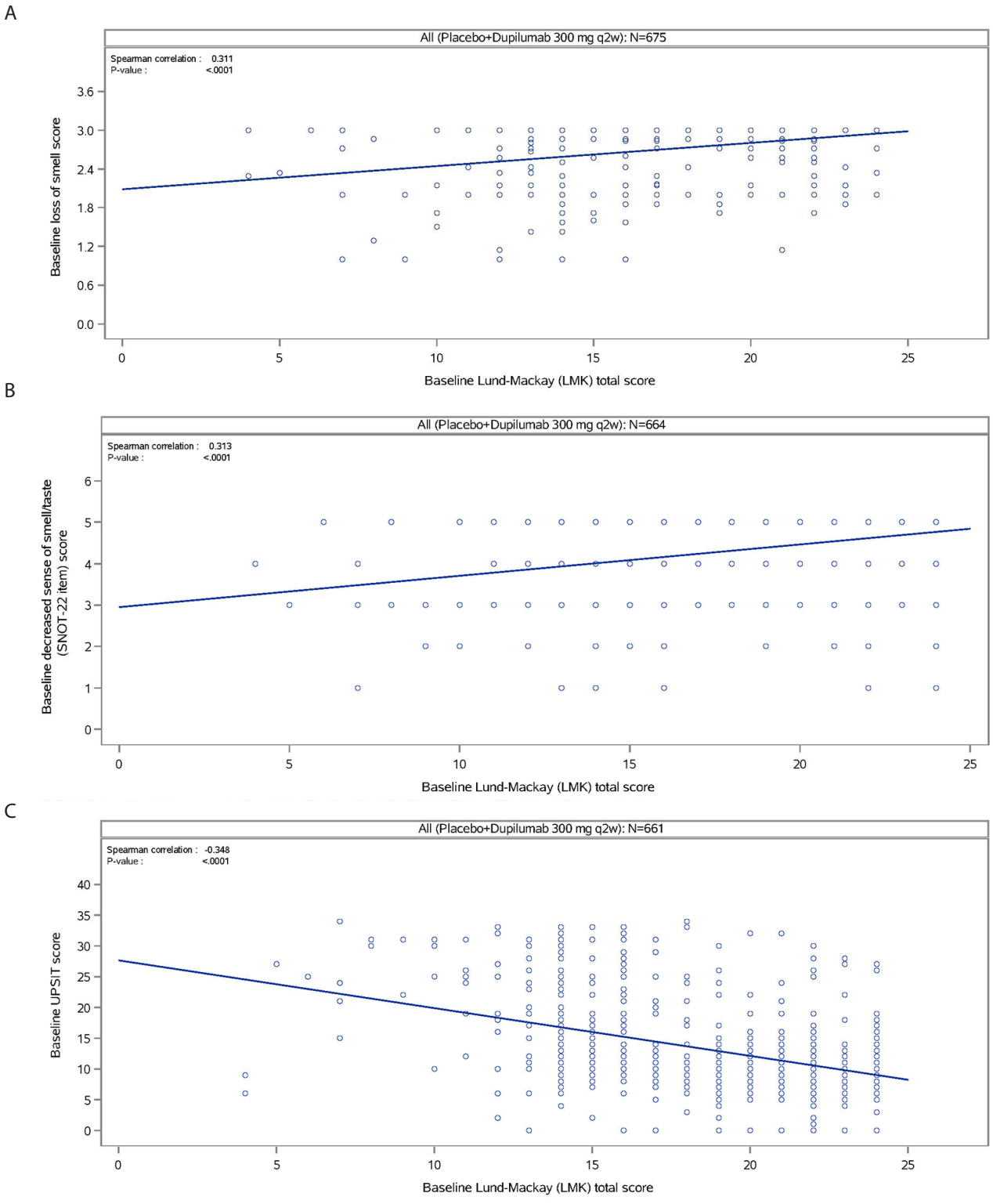


Figure S1. Scatter plots of baseline LMK-CT total score vs. baseline A) loss of smell score, B) SNOT-22 smell/taste item score, and C) UPSIT score. LMK: Lund-Mackay; LMK-CT: LMK computed tomography; q2w: every 2 weeks; SNOT-22: 22-item Sino-Nasal Outcome Test; UPSIT: University of Pennsylvania Smell Identification Test.

