A Randomized Phase 3 Study, SINUS-52, Evaluating the Efficacy and Safety of Dupilumab in Patients With Severe Chronic Rhinosinusitis With Nasal Polyps

Claus Bachert[1,2], Martin Desrosiers[3], Joaquim Mullol[4], Peter W. Hellings[5], Anders Cervin[6], Lawrence Sher[7], John V. Bosso[8], Stella E. Lee[9], Jorge F. Maspero[10], Shigeharu Fujieda[11], Shoji Matsune[12], Xin Lu[13], Chunpeng Fan[13], Steven Draikiwicz[13], Nikhil Amin[14], Siddhesh Kamat[14], Asif Khan[15], Gianluca Pirozzi[13], Neil M.H. Graham[14], Marcella Ruddy[14], Heribert Staudinger[13], Leda P. Mannent[15]

[1]Upper Airways Research Laboratory, Ghent University, Ghent, Belgium; [2]Karolinska Institutet, Stockholm, Sweden; [3]Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), Montreal, QC, Canada; [4]Hospital Clinic, IDIBAPS, Universitat de Barcelona, CIBERES, Barcelona, Catalonia, Spain; [5]University Hospitals Leuven, Leuven, Belgium; [6]University of Queensland and The Royal Brisbane & Women's Hospital, Brisbane, Australia; [7]Peninsula Research Associates, Rolling Hills Estates, CA, USA; [8]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [9]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [10]Allergy and Respiratory Research Unit, Fundación CIDEA, Buenos Aires, Argentina; [11]University of Fukui, Fukui, Japan; [12]Nippon Medical School, Musashi Kosugi Hospital, Kanagawa, Japan; [13]Sanofi, Bridgewater, NJ, USA; [14]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [15]Sanofi, Chilly-Mazarin, France

BACKGROUND

- Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic inflammatory disease of the nasal and paranasal sinuses associated with high symptom burden and poor health-related quality of life (HRQoL)
- CRSwNP predominantly displays a type 2 inflammatory signature with interleukin (IL)-4, IL-5, and IL-13 as prominent cytokines, and tissue infiltration by eosinophils, basophils, and mast cells[1,2]
- Available treatments options for CRSwNP, limited to the chronic use of intranasal corticosteroids (INCS), short courses of systemic corticosteroids (SCS) when symptoms worsen, and surgery when medication fails, do not address the underlying sinus inflammatory disease
- Dupilumab is a fully human VelocImmune®-derived monoclonal antibody[3,4] that blocks the shared receptor subunit for IL-4 and IL-13, key drivers of type 2 inflammation[5]
- Dupilumab is approved in the USA for patients aged ≥ 12 years with moderate-to-severe eosinophilic or oral corticosteroid-dependent asthma[6–8] and for the treatment of adults with inadequately controlled moderate-to-severe atopic dermatitis in several countries[9–11]
- In a phase 2a proof-of-concept study (ClinicalTrials.gov Identifier: NCT01920893), dupilumab on a background of mometasone furoate nasal spray (MFNS) significantly improved endoscopic, radiographic, clinical, and patient-reported outcomes in patients with CRSwNP refractory to INCS[11]
- The phase 3 study SINUS-52 (NCT02898454) was conducted to further investigate dupilumab efficacy and safety in treating patients with severe CRSwNP uncontrolled by standard of care

OBJECTIVE

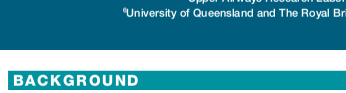
- **To evaluate the efficacy and safety of dupilumab compared with placebo in patients with CRSwNP receiving MFNS background therapy**

METHODS

Study design

- The design of this multinational, multicenter, randomized, double-blind, phase 3, placebo-controlled, parallel-group study is shown in **Figure 1**

Figure 1. Study design of the dupilumab SINUS-52 study (ClinicalTrials.gov Identifier: NCT02898454).



