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Respiratory Infections and Anti-Infective Medication Use From Phase 3

Dupilumab Respiratory Studies

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ABSTRACT

BACKGROUND: Patients with asthma and/or chronic rhinosinusitis with nasal polyps (CRSwNP) experience recurrent respiratory tract infections. Dupilumab targets type 2 inflammation, a common underlying pathophysiology of both conditions, with proven efficacy.

OBJECTIVE: To examine investigator-reported respiratory infection adverse events and anti-infective medication use with dupilumab vs placebo in patients with moderate-to-severe asthma or severe CRSwNP.

METHODS: We performed a *post hoc* analysis of the pivotal phase 3 trials LIBERTY ASTHMA QUEST (NCT02414854) and LIBERTY NP SINUS-52 (NCT02898454) in moderate-to-severe asthma and severe CRSwNP, respectively.

RESULTS: Investigator-reported respiratory infection events occurred at a significantly lower incidence in patients treated with dupilumab vs placebo, in both asthma (22% lower; $P < .0001$; 95% confidence interval [CI] 0.71-0.85) and CRSwNP (38% lower; $P < .0001$; [95% CI 0.51-0.75]). Reported upper and lower respiratory tract infection events were numerically or significantly lower in dupilumab-treated patients in both conditions, as were the number of patients experiencing investigator-reported infections. Significantly less systemic anti-infective medication use occurred in dupilumab vs placebo in asthma (24% lower; $P < .0001$; [95% CI 0.70-0.83]) and CRSwNP patients (49% lower; $P < .0001$; [95% CI 0.43-0.61]), and significantly fewer dupilumab-treated patients used anti-infective medications. When examined by season and month, the data indicated that investigator-reported respiratory infections and anti-infective medication use were less frequent in dupilumab- vs placebo-treated patients throughout the calendar year.

CONCLUSION: Dupilumab treatment was associated with a reduced incidence of investigator-reported respiratory infections in patients with moderate-to-severe asthma or

77 severe CRSwNP. Further studies are required to determine the mechanism behind this
78 reduction.

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What is already known about this topic? Patients with asthma or chronic rhinosinusitis with nasal polyps (CRSwNP) have a predisposition to respiratory infections.

What does this article add to our knowledge? Patients treated with dupilumab vs placebo experienced reduced investigator-reported upper and lower airway respiratory infections and anti-infective medication use in asthma or CRSwNP patients throughout the calendar year.

How does this study impact current management guidelines? Reductions in adverse events of infections and anti-infective medication may benefit quality of life, health care resource utilization, clinical outcomes, and antibiotic stewardship

Key words: Asthma; Chronic rhinosinusitis with nasal polyps; Respiratory tract infections; Anti-infective medication; Antibiotics; Exacerbations; Oral corticosteroids, Dupilumab

92 *Abbreviations used*93 *100PY- 100 patient-years*94 *AD- Atopic dermatitis*95 *CI- Confidence interval*96 *CRSwNP- Chronic rhinosinusitis with nasal polyps*97 *HLGT- High-Level Group Term*98 *HLT- High-Level Term*99 *IL- Interleukin*100 *ICS- Inhaled corticosteroid*101 *ITT- Intention-to-treat*102 *MedDRA- Medical Dictionary for Regulatory Activities*103 *NCS- Nasal congestion/obstruction score*104 *NEC- Not elsewhere classified*105 *NPS- Nasal Polyp Score*106 *OCS- Oral corticosteroid*107 *q2w- Every 2 weeks*108 *SC- Subcutaneous*

INTRODUCTION

Patients with asthma or chronic rhinosinusitis with nasal polyps (CRSwNP) have a predisposition to respiratory infections.^{1,2} In both conditions, type 2 inflammation damages the airway epithelium, increasing susceptibility to upper and lower airway infections^{3,4} which can provoke exacerbations.^{2,5} While type 2 inflammatory cytokines, such as interleukin (IL)-4, IL-5, and IL-13, play pivotal roles in the pathogenesis of asthma and CRSwNP,^{6,7} they are not crucial to host defense mechanisms against most infectious agents. Additionally, type 2 inflammation has been shown to impair type 1 responses necessary to defend the airway against viruses and bacteria.⁸

The shared pathophysiology of asthma and CRSwNP has important implications for their diagnosis and management, particularly as they often occur together.⁹ This provides a compelling rationale for treatments directed at the underlying systemic inflammation in patients with either condition.¹⁰

Dupilumab, a fully human VelocImmune[®]-derived^{11,12} monoclonal antibody, blocks the shared receptor component for IL-4 and IL-13, key and central drivers of type 2 inflammation in multiple diseases.^{13,14} Dupilumab is approved for patients with type 2 inflammatory diseases, including atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyps.¹⁵⁻²⁴

Patients with AD, where skin is the primary organ affected, have an increased risk of serious skin infections.²⁵ Dupilumab vs placebo has demonstrated reduced rates of skin infections in AD patients, with a concomitant reduction in the need for systemic anti-infectives.^{26,27} Early reports have suggested that dupilumab treatment has efficacy in patients with autosomal dominant hyperimmunoglobulin E syndrome, a condition characterized by skin infections, AD, and elevated IgE.²⁸ Whether the benefit of dupilumab in reducing skin infection rates in these two conditions also applies to respiratory infections in asthma and

CRSwNP patients is unknown. Mechanistically, there may be different risk factors involved in airway vs skin infections, and it is likely that the specific pathogens involved vary depending on the anatomical site.

LIBERTY ASTHMA QUEST (NCT02414854)¹⁷ and LIBERTY NP SINUS-52 (NCT02898454)²¹ were phase 3 studies conducted over a 52-week period; they were pivotal in securing the approval of dupilumab for asthma (QUEST) and CRSwNP (SINUS-52). As respiratory infections can cause severe consequences for patients with asthma or CRSwNP, this *post hoc* analysis aimed to compare the rate of investigator-reported adverse events of respiratory infections and the use of anti-infection medication, overall and by season, in patients treated with dupilumab vs placebo during the treatment period of both studies. The analysis also examined whether dupilumab efficacy differed in patients who experienced respiratory infections.

METHODS

Study design and patients

LIBERTY ASTHMA QUEST and LIBERTY NP SINUS-52 were randomized, multicenter, double-blind, placebo-controlled, parallel group studies that assessed the efficacy and safety of dupilumab as an add-on to standard of care. In QUEST, adults and adolescents with uncontrolled moderate-to-severe asthma despite current treatment with medium-to-high-dose inhaled glucocorticoid plus up to two additional controllers were randomized in a 2:2:1:1 ratio to subcutaneous (SC) dupilumab 200 mg (loading dose 400 mg) or 300 mg (loading dose 600 mg) every 2 weeks (q2w) or matched-volume placebo for 52 weeks. Patients remained on medium-to-high dose inhaled corticosteroids (ICS) throughout the treatment period, the dose and regimen of which did not change, with the exception of transient dose increases in addition to the use of a short-acting β_2 -adrenergic receptor agonist as needed for the relief of acute symptoms. Use of systemic steroids was not permitted during the screening or treatment periods. In SINUS-52, adults with severe CRSwNP despite intranasal corticosteroid therapy before randomization and having received systemic corticosteroids in the preceding 2 years or previous sinonasal surgery were randomized 1:1:1 to SC dupilumab 300 mg q2w for 52 weeks; dupilumab 300 mg q2w for 24 weeks then every 4 weeks for the remaining 28 weeks; or placebo q2w for 52 weeks. Saline nasal lavage, systemic antibiotics, short-course systemic corticosteroids, or sinonasal surgery were permitted as needed during the treatment and follow-up periods. Use of systemic steroids for > 2 weeks was not permitted during the screening or treatment periods. Full details of study design and methodology have been reported previously.^{17,21} The co-primary efficacy endpoints of QUEST were annualized rate of severe exacerbations during the 52-week treatment period and change from baseline at Week 12 in pre-bronchodilator forced expiratory volume in 1 second.¹⁷ In SINUS-52, co-primary endpoints were change from

baseline in endoscopic nasal polyp score (NPS) and nasal congestion/obstruction score (NCS) at Week 24.²¹ Both studies were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guideline, and applicable regulatory requirements. All patients provided written informed consent before participating in the trial, and the protocols and consent forms were approved by institutional review boards and local ethics committees prior to patient enrollment.

In this analysis, we examined rates of investigator-reported adverse events of respiratory infections in the safety population of each study, including all patients who received ≥ 1 dose or part of a dose; data were analyzed according to the intervention received. Safety data for dupilumab- and placebo-treated patients were pooled across doses in each of the studies.

