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Efficacy and Safety of Dupilumab in Patients With Chronic Rhinosinusitis With Nasal Polyps: Results From the Randomized Phase 3 SINUS-24 Study

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Speaker disclosures

Han JK: Regeneron Pharmaceuticals, Inc., Sanofi – advisory boards.

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Background

- CRSwNP is a chronic inflammatory disease of the nasal passages and paranasal sinuses associated with a high symptom burden and poor health-related quality of life (QoL)

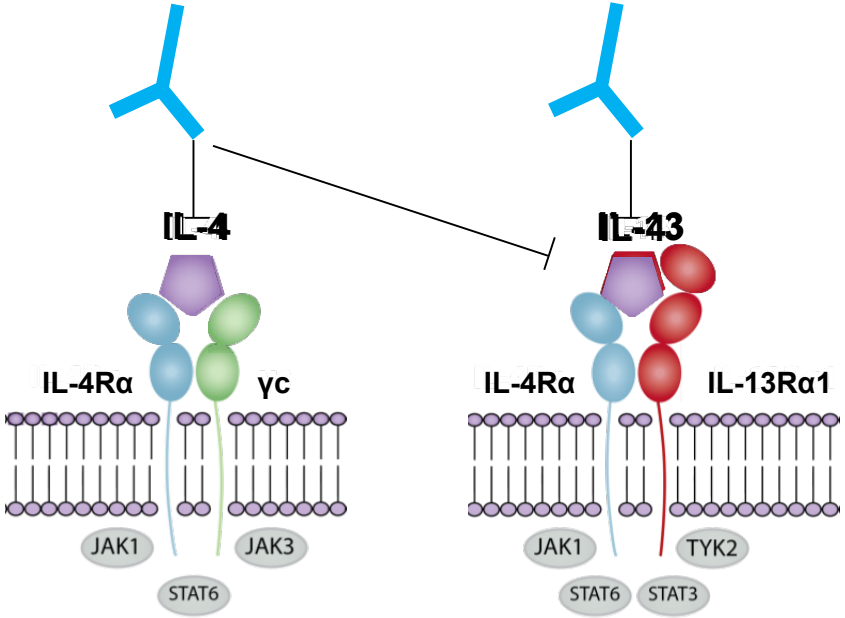
- Pathophysiologically, CRSwNP predominantly displays a type 2 inflammatory signature with IL-4, IL-5, and IL-13 as prominent cytokines and tissue infiltration by eosinophils, lymphocytes, basophils, and mast cells[1]

CRSwNP, chronic rhinosinusitis with nasal polyps; IL, interleukin.

1. Han JK Laryngoscope. 2013.

Background

- Dupilumab is a fully human VelocImmune®-derived monoclonal antibody[1,2] that blocks the shared receptor component for **IL-4** and **IL-13**, which are key drivers of type 2 inflammation[3]
- In a phase 2 study (NCT01920893), dupilumab on a background of MFNS was shown to reduce nasal polyp burden[4]
- Dupilumab is efficacious in other type 2 diseases, including atopic dermatitis and asthma, and has shown efficacy in a proof-of-concept study in eosinophilic esophagitis



Type I receptor

B cells, T cells, monocytes, eosinophils, fibroblasts

Type II receptor

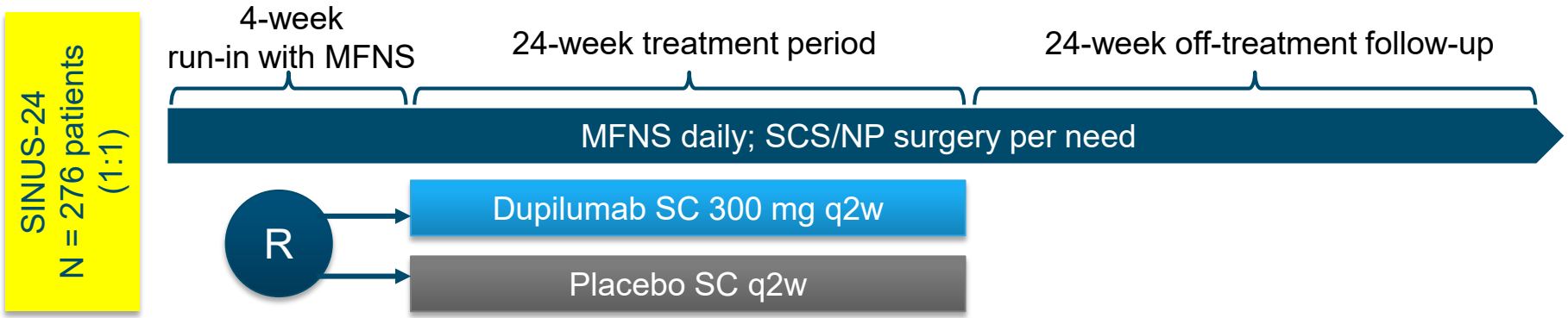
Epithelial cells, smooth muscle cells, fibroblasts, monocytes, activated B cells