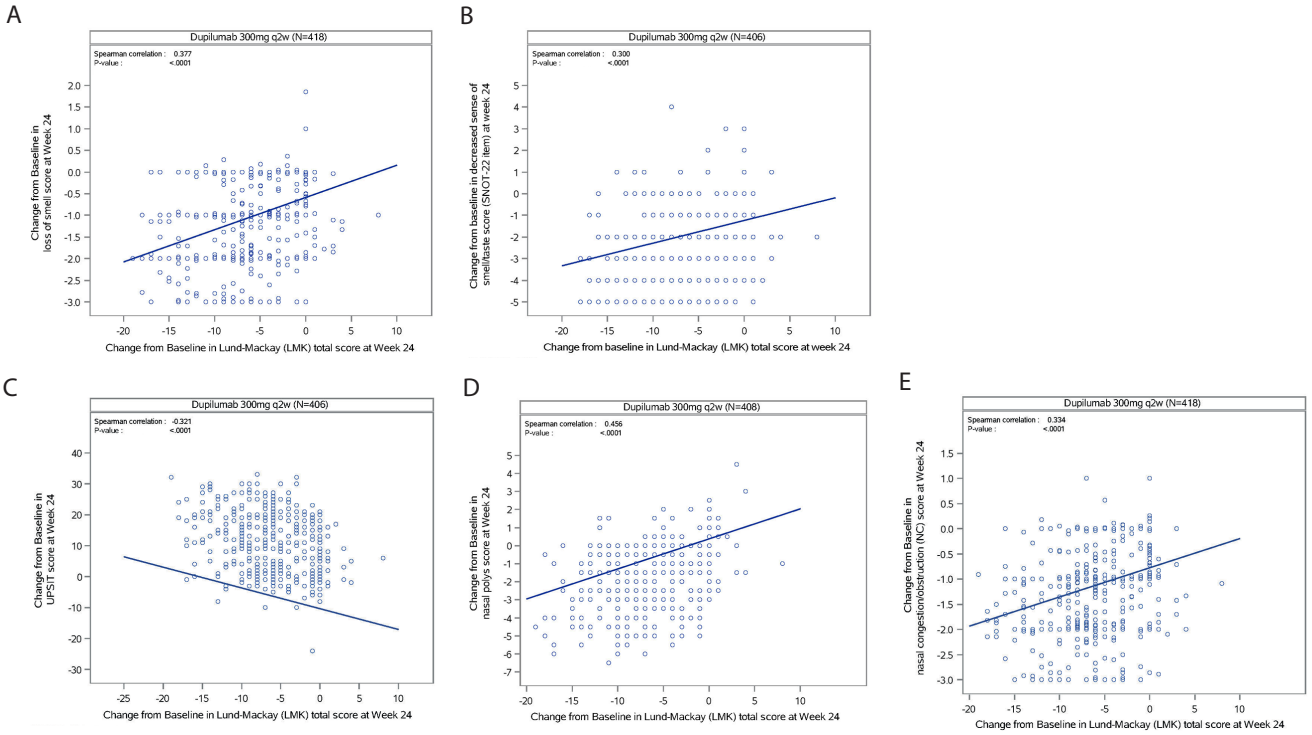


Figure S2. Scatter plots of the associations between change from baseline in LMK-CT score and change from baseline in A) loss of smell score, B) SNOT-22 smell/taste item score, C) UPSIT score, D) NPS, and E) NC score with dupilumab at Week 24 (pooled ITT). ITT: intention-to-treat; LMK: Lund-Mackay; LMK-CT: LMK computed tomography; NC: nasal congestion/obstruction; NPS: nasal polyp score; q2w: every 2 weeks; SNOT-22: 22-item Sino-Nasal Outcome Test; UPSIT: University of Pennsylvania Smell Identification Test.