Study endpoints

Safety was monitored, and adverse events were reported by the investigators at each site. Adverse events were recorded using the Medical Dictionary for Regulatory Activities (MedDRA) hierarchy version in effect at Sanofi at the time of the database lock for each study (QUEST: 20.0; SINUS-52: 21.0). For this analysis, we used the High-Level Group Term (HLGT) “respiratory tract infections,” which contains all forms of respiratory infections, with each infection event classified within one of several High-Level Terms (HLTs). We present data for HLTs that have been divided into 2 groups based on the location of the infection: upper respiratory tract HLTs, including “upper respiratory tract infections not elsewhere classified (NEC),” “viral upper respiratory tract infections,” and “bacterial upper respiratory tract infections”; and lower respiratory tract HLTs, including “lower respiratory tract infections NEC,” “bacterial lower respiratory tract infections,” and “viral lower respiratory tract infections.” Adverse event terms were chosen by the investigator and are not necessarily supported by accompanying laboratory data.

Anti-infective medication use was reported by the investigator using pre-defined categories. This analysis focused on systemic anti-infective use, which included the following categories: anti-bacterials for systemic use, anti-mycotics for systemic use, anti-mycobacterials, anti-virals for systemic use, immune sera, and immunoglobulins.

Data analysis

The annualized rate of respiratory infections was analyzed at both the event level (respiratory infection events per 100 patient-years [100PY]) and the patient level (patients with ≥ 1 respiratory infection per 100PY [patients/100PY]) and was performed on the dataset overall, by season, and by month. Risk ratios for dupilumab vs placebo were estimated using a Poisson regression model with the treatment arm as a covariate and the log value of treatment period duration as the offset variable.

The use of systemic anti-infective medications was also analyzed at both the event level (number of events of anti-infective medication use/100PY) and the patient level (number of patients/100PY). Data were calculated overall and by month.

The efficacy of dupilumab vs placebo was assessed in subgroups of patients who did or did not experience respiratory tract infections. In QUEST, the annualized rate of severe exacerbations was analyzed using a negative binomial regression model, with the total number of events occurring during the 52-week treatment period as the response variable; with treatment groups, age, region, baseline eosinophil strata, baseline ICS dose level (low/medium or high), and number of severe exacerbations in the previous year as covariates; and duration of exposure as the offset variable. During QUEST, patients were permitted to use rescue medication, albuterol/salbutamol or levalbuterol/levosalbultamol metered dose inhaler, as needed. Rescue medication use was recorded by patients using an electronic diary.

In SINUS-52, the proportion of dupilumab- vs placebo-treated patients reporting oral corticosteroid (OCS) use (binary status, i.e., receiving OCS or not) during the treatment

period in subgroups of patients who did or did not experience respiratory tract infections was analyzed using a logistic regression model with treatment, subgroup, and treatment-by-subgroup interactions as fixed factors. The change from baseline in NPS, assessed by endoscopy, and NCS recorded daily by patients in an electronic diary was evaluated in these subgroups.

All *P*-values reported are nominal *P* values from *post hoc* analyses.

Pearson correlation analyses were performed for respiratory infections and exacerbation rate in asthma patients and OCS use in CRSwNP patients.

RESULTS

Patients

In QUEST, the proportion of patients using high-dose ICS at baseline was comparable across treatment arms (around 51%).¹⁷ Similarly, in SINUS-52, the proportion of patients at baseline who reported having used systemic corticosteroids in the preceding 2 years was comparable across treatments (around 80%).²¹ Further baseline characteristics of the overall intention-to-treat (ITT) populations are available in the primary manuscripts.^{17,21}

The safety population of QUEST comprised 1897 patients, of whom 1263 were treated with dupilumab and 634 with matched-volume placebo. The safety population of SINUS-52 comprised 447 patients—297 treated with dupilumab, and 150 with placebo.

Annualized rate of respiratory infections

In QUEST, 22% fewer respiratory tract infection events were reported by investigators in dupilumab- vs placebo-treated asthma patients (103.34 vs 113.08 events/100PY; $P < .0001$; 95% confidence interval [CI] 0.71-0.85). When grouped into upper and lower respiratory tract infections, dupilumab-treated patients had 23% fewer investigator-reported upper respiratory tract infection events ($P < .0001$; 95% CI 0.70-0.85) and 28% fewer lower respiratory tract infection events ($P = .0007$; 95% CI 0.59-0.87). The number of patients experiencing respiratory tract infections was 16% lower in patients treated with dupilumab compared with placebo (82.5 vs 98.5 patients/100PY; $P = .0087$; 95% CI 0.74-0.96) (Table I). This was also the case when grouped into upper respiratory tract infections (20% lower vs placebo; $P = .0015$ [95% CI 0.70-0.92]) and lower respiratory tract infections (21% lower vs placebo; $P = .0532$ [95% CI 0.62-1.00]) (Table I).

Similar findings were observed in CRSwNP patients enrolled in SINUS-52. 38% fewer respiratory tract infection events were reported by investigators in dupilumab-treated vs placebo-treated CRSwNP patients (69.13 vs 111.68/100 PY; $P < .0001$ [95% CI 0.51-

0.75]) (Table I). This was also the case for upper respiratory tract infection events (34% lower vs placebo; $P < .0001$ [95% CI 0.53-0.81]) and lower respiratory tract infection events (49% lower vs placebo; $P = .0122$ [95% CI 0.30-0.86]). The number of dupilumab-treated patients experiencing investigator-reported respiratory tract infections was 43% fewer than placebo-treated patients (51.2 vs 90.5 patients/100PY; $P < .0001$ [95% CI 0.44-0.75]). Fewer CRSwNP patients treated with dupilumab also experienced upper respiratory tract infections (45% less; $P < .0001$ [95% CI 0.42-0.73]) and lower respiratory tract infections (36% less; $P = .1594$ [95% CI 0.34-1.19]) vs placebo-treated patients (Table I).

When the data were categorized by season or by month, an increase in events was reported during winter (Figure 1). In each season, fewer asthma (Figure 1A) and CRSwNP (Figure 1B) patients treated with dupilumab experienced respiratory tract infections compared with placebo-treated patients. In almost all months, fewer patients treated with dupilumab experienced respiratory tract infections compared with placebo in both the Northern and Southern hemispheres. A few exceptions occurred in the summer months (Northern hemisphere: June-August; Southern hemisphere: December-February), where the incidence of infections was lower.

With regard to the severe respiratory infection of pneumonia, the MedDRA-Preferred Term “Pneumonia” was reported by 6 patients in QUEST (2 placebo, 4 dupilumab) and 5 patients in SINUS-52 (3 placebo, 2 dupilumab).

Systemic anti-infection medication use

In QUEST, systemic anti-infective medication use for investigator-reported respiratory infections was 24% lower in dupilumab- vs placebo-treated patients (114.50 vs 149.78/100PY exposure; $P < .0001$ [95% CI 0.70-0.83]) (Table II). In addition, the proportion of asthma patients requiring anti-infection medication to treat respiratory infections was significantly lower among dupilumab-treated patients than in those treated

with placebo (Table II). In the dupilumab group, 66.7 patients/100PY required anti-infectives vs 88.2 patients/100PY in the placebo group (24% less; $P < .0001$ [95% CI 0.66-0.87]).

In CRSwNP patients (SINUS-52), 49% less anti-infection medication use was required to treat investigator-reported respiratory infections in patients treated with dupilumab vs placebo (73.10 vs 143.68/100PY; $P < .0001$ [95% CI 0.43-0.61]). In the dupilumab group, 51.8 patients/100PY vs 75.9 patients/100PY in the placebo group required anti-infectives (32% less; $P = .0074$ [95% CI 0.52-0.90]) (Table II).

For both the asthma and CRSwNP indications, fewer dupilumab-treated than placebo-treated patients received anti-infection medication to treat respiratory infections in almost all months in both the Northern and Southern hemispheres (Figure 2).

Efficacy of dupilumab in asthma or CRSwNP patients who did or did not experience respiratory tract infections

In asthma patients, a statistically significant positive correlation, albeit of low-to-moderate strength, was observed between the occurrence of investigator-reported respiratory infections and severe exacerbations. This was the case irrespective of treatment and for the overall population (correlation coefficients: placebo, 0.2477 [95% CI 0.17-0.32]; dupilumab, 0.3027 [95% CI 0.25-0.35]; overall, 0.2883 [95% CI 0.25-0.33]; all $P < .0001$). Dupilumab significantly reduced the annualized rate of severe exacerbations vs placebo both in patients who had experienced respiratory infections and those who had not; both $P < .0001$ (Figure 3A). Of note, exacerbation rates were statistically significantly lower in the subgroup of patients who had not experienced respiratory infections vs those who had (interaction $P = .0016$). In terms of rescue medication use, in the ITT population, the mean number of puffs of rescue medication per 24-hour period was slightly lower for dupilumab- vs placebo-treated patients at all timepoints from Week 2 to the end of the treatment period (Week 52, mean [SD]: 2.14 [3.60]/1.83 [2.98] dupilumab 200/300 mg vs 2.18 [3.35]/2.06 [3.32]

matched placebos). No clear differences were observed between patients who did vs patients who did not experience respiratory infections in the mean number of puffs of rescue medication per 24-hour period (Figure 3B).