MFNS, mometasone furoate nasal spray.

1. Macdonald LE, et al. PNAS. 2014. 2. Murphy AJ, et al. PNAS. 2014. 3. Gandhi NA, et al. Expert Rev Clin Immunol. 2017. 4. Bachert C, et al. JAMA. 2016.

SINUS-24 phase 3 study design

International, multicenter, randomized, double-blind phase 3 study (ClinicalTrials.gov Identifier: NCT02912468)



- Rescue treatment with SCS, NP surgery, saline nasal lavage, or systemic antibiotics was allowed at investigator's discretion
- Patient population was stratified for comorbid asthma and prior NP surgery

MFNS, mometasone furoate nasal spray; NP, nasal polyps; q2w, every 2 weeks;
R, randomization; SC, subcutaneous; SCS, systemic corticosteroids.

Key inclusion and exclusion criteria

Inclusion

- Adult patients with prior treatment with SCS (or contraindication/intolerance to SCS) in the past 2 years OR prior surgery for NP
- Bilateral NP with NPS ≥ 5 (out of 8) and ≥ 2 for each nostril
- ≥ 2 of the following rhinosinusitis symptoms for ≥8 weeks*
  - Nasal obstruction (symptom severity score [NC] ≥ 2) AND:
  - Rhinorrhea (anterior/posterior) OR:
  - Reduction or loss of smell

Exclusion

- Monoclonal antibody and immunosuppressive treatment within 2 months or anti-IgE therapy (omalizumab) within 130 days of screening
- Sinus surgery (including polypectomy) within 6 months before screening, or sinonasal surgery changing the lateral wall structure of the nose making the evaluation of NPS impossible
- Patients with FEV_1 ≤50% of predicted normal

*≥8 weeks before screening followed by 4 weeks prior to randomization, total 12 weeks of symptoms

FEV_1, forced expiratory volume in 1 second; NC, nasal congestion patient daily severity score; NPS, endoscopic nasal polyp score.

Study objective and endpoints

- To evaluate the efficacy and safety of dupilumab 300 mg q2w compared to placebo in patients with CRSwNP on a background of MFNS
- **Primary efficacy endpoints**
  - Change from baseline in NPS at Week 24
  - Change from baseline in NC at Week 24
- **Key secondary endpoints**
  - Change from baseline at Week 24 in
    - Sinus disease assessed by LMK-CT score
    - Total symptom score (TSS)
    - UPSIT score
    - Daily loss of sense of smell score
    - SNOT-22 score

NC, TSS, daily loss of smell score and SNOT-22 are all patient-reported outcomes.

LMK-CT, Lund–Mackay computed tomography; NC, nasal congestion patient daily severity score; NPS, endoscopic nasal polyp score; SNOT-22, 22-item Sino-Nasal Outcome Test; TSS, total symptom score; UPSIT, University of Pennsylvania Smell Identification Test.

Additional endpoints[a]

The following additional endpoints were evaluated in this population:

- Rescue with SCS or NP surgery
  - Time to first SCS use and/or NP surgery in patients treated with dupilumab or placebo

- Patients with comorbid asthma
  - Change from baseline in FEV_1 at Week 24
  - Change from baseline in the ACQ-6 total score at Week 24

[a]These endpoints were included in the testing hierarchy as pooled analyses with the SINUS-52 study.
Results presented here for these additional endpoints are for SINUS-24 only.
ACQ-6, 6-item Asthma Control Questionnaire.

