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# DUPILUMAB IMPROVES SENSE OF SMELL AND REDUCES ANOSMIA AMONG PATIENTS WITH NASAL POLYPOSIS AND CHRONIC SINUSITIS: RESULTS FROM A PHASE 2A TRIAL

**Robert Naclerio[1], Daniel Hamilos[2], Berrylin J. Ferguson[†3], Claus Bachert[4], Peter Hellings[5], Joaquim Mullol[6], Philippe Gevaert[4], Donghui Zhang[7], Asif Khan[8], Chunpeng Fan[7], Vijay N. Joish[9], Nikhil Amin[9], Gianluca Pirozzi[7], Neil M.H. Graham[9], Heribert Staudinger[7], Annette Grabher[10], Leda Mannent[8]**

[1]The University of Chicago, Chicago, IL, USA; [2]Division of Rheumatology, Allergy & Immunology, Massachusetts General Hospital, Boston, MA, USA; [3]University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, PA, USA; [4]Ghent University Hospital, Ghent, Belgium; [5]Department of Otorhinolaryngology, Head and Neck Surgery, University Hospitals Leuven, Leuven, Belgium; [6]Clinical and Experimental Respiratory Immunoallergy, Hospital Clínic-IDIBAPS, Barcelona, Spain; [7]Sanofi R&D, Bridgewater, NJ, USA; [8]Sanofi R&D, Chilly Mazarin, France; [9]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [10]Sanofi R&D, Berlin, Germany; [†]Deceased

# Disclosure Robert Naclerio

- In relation to this presentation, I declare the following real or perceived conflicts of interest:
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  - Principal investigator of the study

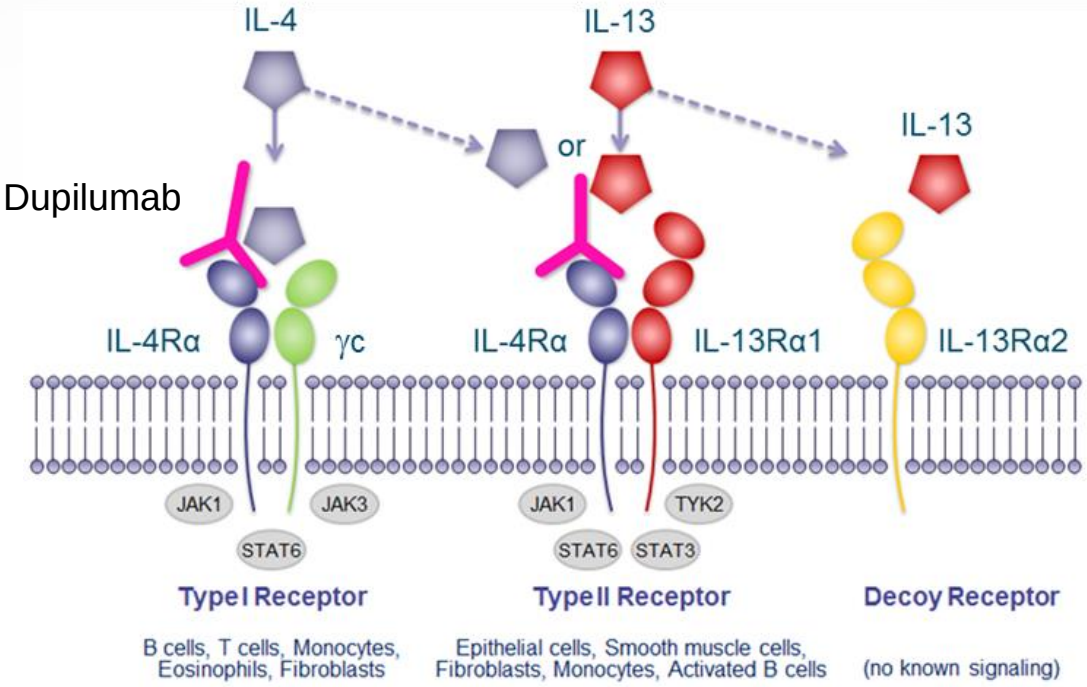
# Background (1)

- Chronic rhinosinusitis with nasal polyposis (CRSwNP) leads to the obstruction of the sinuses and nasal passages[1]
- CRSwNP negatively impacts patients' health-related quality of life[2]
- Hyposmia/anosmia, one of the most troublesome symptoms, is correlated with disease severity, and may be the first sign of disease reoccurrence[3]
  - Impact of hyposmia/anosmia on patients' life may include unawareness of self-hygiene and, failure to perceive fire/smoke, gas leaks, and rancid food, and affects overall well-being[4]

1. Fokkens WJ, et al. Rhinol Suppl. 2007;20:1-136;
2. Khan A, et al. Allergy. 2015;70 Suppl 101:282 [Poster 1536];
3. Simmen DB and Jones NS. Berlin, Heidelberg: Springer; 2010;163-73;
4. Nordin S et al. Acta Otolaryngol. 2011;131:826-32.