In CRSwNP patients, dupilumab vs placebo reduced the proportion of patients requiring OCS to treat disease flares or symptoms; in the overall ITT population, 13.2% of dupilumab-treated patients vs 41.2% of placebo-treated patients received OCS during the treatment period. OCS use was lower in patients who had remained free of investigator-reported respiratory infections vs patients who had experienced at least one such infection (interaction $P = .0017$) (Figure 4A). Low-to-moderate strength statistically significant positive correlations between OCS use and the occurrence of respiratory infections were found in the overall population (correlation coefficient 0.1768 [95% CI 0.09-0.27]; $P = .0002$) and in placebo-treated patients (correlation coefficient 0.2852 [95% CI 0.13-0.43]; $P = .0004$), but not with dupilumab-treated patients (correlation coefficient 0.0304 [95% CI -0.08 to 0.14]; $P = .6026$). In, both, patients who did and did not experience respiratory infections, dupilumab treatment vs placebo reduced NPS (Figure 4B) and NCS (Figure 4C) relative to baseline levels as early as the first assessment at Week 4, and these improvements were maintained throughout the treatment period.

DISCUSSION

In this analysis of safety data from patients with moderate-to-severe asthma (N = 1897) or severe CRSwNP (N = 447) enrolled in phase 3 randomized clinical trials, we have shown that the rates of respiratory infections, of sufficient severity to be reported as adverse events by investigators, were significantly lower in dupilumab- vs placebo-treated patients in both populations. Upper and lower respiratory tract infections were numerically or significantly lower in asthma and CRSwNP patients treated with dupilumab vs placebo. Anti-infection medication use, most likely antibiotics, was also reduced. When examined by season and by month, a lower incidence of respiratory infections and anti-infective medication use was observed in patients treated with dupilumab throughout the calendar year.

These data are consistent with those of Eichenfield and colleagues²⁶ who showed that severe infections, bacterial non-herpetic skin infections, and systemic anti-infective use were significantly lower in dupilumab- vs placebo-treated AD patients. This may be a reflection of similar outcomes occurring in the upper and lower airways, consistent with the one airway hypothesis of interaction between the upper and lower respiratory tracts due to linked epithelial biology and local inflammatory responses.²⁹

In addition to type 2 inflammatory pathways, Th17 pathways have also been implicated in CRSwNP,³⁰ and both pathways are reciprocally regulated in asthma.³¹ The overlap and interplay between these cytokine pathways likely account for the heterogeneous nature of both diseases, where both type 2 and Th17 endotypes coexist and provide targets for therapeutic strategies. Furthermore, type 2 inflammation may impair type 1 responses to viruses and bacteria.² The observed decrease in the reported incidence of respiratory infections in patients treated with dupilumab may possibly be due to this complex regulation of type 2 and Th1/Th17 pathways, as suppression of type 2 is known to normalize Th1 and Th17 immune pathways.³⁰ Indeed, a recent report described how a case of disseminated

coccidioidomycosis rapidly resolved after dupilumab was added to standard antifungal agents, suggesting that the immunomodulatory approach of blocking type 2 immune responses might benefit other severe refractory fungal infections. The authors speculated that such an approach may also have utility in viral and mycobacterial infections.³²

Type 2 inflammation damages the airway epithelium, reducing barrier function in both asthma and CRSwNP.^{3,4} Epithelial tight junctions are critical in regulating permeability across epithelia, and in respiratory tract diseases, impaired barrier function begins with the disruption of tight junctions.³³ Indeed, expression of type 2 cytokines has been observed to negatively correlate with the expression of tight junction proteins,³⁴ and stimulation of airway epithelial cells from CRSwNP patients with IL-4 was found to reduce barrier function.³ Therefore, it could be speculated that as asthma or CRSwNP improves during dupilumab treatment, the mucosal barrier may be restored becoming more resistant to infection. The relative decrease of infection events in the dupilumab-treated group is consistent with the efficacy of dupilumab, which provides improvements in disease control in both asthma and CRSwNP patients.^{17,19} A reduction in infection adverse events may also have other clinical effects in asthma and CRSwNP patients, as respiratory infections are a common cause of exacerbations of these diseases.^{2,5} Indeed, the reduction in investigator-reported infections during treatment may have contributed to the reduction in exacerbations and corresponding decrease in need for OCS observed in dupilumab-treated patients. Alternatively, as corticosteroid use is a known risk factor for infections, the reduction in OCS use in patients treated with dupilumab vs placebo could lead to the reduction in respiratory infections.

When the efficacy data were categorized by respiratory infection occurrence, significantly fewer asthma patients who did not experience investigator-reported respiratory infections had exacerbations during the treatment period compared with those who experienced at least one respiratory infection. Similarly, OCS use for symptom management

was lower in CRSwNP patients who did not experience respiratory infection during treatment vs those who did. However, dupilumab improved outcomes in both subgroups of patients, and no clear differences in the effect of dupilumab on NPS or NCS were observed between patients who did vs patients who did not experience infections.

The positive, albeit not particularly strong, correlations between the occurrence of severe exacerbations and investigator-reported respiratory infections may have been due to fewer infections leading to less exacerbations. Alternatively, fewer exacerbations may have been the primary event and could be interpreted as less need for anti-infective medications. This is of particular relevance to antibiotics, which may have been used to treat exacerbations in general as routine practice.

One of the major strengths of this analysis is the inclusion of two phase 3, randomized, placebo-controlled trials across two respiratory diseases. Limitations include its *post hoc* nature and that the presence of respiratory infection was reported by the investigator and not necessarily supported by accompanying laboratory data such as culture data or viral PCR; exacerbations therefore may have been misinterpreted as infections, as it can be difficult to distinguish between them. Furthermore, respiratory viruses such as rhinoviruses, the most frequent cause of respiratory infection, are known to result in a higher virus load in the presence of IL-4/IL-13 both *in vitro*³⁵ and *in vivo*,³⁶ therefore dual blockade of these cytokines with dupilumab may have resulted in a milder “unreported” infection. Rhinovirus infections also trigger IL-33-dependent type 2 inflammation *in vivo*,³⁶ which could explain why dupilumab might decrease viral-related exacerbations. This also highlights the importance of nasal swabbing to identify the infections agents in respiratory infections, as described by others.³⁷ As the term “respiratory tract infection” does not discriminate between viral or bacterial infections, these issues are important, as the impact of dupilumab on each type of infection is unclear. Finally, as with exacerbations and respiratory infections, allergic

rhinitis is often confused with a sinus infection; so it is also possible that allergic flares in CRSwNP patients were misclassified as respiratory infections. The exact mechanisms behind the reduced rate of investigator-reported respiratory infection observed in patients treated with dupilumab is an important area of future investigation.

In conclusion, in this analysis of phase 3 studies in patients with moderate-to-severe asthma or severe CRSwNP, a reduced incidence of investigator-reported respiratory tract infections and anti-infection medication use was observed in patients treated with dupilumab vs placebo; this may have important implications in terms of quality of life, health care resource utilization, and clinical outcomes.

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REFERENCES

1. Dharmage SC, Perret JL, Custovic A. Epidemiology of asthma in children and adults. *Front Pediatr* 2019;7:246.
2. Tan KS, Yan Y, Ong HH, Chow VTK, Shi L, Wang DY. Impact of respiratory virus infections in exacerbation of acute and chronic rhinosinusitis. *Curr Allergy Asthma Rep* 2017;17:24.
3. Soyka MB, Wawrzyniak P, Eiwegger T, Holzmann D, Treis A, Wanke K, et al. Defective epithelial barrier in chronic rhinosinusitis: the regulation of tight junctions by IFN- γ and IL-4. *J Allergy Clin Immunol* 2012;130:1087-96.
4. Holgate ST. Epithelium dysfunction in asthma. *J Allergy Clin Immunol* 2007;120:1233-44.
5. Busse WW, Lemanske RF Jr, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. *Lancet* 2010;376:826-34.
6. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108(5 Suppl):S147-334.
7. Voehringer D, Reese TA, Huang X, Shinkai K, Locksley RM. Type 2 immunity is controlled by IL-4/IL-13 expression in hematopoietic non-eosinophil cells of the innate immune system. *J Exp Med* 2006;203:1435-46.
8. Feng Lan, XD Wang, HJ Nauwynck, Gabriele Holtappels, L Zhang, SL Johnston, NG Papadopoulos, C Bachert, Nan Zhang. Th2 biased upper airway inflammation is associated with an impaired response to viral infection with Herpes simplex virus 1. *Rhinology* 2016;54(2):141-9.