Patient baseline demographics and disease characteristics

	Placebo (n = 133)	Dupilumab 300 mg q2w (n = 143)
Age, mean (SD), years	50.83 (13.21)	50.17 (13.59)
Male sex, n (%)	70 (52.6)	88 (61.5)
NP duration, mean (SD), years	10.77 (8.57)	11.42 (9.69)
Patients with ≥ 1 prior surgery, n (%)	99 (74.4)	99 (69.2)
Patients with SCS use in the previous 2 years, n (%)	87 (65.4)	92 (64.3)
Patients with any comorbid type 2 medical history including asthma/AERD, n (%)	99 (74.4)	109 (76.2)
Patients with comorbid asthma, n (%)	79 (59.4)	82 (57.3)
Patients with comorbid AERD, n (%)	38 (28.6)	46 (32.2)
Bilateral endoscopic NPS (0–8 score), mean (SD)	5.86 (1.31)	5.64 (1.23)
Nasal congestion (0–3 score), mean (SD)	2.45 (0.55)	2.26 (0.57)
Total LMK-CT score (0–24 score), mean (SD)	19.55 (4.26)	18.55 (4.55)
Loss of sense of smell symptom score (0–3 score), mean (SD)	2.73 (0.51)	2.70 (0.57)
UPSIT score (0–40 score), mean (SD)	14.44 (8.31)	14.68 (8.66)
SNOT-22 total score (0–110 score), mean (SD)	50.87 (20.22)	48.00 (20.16)
Rhinosinusitis disease severity scale (VAS; 0–10 cm scale), mean (SD)	7.96 (2.06)	7.42 (2.01)
Baseline blood eosinophils, mean (SD), cells/μL	435.19 (310.32)	437.76 (353.34)

AERD, aspirin-exacerbated respiratory disease; SD, standard deviation; VAS, Visual Analog Scale.

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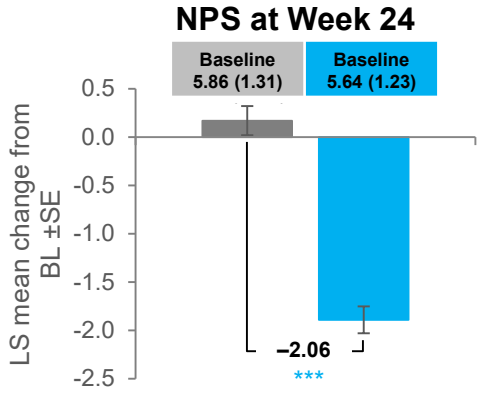
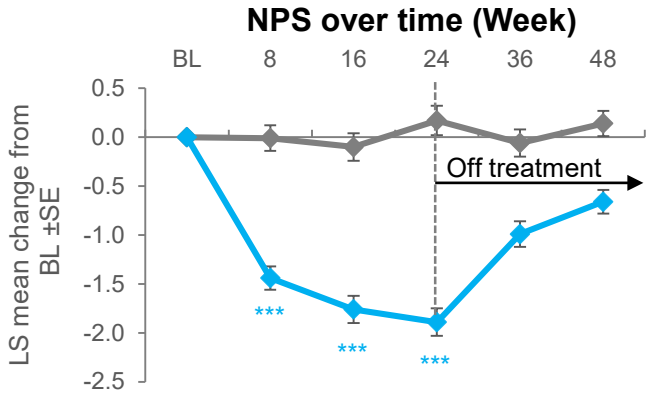
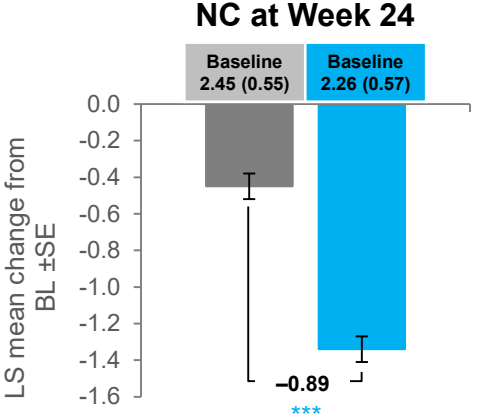
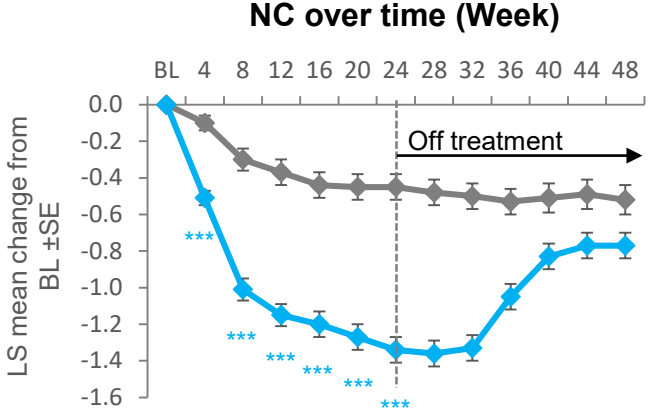
Change from baseline in nasal polyp score and nasal congestion