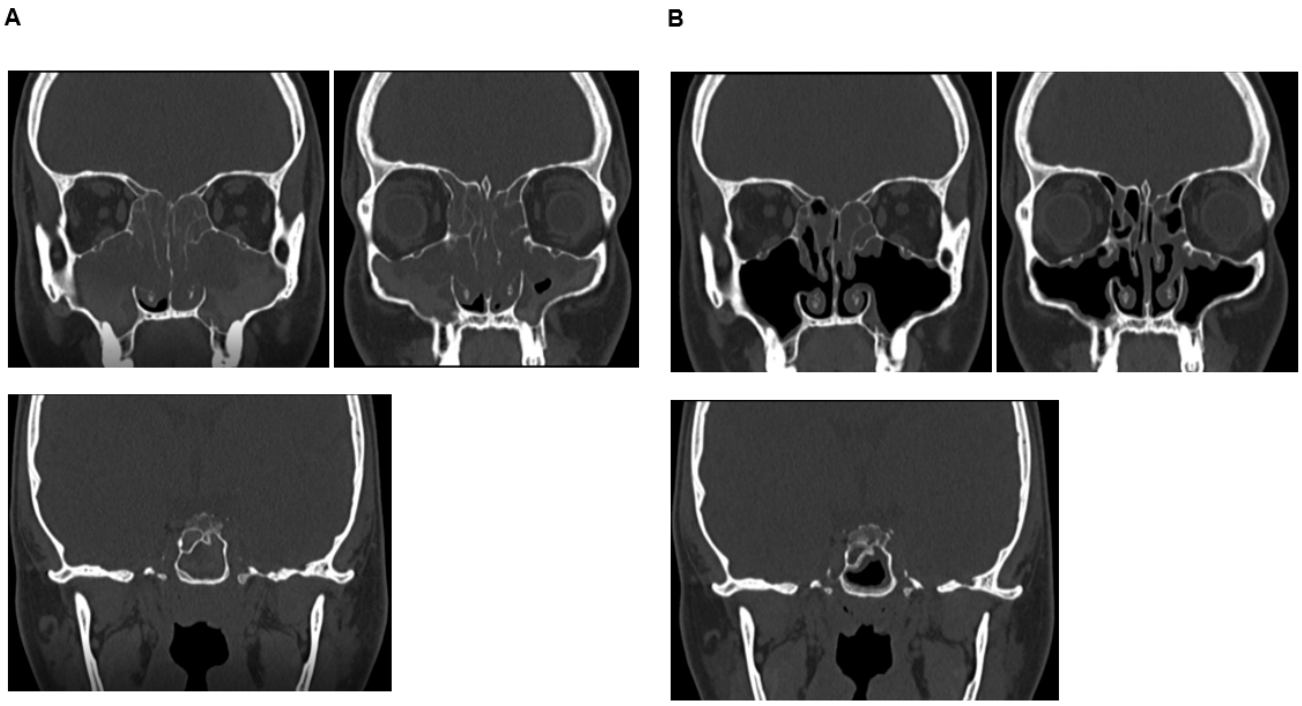
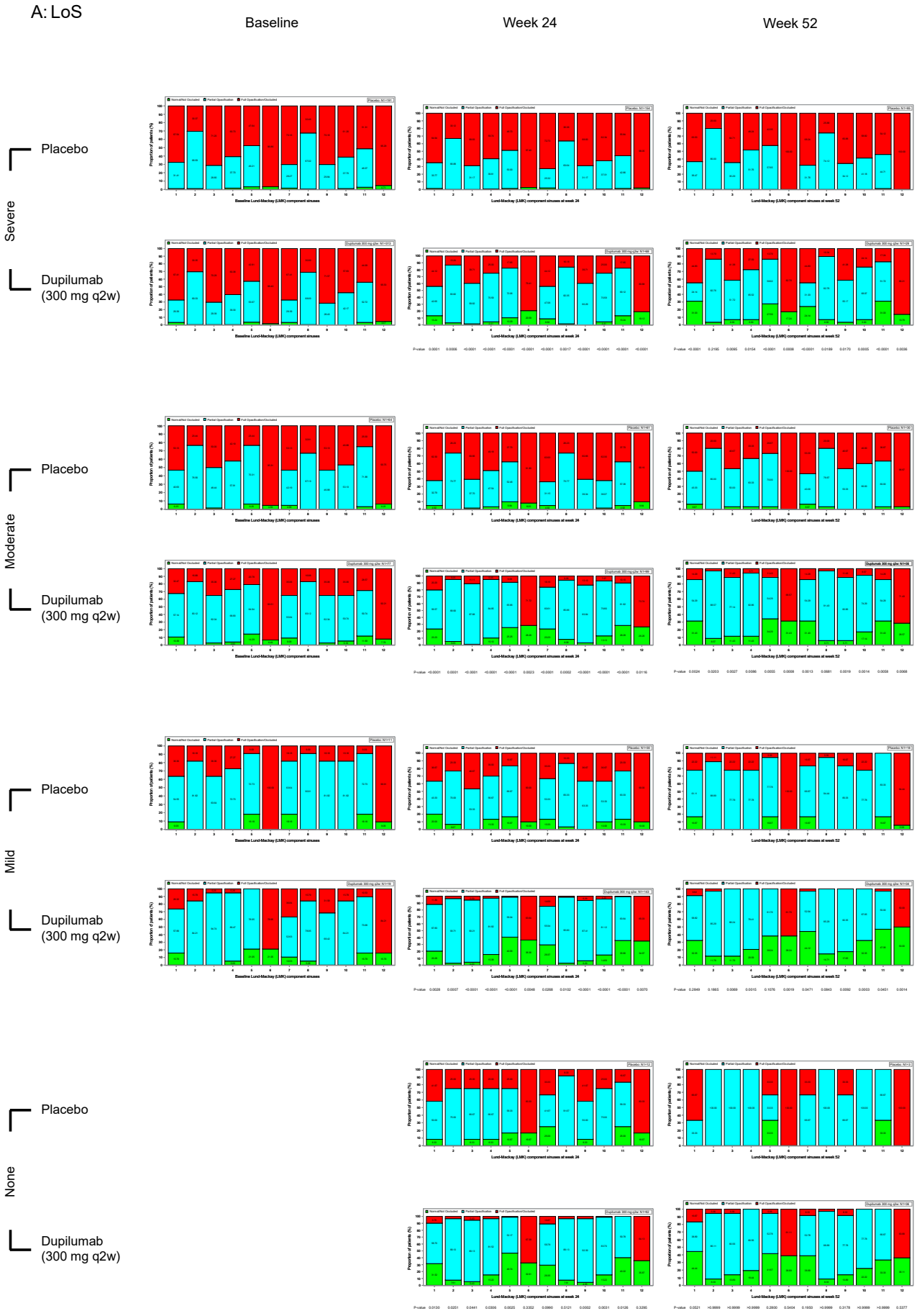