9. Orlandi RR, Kingdom TT, Hwang PH, Smith TL, Alt JA, Baroody FM, et al. International consensus statement on allergy and rhinology: rhinosinusitis. *Int Forum Allergy Rhinol* 2016;6 Suppl 1:S22-209.
10. Laidlaw TM, Mullol J, Woessner KM, Amin N, Mannent LP. Chronic rhinosinusitis with nasal polyps and asthma. *J Allergy Clin Immunol Pract* 2021;9:1133-41.
11. Macdonald LE, Karow M, Stevens S, Auerbach W, Poueymirou WT, Yasenchak J, et al. Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes. *Proc Natl Acad Sci U S A* 2014;111:5147-52.
12. Murphy AJ, McDonald LE, Stevens S, Karow M, Dore AT, Pobursky K, et al. Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice. *Proc Natl Acad Sci U S A* 2014;111:5153-8.
13. Gandhi NA, Pirozzi G, Graham NMH. Commonality of the IL-4/IL-13 pathway in atopic diseases. *Exp Rev Clin Immunol* 2017;13:425-37.
14. Le Floch A, Allinne J, Nagashima K, Scott G, Birchard D, Asrat S, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4R α antibody, is required to broadly inhibit type 2 inflammation. *Allergy* 2020;75:1188-204.
15. DUPIXENT® (dupilumab). Highlights of Prescribing Information. US Food and Drug Administration; 2019. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761055s014lbl.pdf. Accessed May 19, 2021.
16. Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β 2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet* 2016;388:31-44.

17. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018;378:2486-96.
18. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med* 2018;378:2475-85.
19. DUPIXENT® (dupilumab). Summary of Product Characteristics. European Medicines Agency. Available from: https://ec.europa.eu/health/documents/community-register/2019/20190801145601/anx_145601_en.pdf. Accessed June 1, 2021.
20. DUPIXENT® (dupilumab). Japan PMDA. Available from: <https://www.pmda.go.jp/PmdaSearch/iyakuDetail/GeneralList/4490405>. Accessed June 1, 2021.
21. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, 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;394:1638-50.
22. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet* 2017;389:2287-303.
23. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med* 2016;375:2335-48.
24. Thaçi D, Simpson EL, Beck LA, Bieber T, Blauvelt A, Papp K, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled

by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial.

Lancet 2016;387:40-52.

25. Bieber T. Atopic dermatitis. N Engl J Med 2008;358:1483-94.

26. Eichenfield LF, Bieber T, Beck LA, Simpson EL, Thaçi D, de Bruin-Weller M, et al.

Infections in dupilumab clinical trials in atopic dermatitis: a comprehensive pooled

analysis. Am J Clin Dermatol 2019;20:443-56.

27. Fleming P, Drucker AM. Risk of infection in patients with atopic dermatitis treated with

dupilumab: a meta-analysis of randomized controlled trials. J Am Acad Dermatol

2018;78:62-69.e1.

28. West L, Chong H. Biologics in STAT3 loss-of-function hyper IgE syndrome: a report of

3 cases demonstrating improved clinical outcomes. J Clin Immunol 2020;40:S40.

29. Giavina-Bianchi P, Aun MV, Takejima P, Kalil J, Agondi RC. United airway disease:

current perspectives. J Asthma Allergy 2016;9:93-100.

30. Wang M, Zhang N, Zheng M, Li Y, Meng L, Ruan Y, et al. Cross-talk between T_H2 and

T_H17 pathways in patients with chronic rhinosinusitis with nasal polyps. J Allergy Clin

Immunol 2019;144:1254-64.

31. Choy DF, Hart KM, Borthwick LA, Shikotra A, Nagarkar DR, Siddiqui S, et al. TH2 and

TH17 inflammatory pathways are reciprocally regulated in asthma. Sci Transl Med

2015;7:301ra129.

32. Tsai M, Thauland TJ, Huang AY, Bun C, Fitzwater S, Krogstad P, et al. Disseminated

coccidioidomycosis treated with interferon- γ and dupilumab. N Engl J Med

2020;382:2337-43.

33. Yuksel H, Turkeli A. Airway epithelial barrier dysfunction in the pathogenesis and

prognosis of respiratory tract diseases in childhood and adulthood. Tissue Barriers

2017;5:e1367458.

34. Schleimer RP. Immunopathogenesis of chronic rhinosinusitis and nasal polyposis. *Annu Rev Pathol* 2017;12:331-57.
35. Contoli M, Ito K, Padovani A, Poletti D, Marku B, Edwards MR, Stanciu LA, Gnesini G, Pastore A, Spanevello A, Morelli P, Johnston SL, Caramori G, Papi A. Th2 cytokines impair innate immune responses to rhinovirus in respiratory epithelial cells. *Allergy* 2015;70(8):910-20.
36. Jackson DJ, Makrinioti H, Rana BM, Shamji BW, Trujillo-Torralbo MB, Footitt J, Jerico Del-Rosario, Telcian AG, Nikonova A, Zhu J, Aniscenko J, Gogsadze L, Bakhsoliani E, Traub S, Dhariwal J, Porter J, Hunt D, Hunt T, Hunt T, Stanciu LA, Khaitov M, Bartlett NW, Edwards MR, Kon OM, Mallia P, Papadopoulos NG, Akdis CA, Westwick J, Edwards MJ, Cousins DJ, Walton RP, Johnston SL. IL-33-dependent type 2 inflammation during rhinovirus-induced asthma exacerbations in vivo. *Am J Respir Crit Care Med* 2014;190(12):1373-82.
37. Willis AL, Calton JB, Calton J, Kim AS, Lee R, Torabzadeh E, Billheimer DD, Le CH, Martinez FD, Chang EH. RV-C infections result in greater clinical symptoms and epithelial responses compared to RV-A infections in patients with CRS. *Allergy* 2020 Dec;75(12):3264-3267.

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538 **TABLES AND FIGURES**

539 **TABLE I.** Annualized rate of specific treatment-emergent investigator-reported respiratory tract infections in asthma and CRSwNP at event
 540 level and patient level

	Placebo	Dupilumab	Dupilumab vs placebo risk ratio (95% CI)	<i>P</i> value
Asthma (QUEST)				
n	634	1263		
Number of events (events/100PY)				
HLGT respiratory tract infections	813 (113.08)	1250 (103.34)	0.78 (0.71-0.85)	< .0001
Upper respiratory tract HLTs [#]	606 (99.199)	926 (76.553)	0.77 (0.70-0.85)	< .0001
Lower respiratory tract HLTs [¶]	176 (28.810)	250 (20.668)	0.72 (0.59-0.87)	.0007
Number of patients (patients/100PY)				
HLGT respiratory tract infections	378 (98.47)	671 (82.50)	0.84 (0.74-0.96)	.0087
Upper respiratory tract HLTs [#]	330 (80.706)	552 (63.730)	0.80 (0.70-0.92)	.0015
Lower respiratory tract HLTs [¶]	105 (19.353)	170 (15.310)	0.79 (0.62-1.00)	.0532

CRSwNP (SINUS-52)				
n	150	297		
Number of events (events/100PY)				
HLGT respiratory tract infections	185 (111.68)	244 (69.13)	0.62 (0.51-0.75)	< .0001
Upper respiratory tract HLTs [#]	153 (92.364)	214 (60.634)	0.66 (0.53-0.81)	< .0001
Lower respiratory tract HLTs [¶]	26 (15.696)	28 (7.933)	0.51 (0.30-0.86)	.0122
Number of patients (patients/100PY)				
HLGT respiratory tract infections	91 (90.47)	132 (51.23)	0.57 (0.44-0.75)	< .0001
Upper respiratory tract HLTs [#]	85 (85.280)	121 (46.505)	0.55 (0.42-0.73)	< .0001
Lower respiratory tract HLTs [¶]	17 (11.119)	24 (7.118)	0.64 (0.34-1.19)	.1594

541 *CI*, confidence interval; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *HLGT*, High-Level Group Term; *HLT*, MedDRA High-Level Term; *MedDRA*,

542 Medical Dictionary for Regulatory Activities; *NEC*, not elsewhere classified; *PY*, patient-years.

543 [#]Includes the HLTs within the HLGT respiratory tract infections: upper respiratory tract infections NEC, viral upper respiratory tract infections, and bacterial
 544 upper respiratory tract infections.

545 [¶]Includes the HLTs within the HLGT respiratory tract infections: lower respiratory tract infections NEC, bacterial lower respiratory tract infections, and viral
 546 lower respiratory tract infections.

547 **TABLE II.** Systemic anti-infective medication use in asthma and CRSwNP at event level and patient level

	Placebo	Dupilumab	Dupilumab vs placebo risk ratio (95% CI)	P value
Asthma (QUEST)				
n	634	1263		
Number of events (events/100PY)	915 (149.78)	1385 (114.50)	0.76 (0.70-0.83)	< .0001
Number of patients (patients/100PY)	345 (88.16)	576 (66.74)	0.76 (0.66-0.87)	< .0001
CRSwNP (SINUS-52)				
n	150	297		
Number of events (events/100PY)	238 (143.68)	258 (73.10)	0.51 (0.43-0.61)	< .0001
Number of patients (patients/100PY)	79 (75.87)	132 (51.85)	0.68 (0.52-0.90)	.0074

548 *CI*, confidence interval; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *PY*, patient-years

FIGURE 1. Annualized rate of specific treatment-emergent investigator-reported respiratory tract infections in **(A)** asthma and **(B)** CRSwNP by season and by month in each hemisphere. Seasons by calendar month of year in Northern hemisphere: Winter (Dec-Feb), Spring (Mar-May), Summer (Jun-Aug), Autumn (Sept-Nov). Seasons by calendar month of year in Southern hemisphere: Winter (Jun-Aug), Spring (Sept-Nov), Summer (Dec-Feb), Autumn (Mar-May). *TEAE*, treatment-emergent adverse event.