- Improvement by ≥ 1 point in NPS: 65.0% dupilumab vs 17.3% placebo ($P < 0.0001$)
- Improvement by ≥ 2 points in NPS: 46.2% dupilumab vs 4.5% placebo ($P < 0.0001$)

Placebo
Dupilumab 300 mg q2w
Treatment ended at Week 24
***$P < 0.0001$

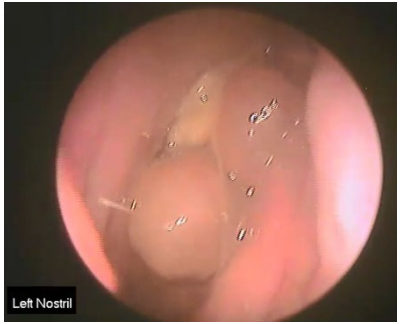
BL, baseline; LS, least squares; SE, standard error.

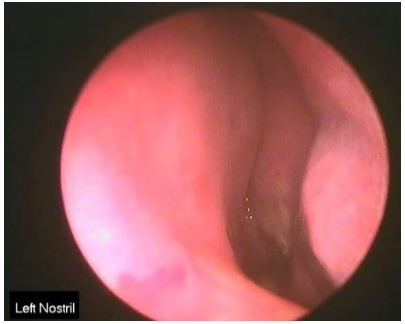
Change in nasal polyps after 24 weeks of treatment

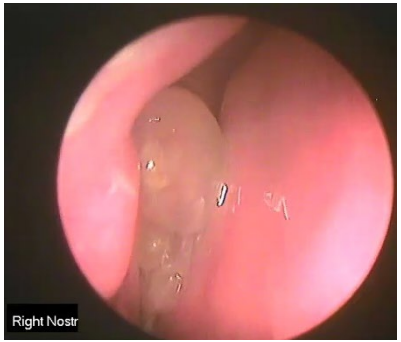
Baseline
NPS = 6

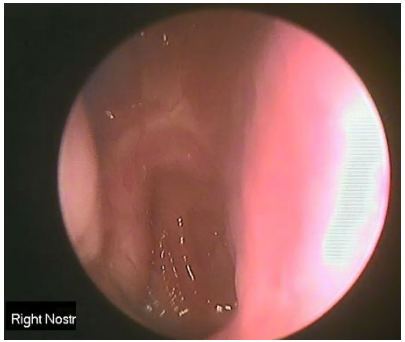
→

Week 24
NPS = 0



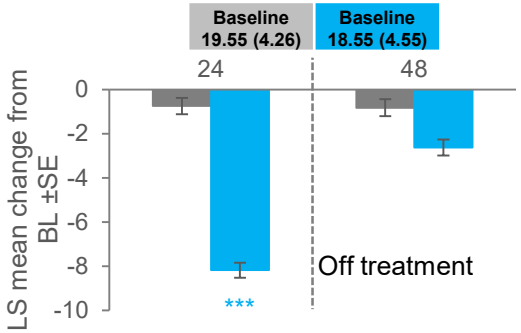




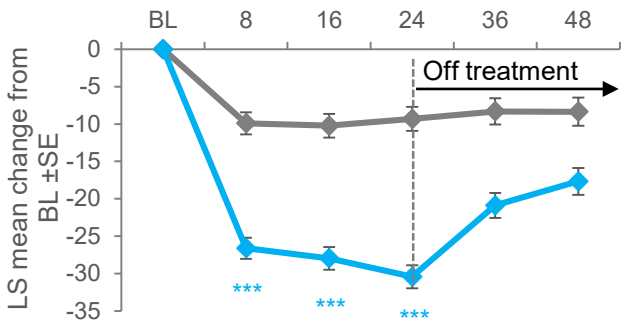


Change from baseline in sinus disease (LMK-CT), QoL (SNOT-22), total symptom score, and loss of smell