# Background (2)

- CRSwNP is characterized by Type 2/T helper 2 cell (Th2)-mediated inflammation[1]
- Dupilumab, a fully human anti-IL-4Rα monoclonal antibody, inhibits IL-4 and IL-13 signaling, key drivers of Type 2/Th2-mediated inflammation




IL, interleukin; JAK, Janus kinase; Rα, receptor alpha; STAT, signal transducers and activators of transcription; TYK, tyrosine kinase.

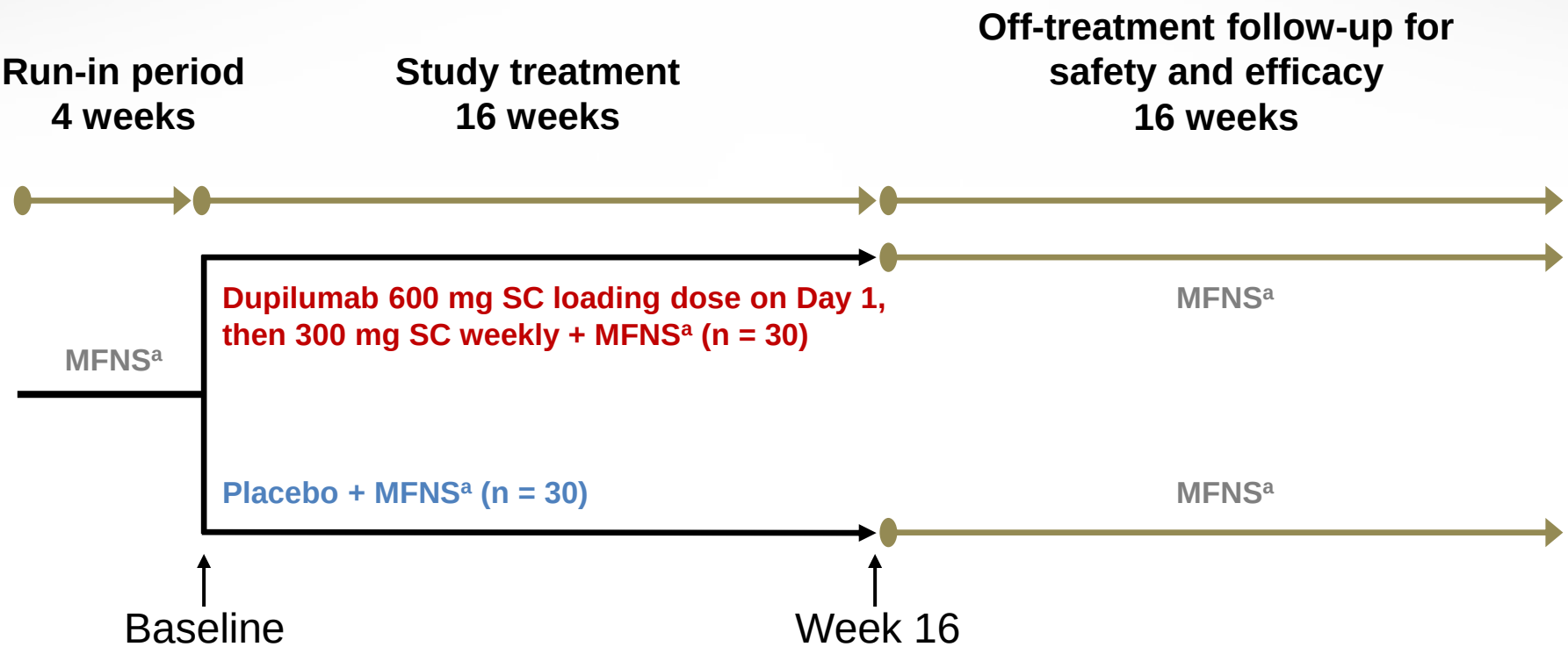
1. Fokkens WJ, et al. Rhinol Suppl. 2007;20:1-136.