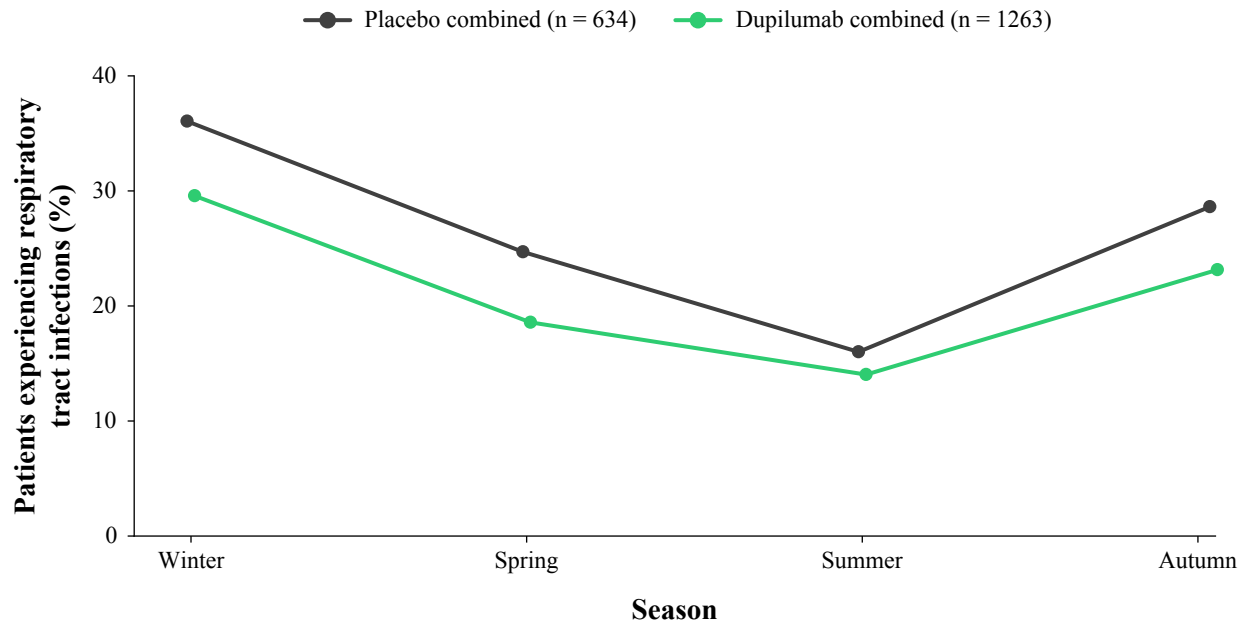
FIGURE 2. Systemic anti-infection medication use in **(A)** asthma and **(B)** CRSwNP by month in each hemisphere.

FIGURE 3. The effect of dupilumab vs placebo in patients with asthma who did vs patients who did not experience investigator-reported respiratory infections during the treatment period for **(A)** annualized rate of severe exacerbations and **(B)** rescue medication use. *CI*, confidence interval; *SD*, standard deviation.

FIGURE 4. The effect of dupilumab vs placebo on **(A)** OCS use, **(B)** nasal polyp score and **(C)** nasal congestion/obstruction score in patients with CRSwNP who did vs did not experience investigator-reported respiratory infections during the treatment period.

(A) Asthma patients (QUEST)

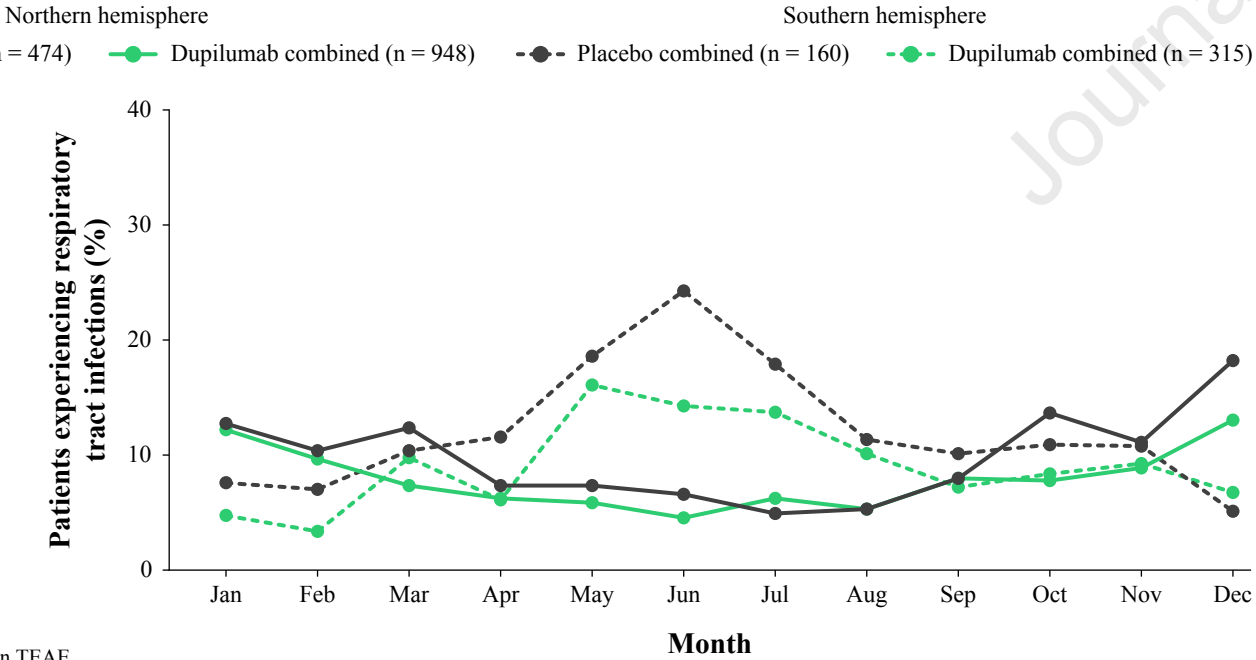
By season



Patients (n)/Patients remaining in TEAE period for respective season (n)

Placebo	224/620	155/627	100/621	175/614
Dupilumab	364/1231	227/1229	172/1230	284/1225

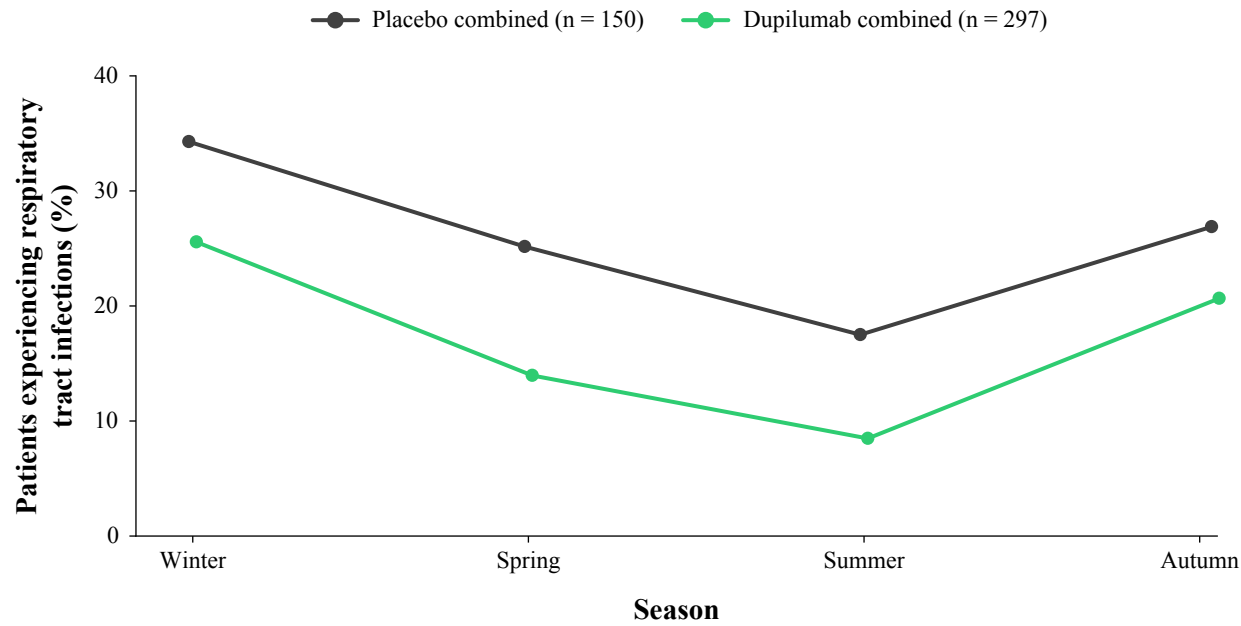
By month



Patients (n)/Patients remaining in TEAE period for respective calendar month (n)