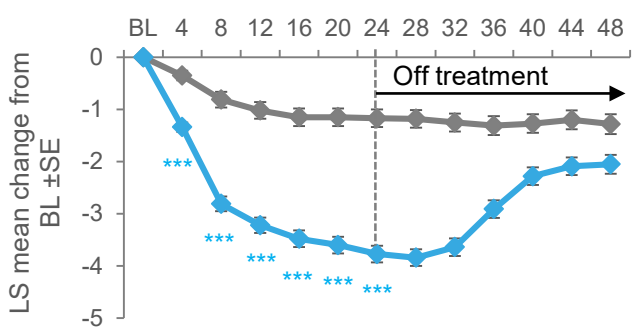
LMK-CT (Week)



SNOT-22 (Week)

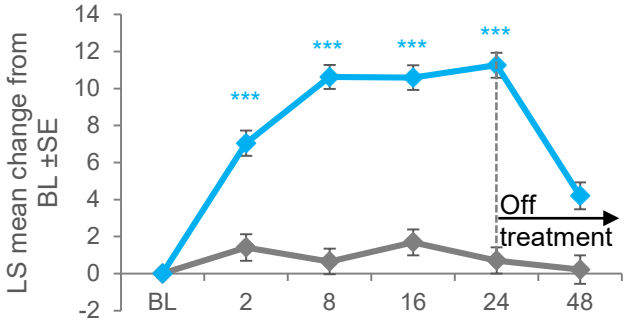


TSS (Week)

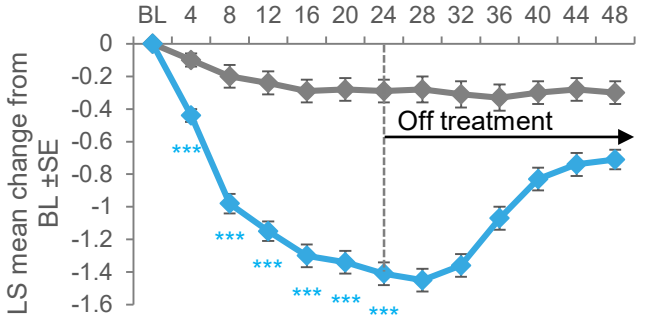


Change from BL at Week 24	LS mean difference vs placebo
LMK-CT	–7.44 ($P < 0.0001$)
SNOT-22	–21.12 ($P < 0.0001$)
TSS	–2.61 ($P < 0.0001$)
UPSIT	10.56 ($P < 0.0001$)
Daily loss of smell	–1.12 ($P < 0.0001$)

UPSIT (Week)