NP, nasal polyp; q2w, every 2 weeks; q4w, every 4 weeks; R, randomization; SC, subcutaneous

- Patients received a background therapy of 400 µg MFNS daily
- Patients were randomized 1:1:1 as follows:
  - Arm A: SC dupilumab 300 mg q2w until Week 52
  - Arm B: SC dupilumab 300 mg q2w until Week 24 followed by 300 mg q4w until Week 52
  - Arm C: placebo matching SC dupilumab q2w until Week 52
- Rescue treatment with systemic corticosteroids, NP surgery, saline nasal lavage, and systemic antibiotics was allowed at the investigator's discretion
- The patient population was stratified for comorbid asthma/AERD (aspirin and nonsteroidal anti-inflammatory drug-exacerbated respiratory disease) and prior NP surgery

Main inclusion criteria

- Adult patients aged ≥ 18 years who have undergone prior treatment with or have contraindication/intolerance to SCS in the past 2 years, or have had prior surgery for NPs, with bilateral endoscopic nasal polyp score (NPS) ≥ 5 (out of 8), with ≥ 2 for each nostril
- 2 or more of the following rhinosinusitis symptoms:
  - Nasal obstruction (symptom severity score of 2 or 3), AND
  - Rhinorrhea (anterior/posterior) OR
  - Reduction or loss of smell

Main exclusion criteria

- Monoclonal antibody and immunosuppressant treatment within 2 months or anti-IgE therapy (omalizumab) within 130 days before 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 forced expiratory volume in 1 second (FEV_1) ≤ 50% of predicted normal

Assessment

- Co-primary efficacy endpoints
  - Change from baseline in endoscopic NPS at Week 24 for dupilumab (pooled Arm A+B) vs placebo
  - Change from baseline in patient-reported nasal congestion (NC) score at Week 24 for dupilumab (pooled Arm A+B) vs placebo
- Key secondary endpoints
  - Change from baseline in sinus opacification using sinus computed tomography Lund–Mackay (LMK-CT) score for dupilumab (pooled Arm A+B) vs placebo at Week 24
  - Change from baseline in patient-reported total symptom score (TSS), University of Pennsylvania Smell Identification Test (UPSIT) score, daily loss-of-smell score, and 22-item Sino-Nasal Outcome Test (SNOT-22) score at Week 24 for dupilumab (pooled Arm A+B) vs placebo
  - Change from baseline in endoscopic NPS, NC score, and SNOT-22 score at Week 52 for dupilumab (Arm A) vs placebo
- The following additional endpoints were also evaluated:
  - Proportion of patients during study treatment who received SCS and/or had surgery for NP
  - For patients with comorbid asthma, change from baseline to Week 24 in lung function (FEV_1, [L]), and asthma control, measured by the 6-item Asthma Control Questionnaire (ACQ-6)
- Safety
  - Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events

Statistical methods

- Each of the 2 co-primary efficacy endpoints and the key secondary endpoints were prospectively defined and multiplicity adjusted, and were analyzed using a hybrid method of the worst-observation carried forward and multiple imputation methods
- Pooling of treatment arms for efficacy analyses
  - For analyses of change from baseline to Week 24, Arm A (300 mg q2w) was pooled with Arm B (300 mg q2w–q4w) as both groups were receiving 300 mg q2w up to Week 24
  - The pooled Arm A+B was compared with Arm C (placebo) at Week 24
  - Arm A (300 mg q2w for 52 weeks) and Arm B (300 mg q2w–q4w) were compared separately with Arm C (placebo)

RESULTS

Patients

- A total of 448 patients were randomized (intention-to-treat [ITT] population: Arm A, n = 150; Arm B, n = 145; Arm C, n = 153)
- Patient baseline demographics and clinical characteristics were comparable between treatment groups and consistent with a severe, uncontrolled CRSwNP setting (**Table 1**)
- 82.4% had type 2 comorbid disease, including 59.6% with asthma

Table 1. Baseline demographics and clinical characteristics of treatment groups.