# Objective

- To evaluate the effect of dupilumab on olfactory function in adult patients with CRSwNP refractory to intranasal corticosteroids

# Study Design

**Multicenter, international, randomized, double-blind, phase 2 study (ClinicalTrials.gov Identifier: NCT01920893)**




[a]100 µg MFNS in each nostril twice daily.
MFNS, mometasone furoate nasal spray; SC, subcutaneous.

# Key Inclusion and Exclusion Criteria

## Inclusion[1]

- Adult aged ≥ 18–65 years
- Bilateral nasal polyposis (NP) despite intranasal corticosteroids (INCS) treatment ≥ 2 months, with NPS ≥ 5 (out of 8)
  - ≥ 2 for each nostril
- ≥ 2 rhinosinusitis symptoms[2]
  - Nasal obstruction[a]
  - Nasal discharge[a]
  - Facial pain or pressure
  - Reduction or loss of smell

## Exclusion[1]

- 22-item sinonasal outcome test (SNOT-22) score < 7
- INCS drops within 2 months of screening
- Systemic corticosteroids within 2 months before screening or scheduled during study period
- Monoclonal antibody and immunosuppressive treatment, within 2 months or anti-IgE therapy (omalizumab) within 130 days of screening
- Surgery within 6 months before screening or > 2 surgeries for NP in the past
- For patients with comorbid asthma: exacerbation within 3 months of screening, high-dose inhaled corticosteroid (> 1,000 µg), or predicted forced expiratory volume in 1 second ($FEV_1$) ≤ 60%

[a]At least one of these two symptoms should always be present.

1. Bachert C, et al. JAMA. 2016;315:469-79;
2. Fokkens WJ, et al. Rhinology. 2012;50:1-12.

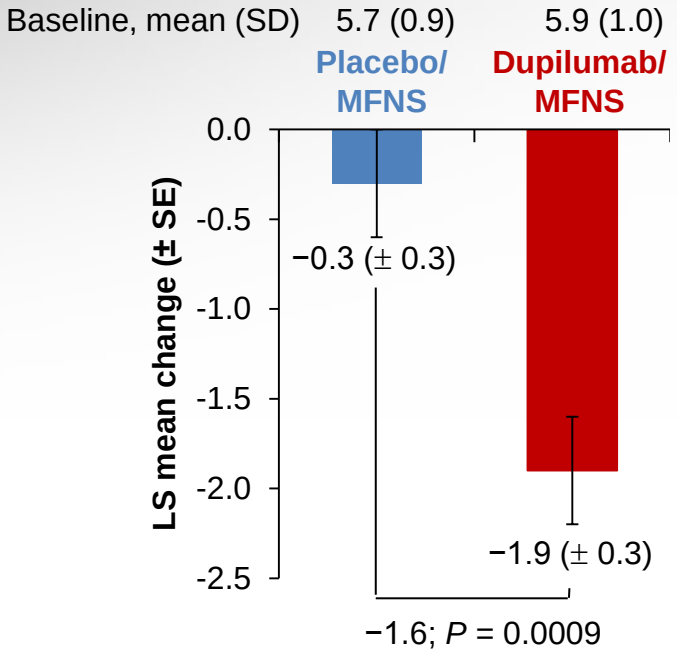
# Baseline Demographics and Disease Characteristics (ITT Population)

| | Placebo/MFNS (n = 30) | Dupilumab/MFNS (n = 30) |
|---|---|---|
| Age, mean (SD), years | 49.3 (9.1) | 47.4 (9.8) |
| Male sex, n (%) | 16 (53) | 18 (60) |
| NP duration, mean (SD), years | 11.5 (8.7) | 7.6 (6.1) |
| Bilateral endoscopic NPS, mean (SD) *0–8 score*[a] | 5.7 (0.9) | 5.9 (1.0) |
| Lund-Mackay total CT score, mean (SD) *0–24 score*[a] | 18.7 (5.5) | 18.6 (5.0) |
| Smell test (UPSIT) score, mean (SD) *0–40 score*[b] | 15.6 (7.9) | 12.8 (8.3) |
| Sense of smell loss (AM), mean (SD) *0–3 score*[c] | 2.8 (0.5) | 2.4 (0.9) |
| SNOT-22 total score, mean (SD) *0–110 score*[a] | 40.6 (19.9) | 41.4 (18.2) |
| SNOT-22 item 12 “decreased sense of smell/taste” *0–5 score*[a] | 4.53 (1.01) | 4.17 (1.15) |
| CRSwNP disease severity (VAS), mean (SD), *0–10 cm scale*[a] | 6.4 (2.7) | 6.4 (2.7) |
| $FEV_1$ in patients with asthma, mean (SD), L | 2.7 (0.8) | 2.7 (0.7) |
| ACQ-5 score in patients with asthma, mean (SD)[d] | 1.5 (0.9) | 1.6 (1.1) |
| Patients with ≥ 1 prior surgery, n (%) | 19 (63) | 16 (53) |
| Patients with comorbid medical history, n (%) | 21 (70.0) | 22 (73.3) |