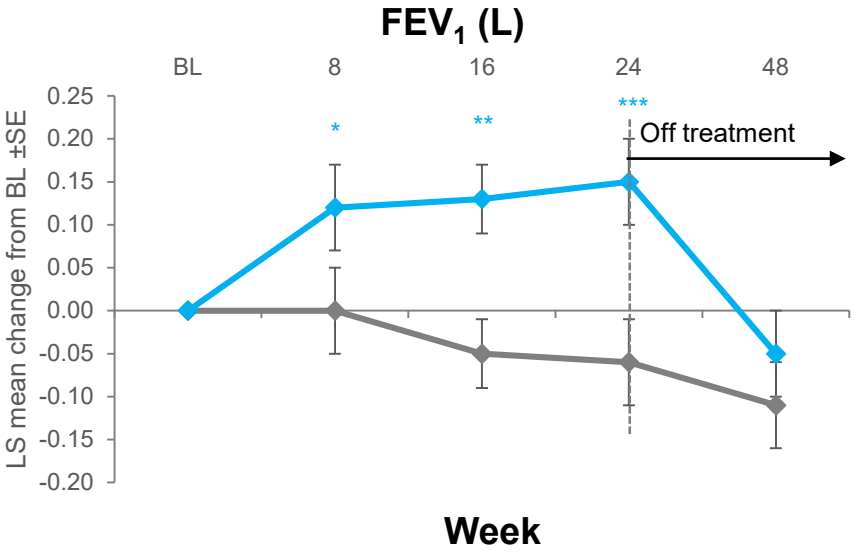


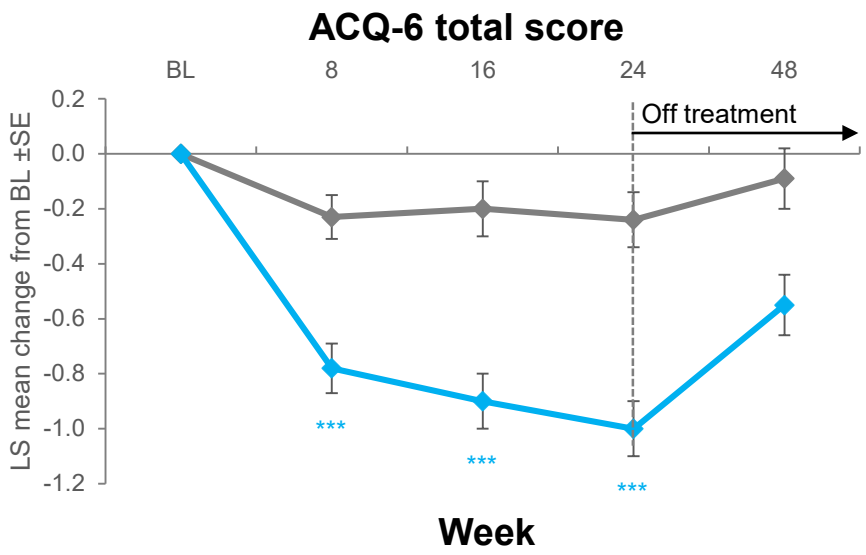
Daily loss of smell (Week)



Treatment ended at Week 24 ***$P < 0.0001$ Placebo Dupilumab 300 mg q2w

Change from baseline in FEV_1 and ACQ-6 in patients with comorbid asthma



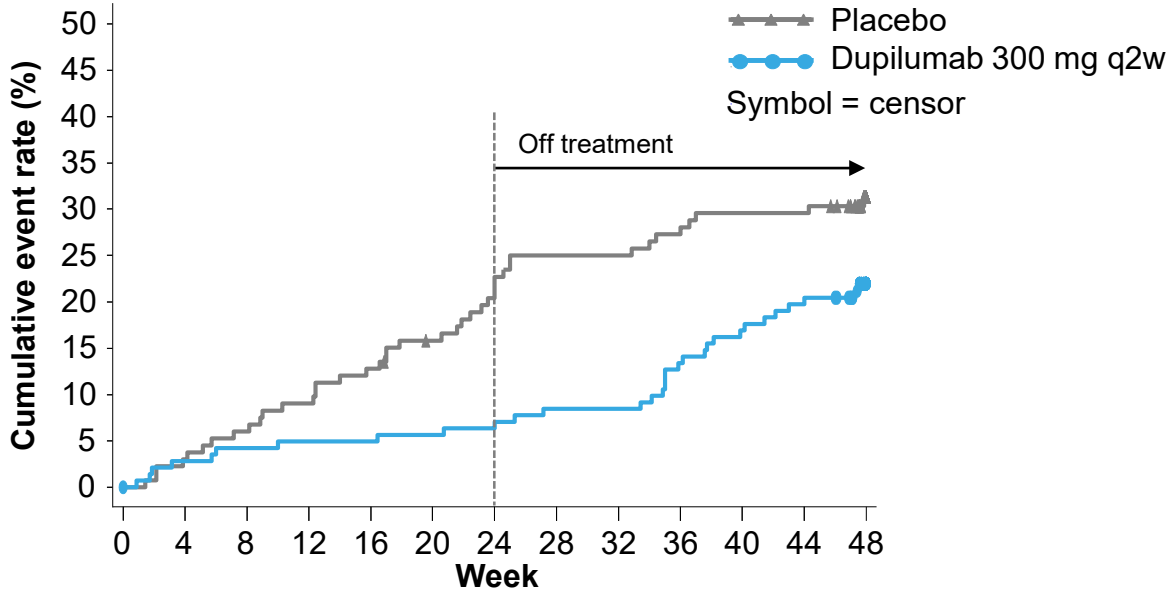


	Placebo (n = 79)		Dupilumab 300 mg q2w (n = 82)		LS mean difference vs placebo
	Baseline mean (SD)	LS mean change from BL at Week 24	Baseline mean (SD)	LS mean change from BL at Week 24	
FEV_1 (L)	2.66 (0.87)	–0.06	2.71 (1.05)	0.15	**0.21** (P = 0.0004)
ACQ-6	1.70 (1.16)	–0.24	1.55 (1.11)	–1.00	**–0.76** (P < 0.0001)