	Placebo (n = 153)	Dupilumab 300 mg q2w (n = 150)	Dupilumab 300 mg q2w–q4w (n = 145)
Age, years; mean (SD)	51.67 (12.66)	51.91 (11.88)	52.28 (12.87)
Male, n (%)	95 (62.1)	97 (64.7)	87 (60.0)
NP duration, years; mean (SD)	10.88 (9.40)	11.28 (10.38)	10.67 (9.12)
Patients with ≥ 1 prior surgery, n (%)	88 (57.5)	88 (58.7)	85 (58.6)
Patients with SCS use in the previous 2 years, n (%)	122 (79.7)	121 (80.7)	116 (80.0)
Patients with any comorbid type 2 medical history including asthma/AERD, n (%)	127 (83.0)	122 (81.3)	120 (82.8)
Patients with comorbid asthma	91 (59.5)	85 (56.7)	91 (62.8)
Patients with comorbid AERD	44 (28.8)	35 (23.3)	41 (28.3)
Bilateral endoscopic NPS,[a] range 0–8; mean (SD)	5.96 (1.21)	6.07 (1.22)	6.29 (1.20)
Daily NC score,[a] range 0–3; mean (SD)	2.38 (0.54)	2.48 (0.62)	2.44 (0.59)
LMK-CT score,[a] range 0–24; mean (SD)	17.65 (3.78)	18.42 (3.61)	17.81 (3.89)
TSS,[a] range 0–9; mean (SD)	7.08 (1.38)	7.31 (1.41)	7.28 (1.55)
Smell test (UPSIT) score,[a] range 0–40; mean (SD)	13.78 (8.31)	13.46 (8.20)	13.60 (7.57)
Loss of smell (daily, morning) score,[a] range 0–3; mean (SD)	2.72 (0.52)	2.81 (0.46)	2.73 (0.59)
SNOT-22 total score,[a] range 0–110; mean (SD)	53.48 (21.85)	50.16 (19.72)	51.89 (21.05)
CRSwNP severity (VAS) score,[a] range 0–10 cm; mean (SD)	7.98 (2.22)	8.24 (1.77)	7.78 (2.20)
Blood eosinophils, Gig/L; mean (SD)	0.45 (0.38)	0.45 (0.39)	0.40 (0.30)
Total serum IgE, kU/mL; mean (SD)	227.80 (267.13)	210.82 (256.78)	282.28 (463.72)
In patients with asthma			
FEV_1, L; mean (SD)	2.58 (0.80)	2.53 (0.91)	2.59 (0.78)
FEV_1, % predicted; mean (SD)	83.46 (16.64)	82.47 (20.92)	84.18 (15.51)
ACQ-6 score,[b] range 0–6; mean (SD)	1.63 (1.03)	1.45 (0.99)	1.65 (1.23)

[a]Higher scores indicate greater disease severity except for UPSIT, where higher scores indicate lower disease severity.
[b]SD, standard deviation; VAS, Visual Analog Scale.

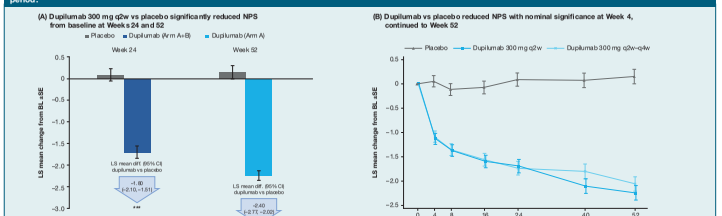
Co-primary efficacy endpoints

- Dupilumab significantly reduced nasal polyp size (measured by NPS) and patient-reported severity of nasal congestion (determined by NC score) from baseline at Week 24 ($P < 0.0001$ vs placebo for both) (**Figure 2A–D**)