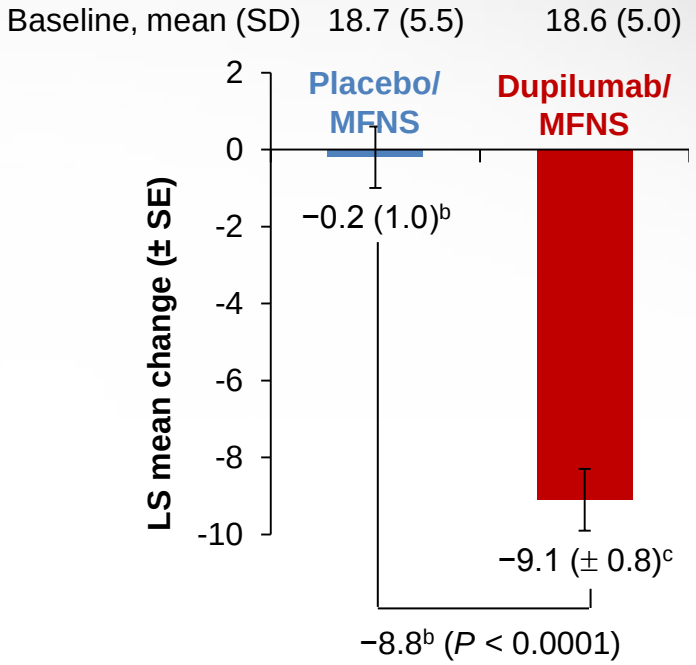
[a]Higher scores indicate worse status; [b]Higher scores indicate better status;
[c]0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms; [d]7-point scale (0 = no impairment, 6 = maximum impairment), MCID 0.5. CT, computerized tomography; ITT, intent-to-treat; SD, standard deviation; VAS, visual analog scale.

# Main Findings of the Phase 2a Trial With Dupilumab in CRSwNP patients

## NPS Score[a]




## Lund-Mackay Total CT Score[b]




| Exploratory endpoints in patients with comorbid asthma; LS mean change at Week 16 (± SE) | Placebo/MFNS (n = 19) | Dupilumab/MFNS (n = 16) | *P* value |
|---|---|---|---|
| $FEV_1$, L | 0.08 (± 0.09) | 0.31 (± 0.10) | 0.0739 |
| $FEV_1$ % predicted | 1.9 (± 2.8) | 9.0 (± 3.0) | 0.0397 |
| ACQ-5 score[d] | −0.3 (± 0.3) | −1.4 (± 0.4) | < 0.0001 |