Treatment ended at Week 24 *P < 0.05, **P < 0.01, ***P < 0.0001 Placebo Dupilumab 300 mg q2w

Time to first systemic corticosteroid use and/or need for NP surgery

- Proportion of patients requiring SCS use/NP surgery during the 24-week treatment period was 7.2% in the dupilumab group vs 23.3% in the placebo group (hazard ratio [95% confidence interval] 0.268 [0.131–0.549], nominal *P* = 0.0003)



Safety

	Placebo (n = 132)	Dupilumab 300 mg q2w (n = 143)
Any TEAE	93 (70.5)	93 (65.0)
Any serious TEAE	19 (14.4)	6 (4.2)
Any TEAE leading to death	0	0
Any TEAE leading to permanent treatment discontinuation	3 (2.3)	5 (3.5)
TEAEs occurring in ≥ 5% of patients (MedDRA PT)		
Nasopharyngitis	20 (15.2)	19 (13.3)
Bronchitis	8 (6.1)	0
Headache	11 (8.3)	7 (4.9)
Nasal polyps	24 (18.2)	17 (11.9)
Epistaxis	4 (3.0)	11 (7.7)
Cough	7 (5.3)	4 (2.8)
Asthma	10 (7.6)	3 (2.1)
Injection-site erythema	12 (9.1)	8 (5.6)

Values are n (%).

MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; TEAE, treatment-emergent adverse event.

Conclusions

- In patients with severe uncontrolled CRSwNP, dupilumab significantly improved all disease components (nasal polyp size, sinus opacification, rhinosinusitis symptoms), reduced anosmia and improved health-related quality-of-life
  - Dupilumab showed improvement as early as Week 4, which continued up to Week 24
- Treatment with dupilumab reduced the proportion of patients requiring systemic corticosteroids and sinonasal surgery by 73%
- 75% of patients had a history of other comorbid type 2 diseases, and 58% of patients had comorbid asthma
- Dupilumab showed meaningful improvements in lung function and asthma control in CRSwNP patients with comorbid asthma, a difficult-to-treat population
- Dupilumab was safe and generally well tolerated

Disclosures

Han JK: Regeneron Pharmaceuticals, Inc., Sanofi – advisory boards. **Bachert C**: ALK, ASIT Biotech, AstraZeneca, Intrexon Actobiotics, Novartis, Sanofi, Stallergenes Greer – advisory boards. **Desrosiers M:** AstraZeneca, GSK, Probionase Therapies, Sanofi – clinical trial funding; Regeneron Pharmaceuticals, Inc., Sanofi – advisory boards; Probionase Therapies – equity. **Laidlaw TM:** Allakos, GSK, sanofi-aventis – national and international scientific advisory boards. **Hopkins C:** GSK, Optinose, Sanofi Genzyme, Smith and Nephew – advisory boards. **Fokkens WJ:** BioInspire, GSK, Meda Pharmaceuticals, Sanofi – research grants. **Paggiaro P:** AstraZeneca, Chiesi, GSK, Novartis, Sanofi – research grants, advisory boards. **Cho S:** Sanofi – research grant. **Olze H:** No conflicts of interest to disclose. **Greos LS:** Glenmark Pharmaceuticals**,** Novartis, Roxane Laboratories, Sandoz, sanofi-aventis – research grants. **Zhang M, Fan C, Draikiwicz S, Khan A, Pirozzi G, Staudinger H, Mannent LP:** Sanofi – employees, may hold stock and/or stock options in the company. **Amin N, Kamat S, Graham NMH, Ruddy M:** Regeneron Pharmaceuticals, Inc. – employees and shareholders.

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Back up

LS mean change from baseline at Week 24 versus placebo in LMK-CT, TSS, daily loss of smell, UPSIT and SNOT-22