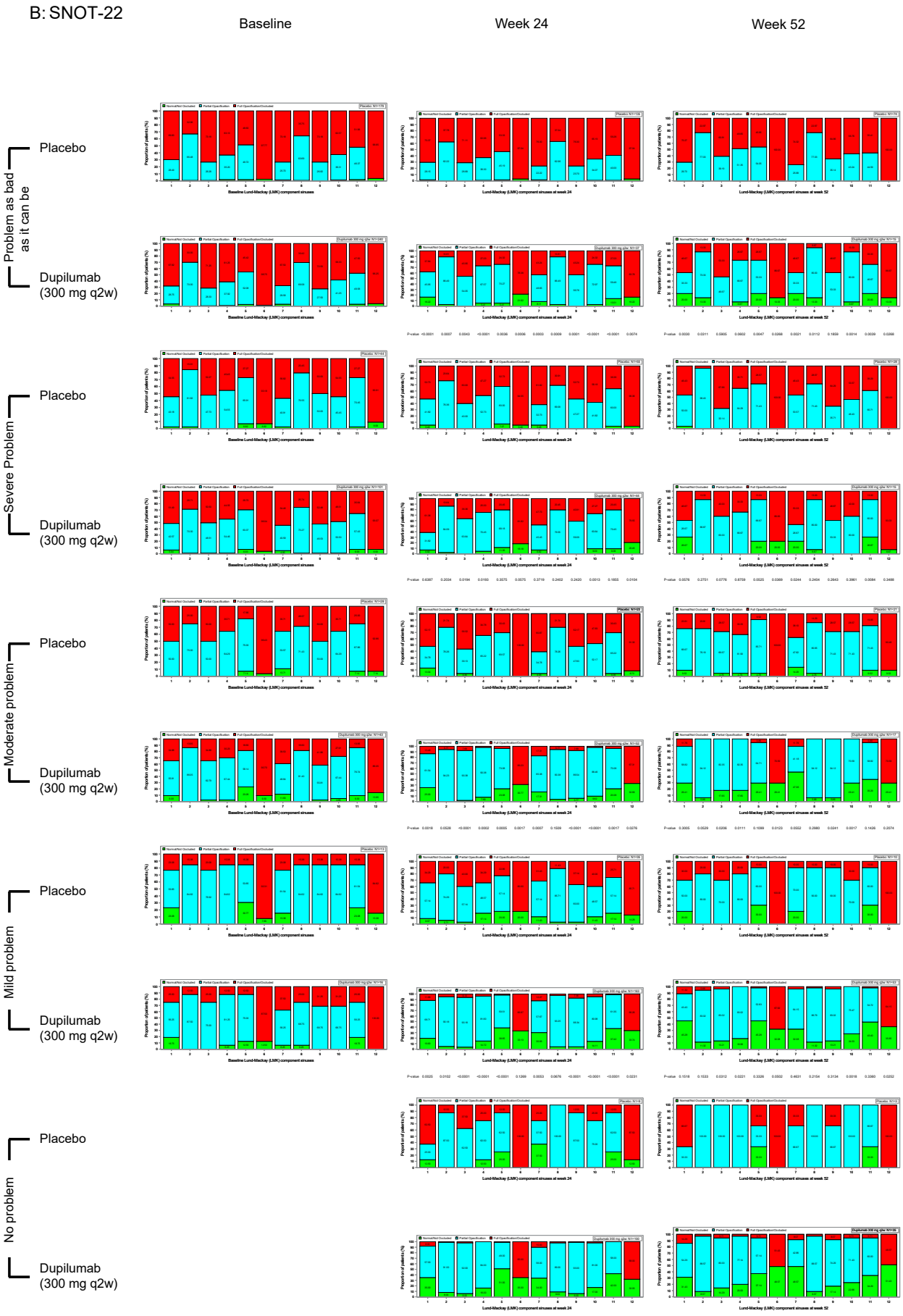