Northern hemisphere	Placebo	58/454	47/458	57/462	34/461	34/459	30/457	22/453	24/454	36/454	61/448	50/449	82/451
	Dupilumab	108/895	85/893	65/899	55/900	53/911	41/913	55/912	47/910	72/907	70/906	79/904	118/905
Southern hemisphere	Placebo	12/158	11/157	16/155	18/154	29/155	38/156	28/156	18/158	16/157	17/157	17/157	8/157
	Dupilumab	14/299	10/300	29/297	18/300	49/305	44/307	42/305	31/308	22/308	26/306	28/303	20/300

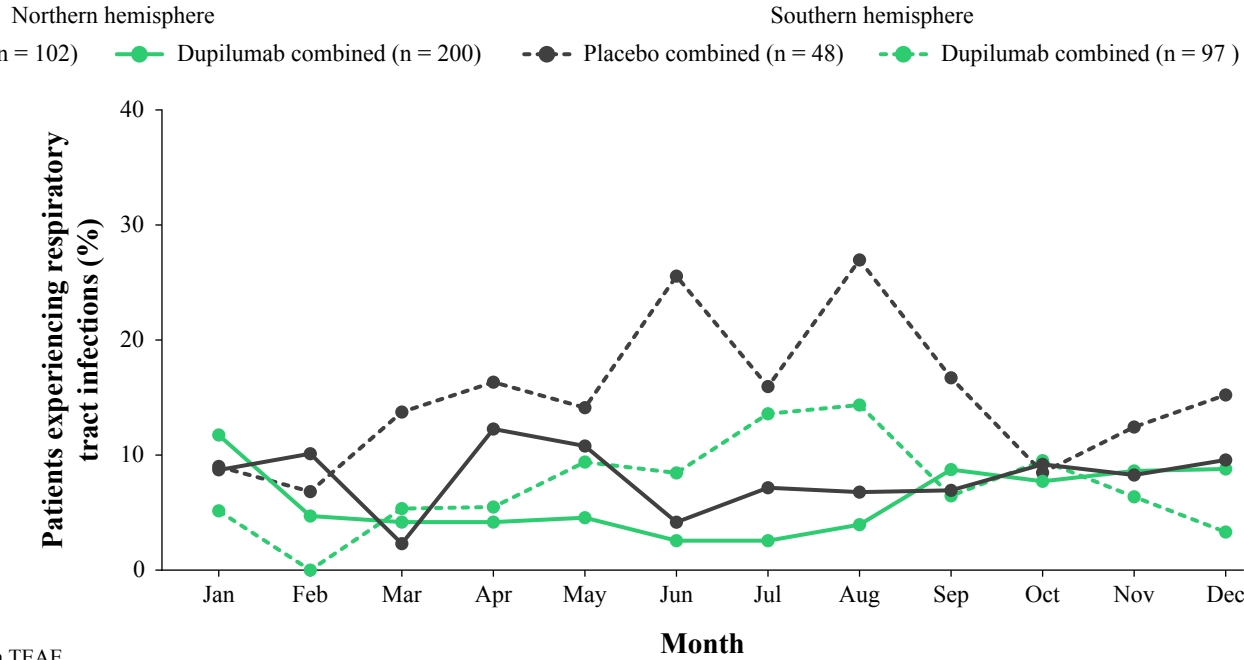
By season



Patients (n)/Patients remaining in TEAE period for respective season (n)

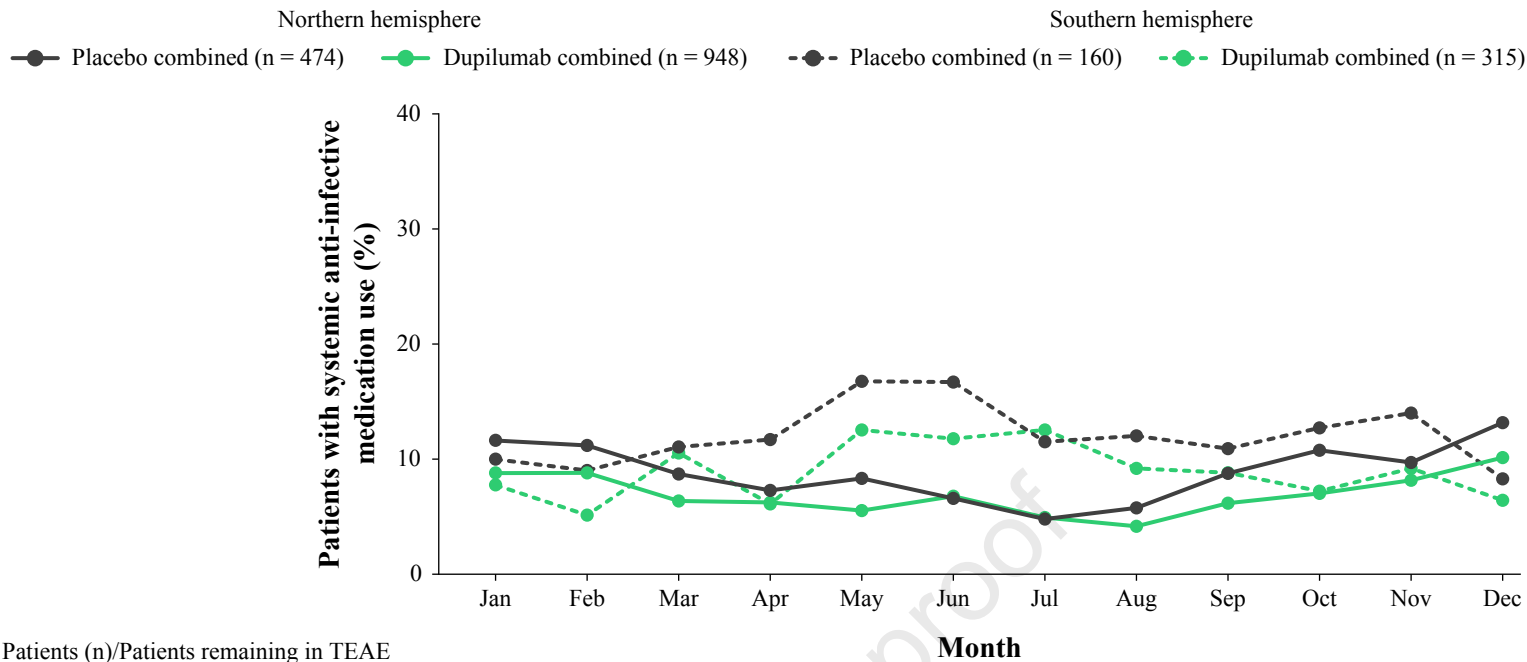
Placebo	49/143	36/143	26/148	39/145
Dupilumab	75/293	41/292	25/296	60/292