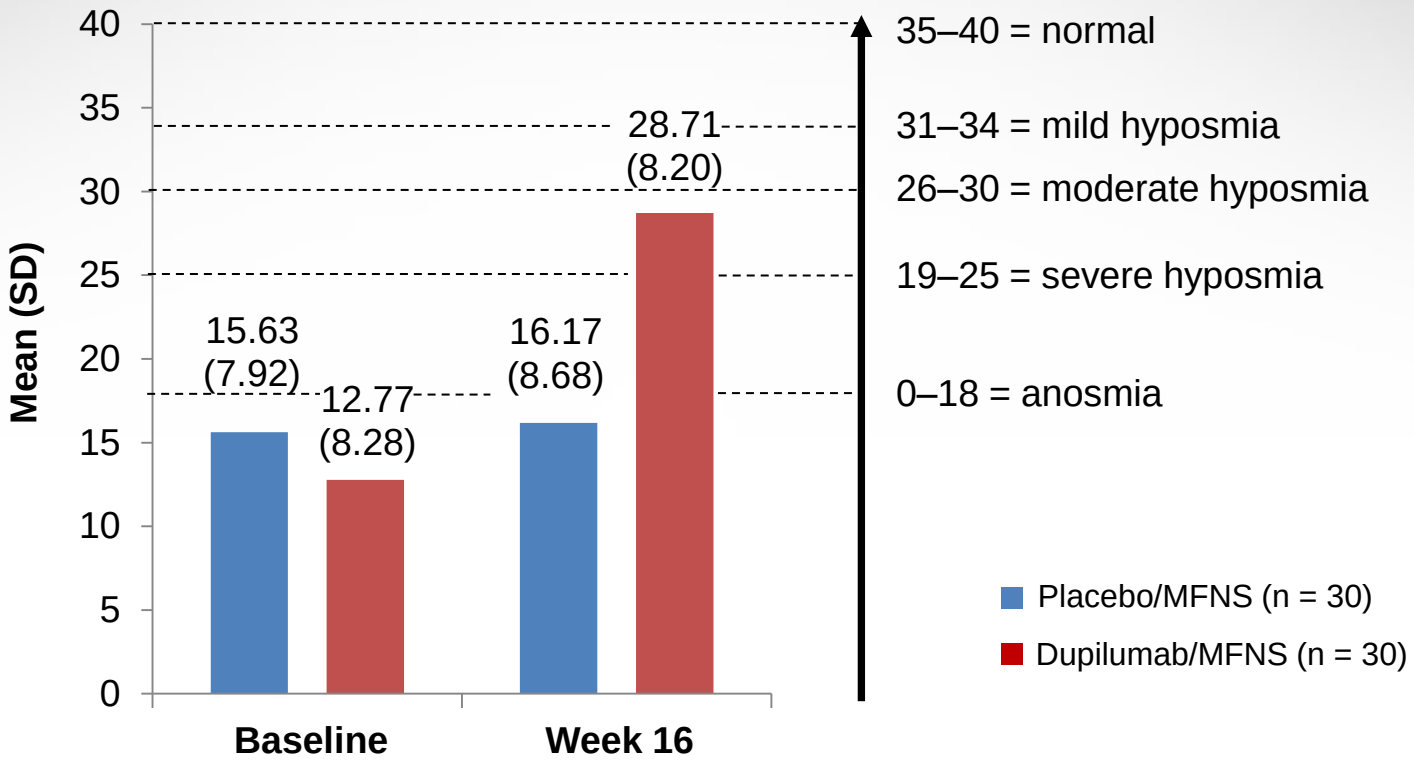
[a]0–8 bilateral score range (0 = no polyps, 4 = large polyps causing complete obstruction of the inferior nasal cavity);[b]0–24 bilateral point range (0 = normal, 24 = total opacification of each sinus and occluded osteomeatal complex); [c]difference due to rounding; [d]7-point scale (0 = no impairment, 6 = maximum impairment), MCID 0.5; LS, least squares.

Bachert C, et al. JAMA. 2016;315:469-79.

# Smell Assessment

- University of Pennsylvania Smell Identification Test (UPSIT) score ranging from 0 to 40 based on 40 possible correct answers:
  - 0–18 = anosmia, 19–25 = severe hyposmia, 26–30 = moderate hyposmia, 31–34 = mild hyposmia, and 35–40 = normal
- Daily (AM) patient assessment of loss of sense of smell (range 0–3)
  - 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms
- SNOT-22 item 12: “decreased sense of smell/taste” (range 0–5)