Figure S3. LMK-CT scans of a patient considered to be a dupilumab responder at baseline and Week 24 (SINUS-24). Responder defined as improvement in LMK-CT total score of ≥5 (clinically meaningful improvement for this measure [see Methods]) [23]. (A) Baseline CT scans (LMK-CT total score = 23); (B) Week 24 CT scans (LMK-CT total score = 10). Provided by Dr. Joseph Han, Division of Allergy, Eastern Virginia Medical School, Norfolk, VA, USA. CT: computed tomography; LMK-CT: Lund-Mackay CT.


A: LoS
Baseline
Week 24
Week 52
Severe
Placebo
Dupilumab (300 mg q2w)
Moderate
Placebo
Dupilumab (300 mg q2w)
Mild
Placebo
Dupilumab (300 mg q2w)
None
Placebo
Dupilumab (300 mg q2w)


B: SNOT-22
Baseline
Week 24
Week 52
Problem as bad as it can be
Placebo
Dupilumab (300 mg q2w)
Severe Problem
Placebo
Dupilumab (300 mg q2w)
Moderate problem
Placebo
Dupilumab (300 mg q2w)
Mild problem
Placebo
Dupilumab (300 mg q2w)
No problem
Placebo
Dupilumab (300 mg q2w)

C: UPSIT

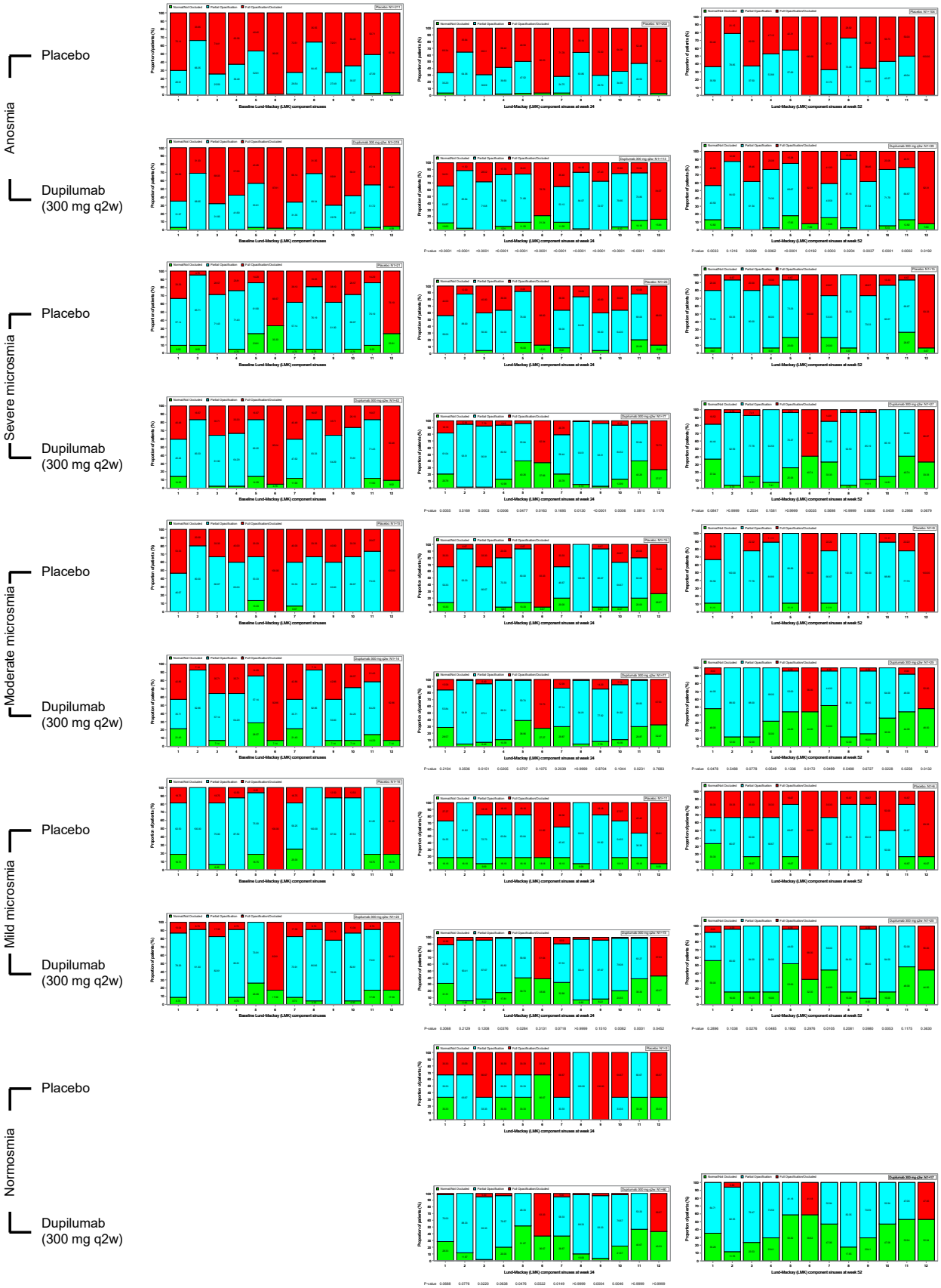

Baseline
Week 24
Week 52
Anosmia
Placebo
Dupilumab (300 mg q2w)
Severe microsmia
Placebo
Dupilumab (300 mg q2w)
Moderate microsmia
Placebo
Dupilumab (300 mg q2w)
Mild microsmia
Placebo