By month



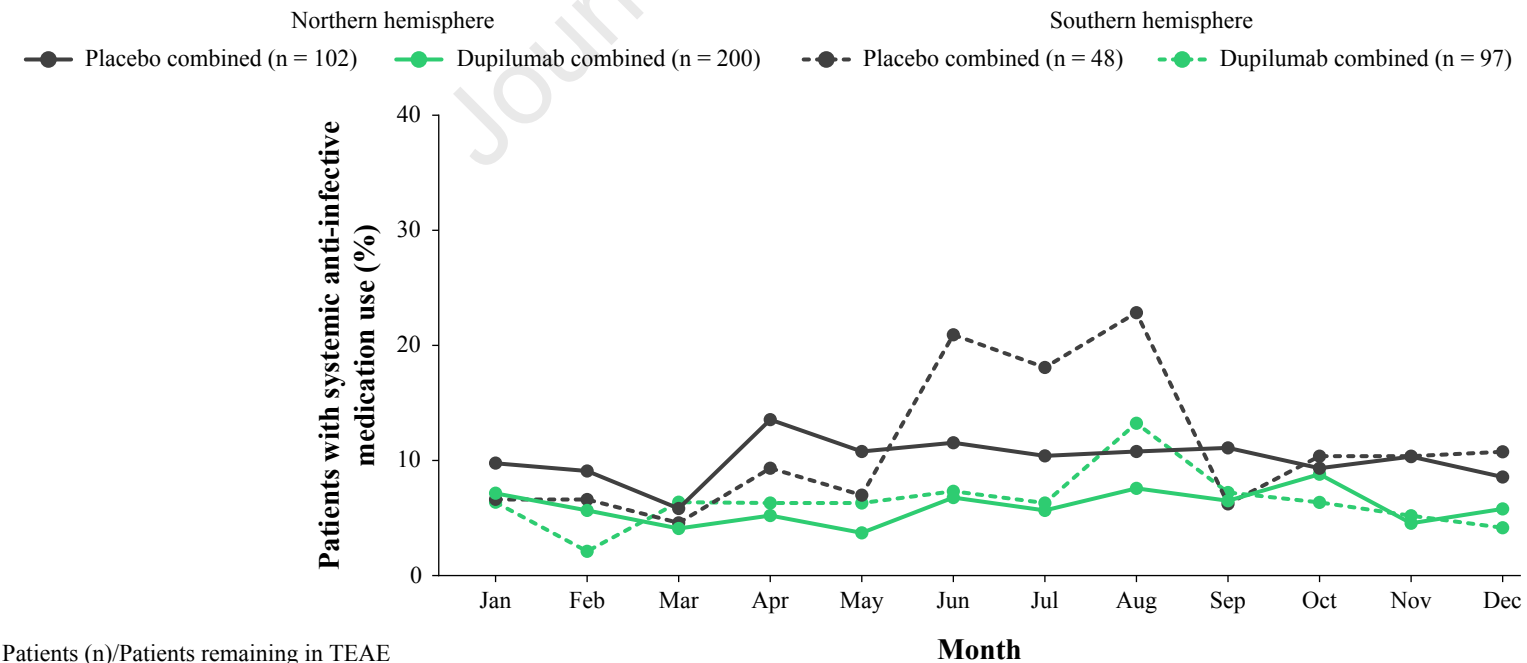
Patients (n)/Patients remaining in TEAE period for respective calendar month (n)

Northern hemisphere	Placebo	8/92	9/89	2/88	11/89	10/93	4/96	7/97	7/102	7/100	9/98	8/97	9/94
	Dupilumab	23/195	9/194	8/192	8/195	9/196	5/194	5/194	8/198	17/197	15/197	17/197	17/196
Southern hemisphere	Placebo	4/45	3/45	6/44	7/43	6/43	11/43	7/44	13/48	8/48	4/48	6/48	7/46
	Dupilumab	5/95	0/95	5/94	5/94	9/95	8/96	13/96	14/97	6/96	9/95	6/95	3/95



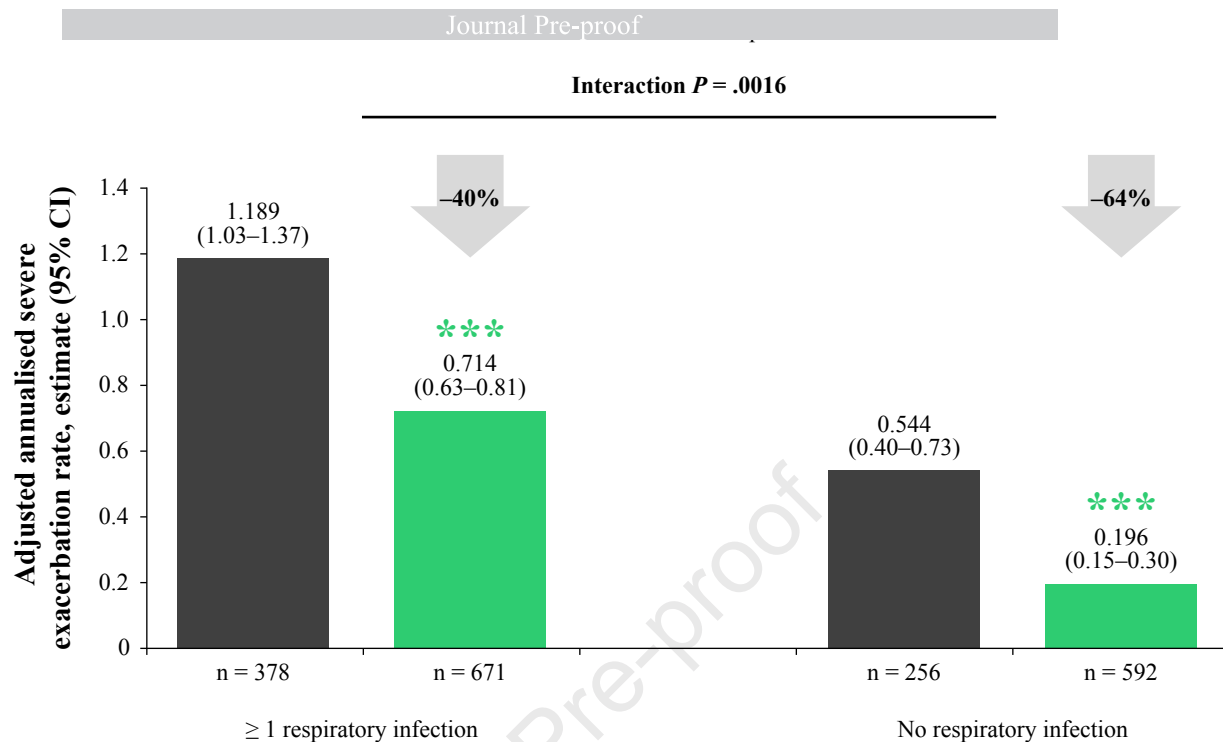
Patients (n)/Patients remaining in TEAE period for respective calendar month (n)		Month											
Northern hemisphere	Placebo	53/454	51/458	40/462	33/461	38/459	30/457	21/453	26/454	40/454	48/448	43/449	59/451
	Dupilumab	78/895	78/893	57/899	57/900	50/911	62/913	45/912	38/910	55/907	64/906	73/904	91/905
Southern hemisphere	Placebo	16/158	14/157	17/155	18/154	26/155	26/156	18/156	19/158	17/157	20/157	22/157	13/157
	Dupilumab	23/299	15/300	31/297	18/300	38/305	36/307	38/305	28/308	27/308	22/306	28/303	19/300

(B) CRSwNP patients (SINUS-52)

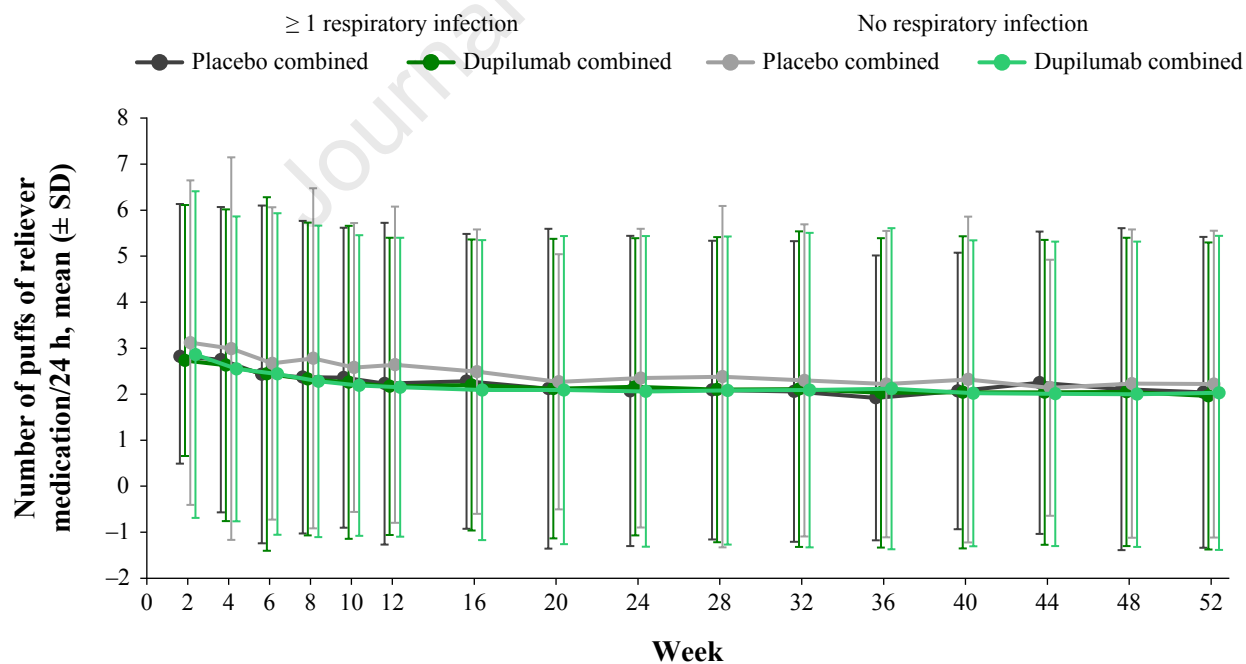


Patients (n)/Patients remaining in TEAE period for respective calendar month (n)		Month											
Northern hemisphere	Placebo	9/92	8/89	5/88	12/89	10/93	11/96	10/97	11/102	11/100	9/98	10/97	8/94
	Dupilumab	14/195	11/194	8/192	10/195	7/196	13/195	11/194	15/198	13/197	17/197	9/197	11/196
Southern hemisphere	Placebo	3/45	3/45	2/44	4/43	3/43	9/43	8/44	11/48	3/48	5/48	5/48	5/46
	Dupilumab	6/95	2/95	6/94	6/94	6/95	7/96	6/96	13/97	7/96	6/95	5/95	4/95