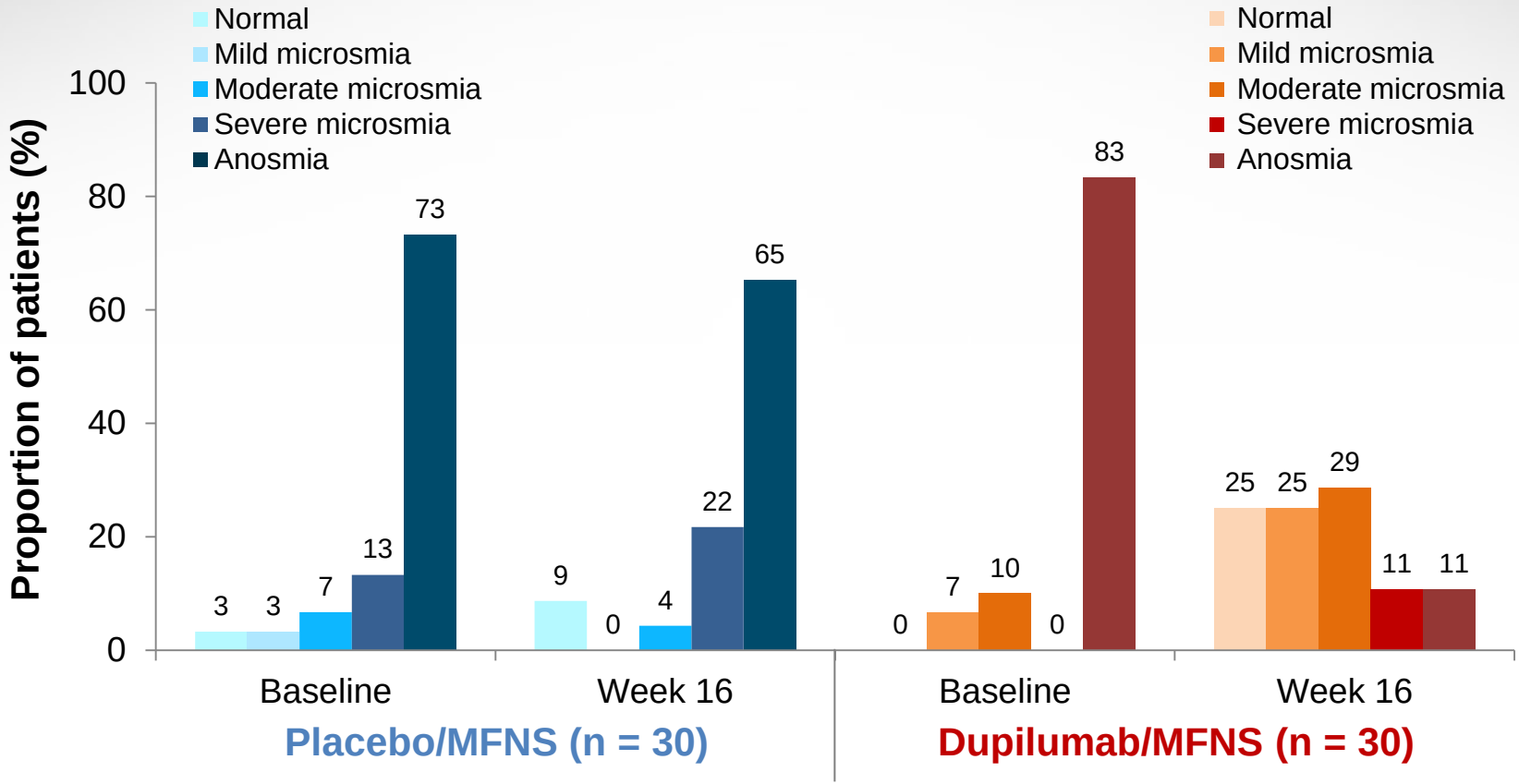
# Change in UPSIT at Week 16




- At Week 16, dupilumab treatment had a significant improvement in UPSIT (LS mean difference [95% CI] 14.78 [10.90, 18.65]; $P < 0.0001$ vs placebo)