Dupilumab (300 mg q2w)
Normosmia
Placebo
Dupilumab (300 mg q2w)

Figure S4. Distribution of LMK-CT scores by sinus at baseline and Week 24 (pooled studies) and Week 52 (SINUS-52) in patients with impaired smell at baseline. Percentage of patients with no, partial, or total sinus opacification (0, 1, or 2 by LMK-CT staging) after 24 weeks (pooled SINUS-24 and SINUS-52) and 52 weeks (SINUS-52) of treatment with placebo or dupilumab 300 mg q2w. Results are given by sinus and by loss of smell severity by A) LoS, B) SNOT-22 smell/taste item, and C) UPSIT. Ostiomeatal complex measured as 0 (no abnormality) or 2 (total opacification). 1, Left frontal; 2, left maxillary; 3, left anterior ethmoid; 4, left posterior ethmoid; 5, left sphenoid; 6, left ostiomeatal complex; 7, right frontal; 8, right maxillary; 9, right anterior ethmoid; 10, right posterior ethmoid; 11, right sphenoid; 12, right ostiomeatal complex. [a] No patients from the placebo group had normosmia (UPSIT) at Week 52. LMK: Lund-Mackay; LMK-CT: LMK computed tomography; LoS: loss of smell score; q2w: every 2 weeks; SNOT-22: 22-item Sino-Nasal Outcome Test; UPSIT: University of Pennsylvania Smell Identification Test.