(A)



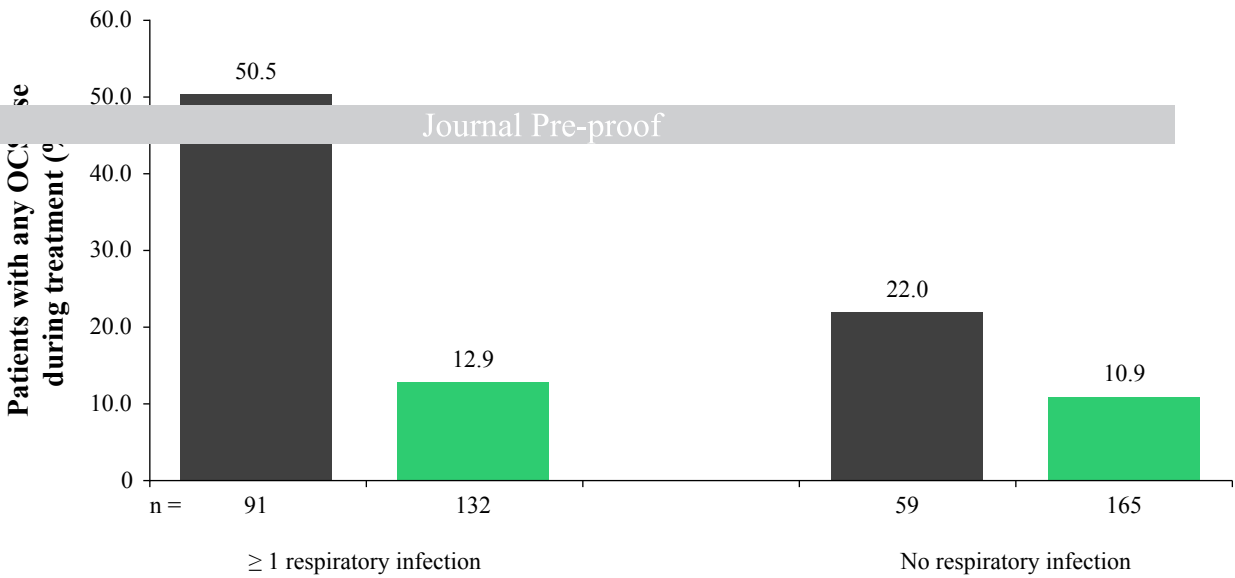
(B)



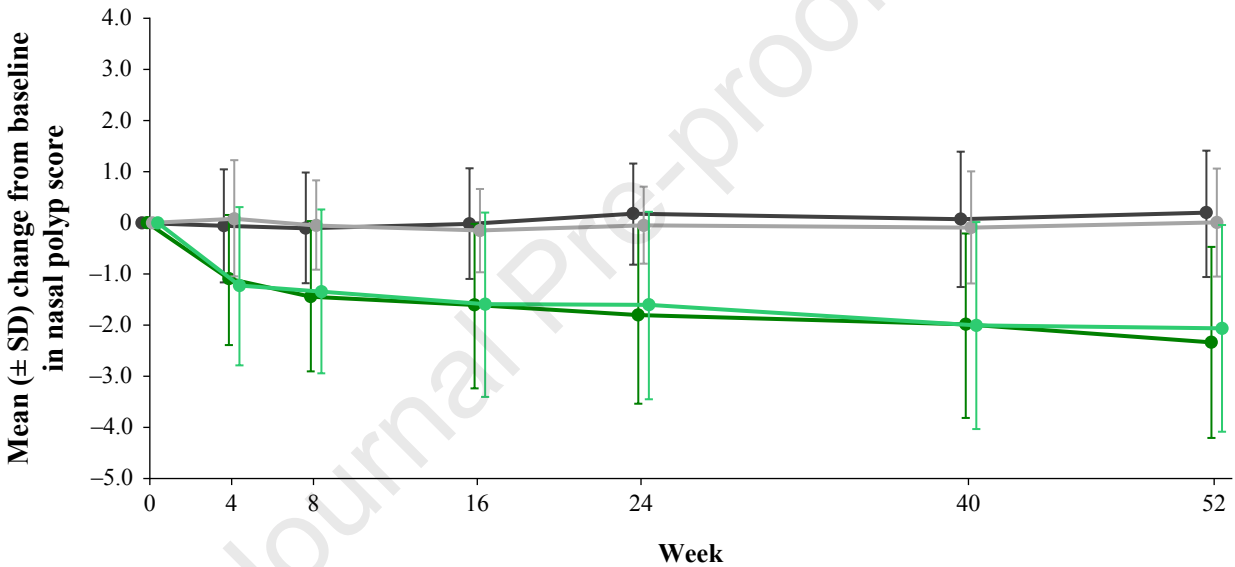
≥ 1 respiratory infection	Placebo, n	374	376	375	374	371	373	370	364	356	353	349	343	338	335	332	319
	Dupilumab, n	668	668	658	657	655	653	655	647	634	629	626	615	609	591	589	572
No respiratory infection	Placebo, n	255	253	247	246	243	241	241	235	236	232	229	227	227	220	214	214
	Dupilumab, n	585	581	579	568	568	562	565	553	538	528	520	509	506	504	490	473

(A) Placebo combined Dupilumab combined

Interaction $P = .0017$

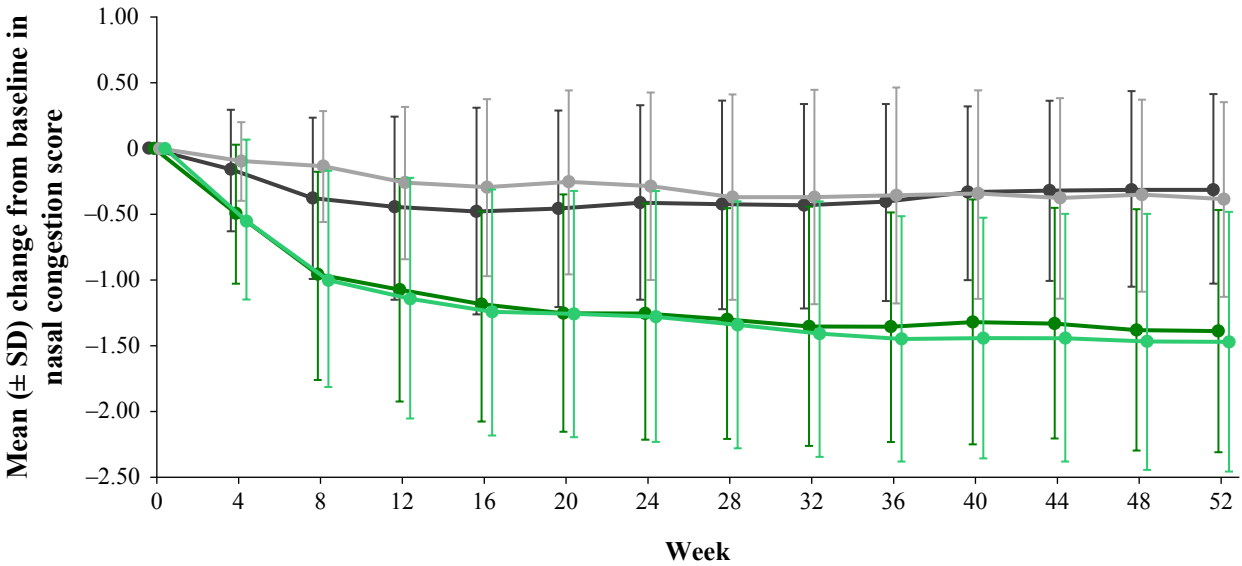


(B) ≥ 1 respiratory infection No respiratory infection
Placebo combined Dupilumab combined Placebo combined Dupilumab combined



≥ 1 respiratory infection	Placebo, n	90	91	89	91	88	88
	Dupilumab, n	129	128	125	127	128	127
No respiratory infection	Placebo, n	57	54	55	52	51	52
	Dupilumab, n	151	161	154	158	156	157

(C) ≥ 1 respiratory infection No respiratory infection
Placebo combined Dupilumab combined Placebo combined Dupilumab combined



≥ 1 respiratory infection	Placebo, n	91	91	91	91	90	90	89	89	89	89	89	89
	Dupilumab, n	132	132	132	132	131	131	131	130	129	131	130	129
No respiratory infection	Placebo, n	59	59	57	57	56	55	54	54	54	54	53	53
	Dupilumab, n	165	164	162	161	160	160	160	160	159	160	160	160