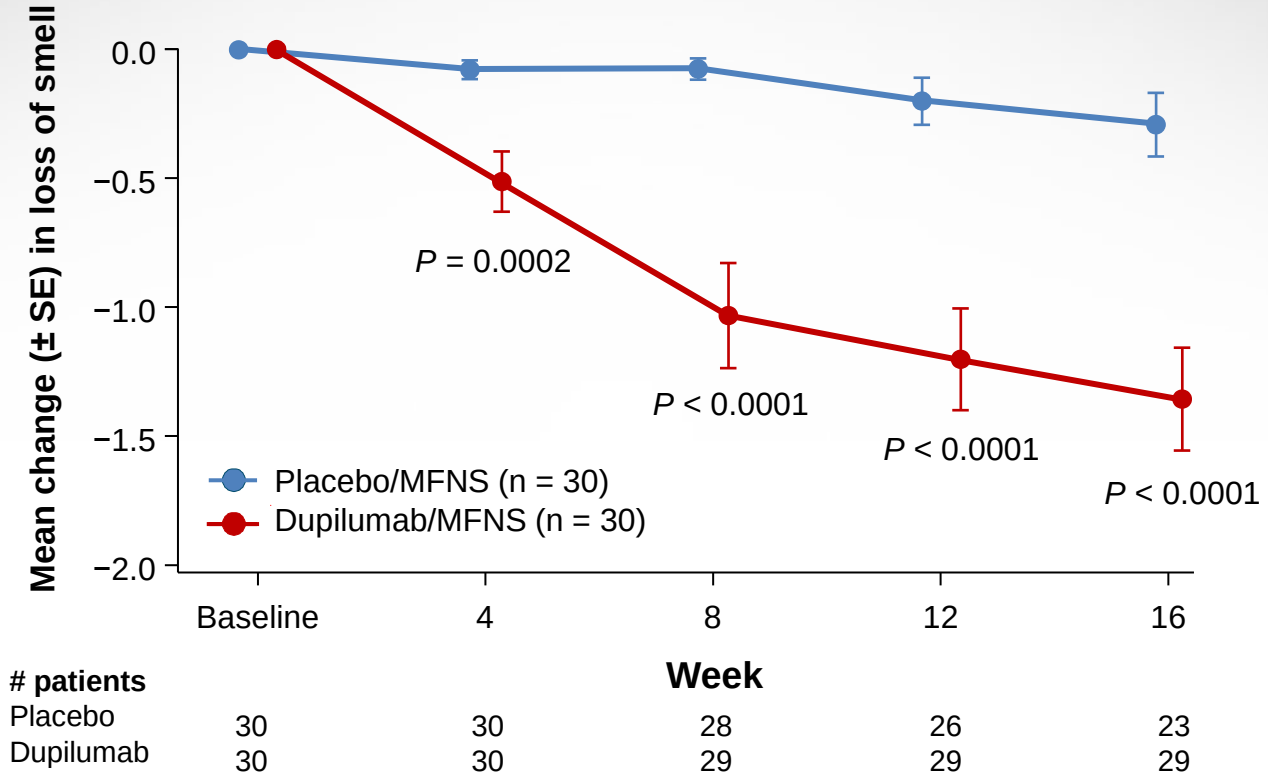
CI, confidence interval.

# Distribution of Patients by Severity of Loss of Smell



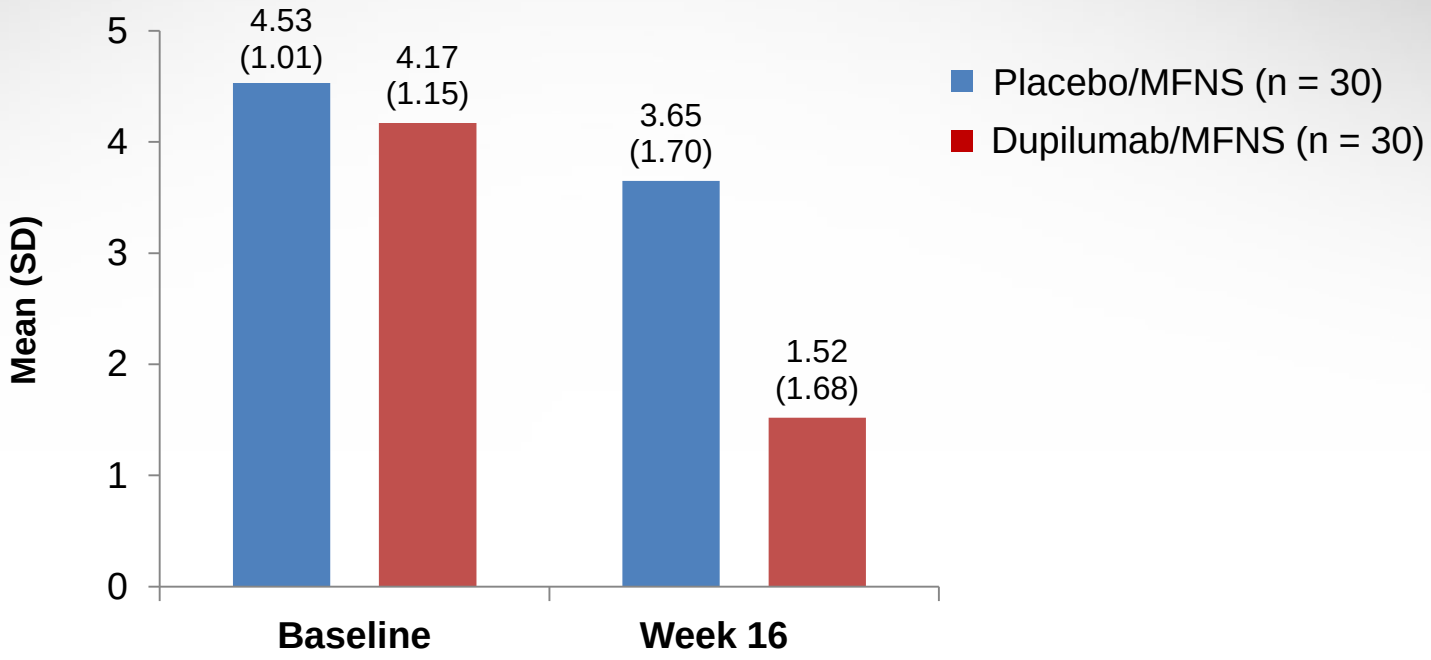

- At Week 16, patients with anosmia decreased from 83% to 11% with dupilumab versus 73% to 65% with placebo

# Change in Patient Daily Assessment of Loss of Smell Severity




- At Week 16, dupilumab significantly improved ($P < 0.0001$ vs placebo) daily (AM) patient assessment of loss of smell severity
- Functional assessment of “loss of smell” (UPSIT) correlated with patient-reported severity in daily loss of smell (baseline: placebo [$r = -0.7433$; $P < 0.0001$]; dupilumab [$r = -0.6385$; $P = 0.0001$])

# Change in SNOT-22 Item 12 “Decreased Sense of Smell/Taste”




- At Week 16, dupilumab significantly improved the SNOT-22 item assessing decreased sense of smell/taste (LS mean difference [95% CI] −2.06 [−2.88, −1.24]; *P* < 0.0001 vs placebo)
- This item was the first of top-5 symptoms, reported by 90% of the patients, considered as the most important item affecting their health
- Functional assessment of “loss of smell” (UPSIT) correlated with SNOT-22 item (baseline: placebo [*r* = −0.7435; *P* < 0.0001]; dupilumab [*r* = −0.7615; *P* < 0.0001])

# Treatment-Emergent Adverse Events

| Patients With TEAEs,[a], n (%) | Placebo/MFNS (n = 30) | Dupilumab/MFNS (n = 30) |
|---|---|---|
| Any TEAE | 25 (83) | 30 (100) |
| TEAEs reported in > 10% of patients in either treatment group | | |
| Nasopharyngitis | 10 (33) | 14 (47) |
| Injection-site reaction | 2 (7) | 12 (40.0) |
| Epistaxis | 2 (7) | 7 (23) |
| Oropharyngeal pain | 2 (7) | 7 (23) |
| Headache | 5 (17) | 6 (20) |
| Upper respiratory tract infection | 0 | 4 (13) |
| Bronchitis | 4 (13) | 1 (3) |

[a]TEAEs were defined as events occurring from the first administration of study medication to the end of the post-treatment period; Medical Dictionary for Regulatory Activities (MedDRA) preferred term.

TEAE, treatment-emergent adverse event.

# Conclusion

- Decreased sense of smell/taste was reported by 90% of the patients as the most important item affecting their health and quality of life
- The smell test assessment (UPSIT) correlated with patient-reported smell assessment severity
- In CRSwNP patients refractory to intranasal corticosteroids, dupilumab significantly and rapidly improved the sense of smell and reduced anosmia over a 16-week treatment period
  - The proportion of patients with anosmia decreased from 83% at baseline to 11% at Week 16 in the dupilumab group versus 73% to 65% in placebo
- In this study, nasopharyngitis, injection-site reactions, and headache were the most frequent adverse events (placebo and dupilumab groups combined)

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Julia Arebro
Lars Olaf Cardell
Karin Jonstam

**Spain:**

*Barcelona*
Freddy Enrique Agredo
Xavier González Compta
Francesc Cruellas
Eduardo Lehrer
Manel Manos
Joaquim Mullol
Maria Del Carmen Vennera

*Valencia*
Miguel Armengot
Rosa Hernández

*Madrid*
Carlos Cenjor
Álvaro Sánchez Barrueco
Jessica Santillan Coello
Jose Miguel Villacampa

*Cádiz*
Maria Agustina Ariza
Gregorio Soto Campos
Bernal Alfonso Del Cuvillo

**USA:**

*Lake Oswego, OR*
James Baker

*Centennial, CO*
Leon Greos

*Boston, MA*
Daniel Hamilos

*Pittsburgh, PA*
Berrylin J. Ferguson
Stella Lee

*Rolling Hills Estates, CA*
Lawrence Sher

**Sanofi**

Annette Grabher
Patricia Rohane
Ariel Teper
Blandine Nembo
Sebastien Paoli
Suzana Todorovic
Nian Tian
Florence Benderitter
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Linda Williams

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