Key secondary endpoints

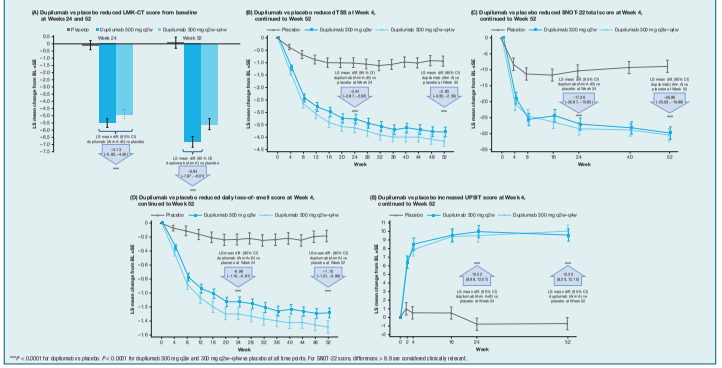
- Dupilumab reduced sinus opacification, measured by LMK-CT score, from baseline at Weeks 24 and 52 ($P < 0.0001$ vs placebo for all) (**Figure 3A**)
- Dupilumab reduced symptoms and improved HRQoL (assessed by TSS and SNOT-22 score), and also significantly improved sense of smell (assessed by daily loss-of-smell score and UPSIT score) from baseline at Weeks 24 and 52 ($P < 0.0001$ vs placebo for all) (**Figure 3B–E**)
- In the dupilumab arm, there was a reduction in the proportion of patients with anosmia, determined by UPSIT score, from 79% at baseline to 30% at Week 24 compared with no change in the placebo arm
- Dupilumab reduced NPS, NC score, and SNOT-22 score with nominal significance from baseline at Week 52 ($P < 0.0001$ vs placebo for all) (**Figure 2A–D** and **3C**)

Figure 2. Dupilumab treatment (300 mg q2w and 300 mg q2w–q4w) vs placebo significantly improved NPS and NC score in the ITT population, over the 52-week treatment period.



***P < 0.0001 for dupilumab vs placebo. $P < 0.001$ for dupilumab 300 mg q2w and 300 mg q2w–q4w vs placebo at all time points. CI, confidence interval; LS, least squares; SE, standard error.

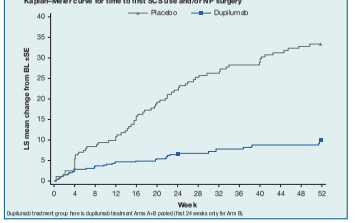
Figure 3. Dupilumab treatment (300 mg q2w and 300 mg q2w–q4w) vs placebo improved clinical and patient-reported outcomes in the ITT population.



***P < 0.0001 for dupilumab vs placebo. $P < 0.001$ for dupilumab 300 mg q2w and 300 mg q2w–q4w vs placebo at all time points. For SNOT-22 score, difference > 8.9 are considered clinically relevant.

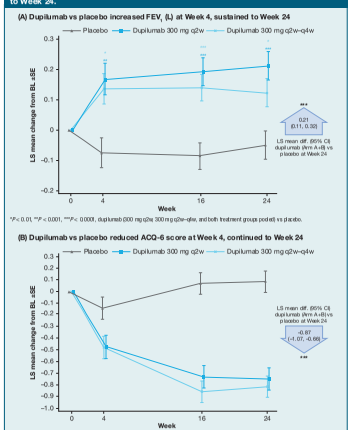
- The magnitude of the additional improvements observed from Week 24 to 52 in NPS and sinus opacification (LMK-CT score) were numerically greater in the patients who continued on the 300 mg q2w regimen than those who switched to q4w dosing at Week 24 (NPS: −0.53 and −0.31 for 300 mg q2w and 300 mg q2w–q4w, respectively; LMK-CT scan score: −1.37 and −0.62 for 300 mg q2w and 300 mg q2w–q4w, respectively)
- Dupilumab reduced the proportion of patients requiring SCS or NP surgery vs placebo: hazard ratio (HR) [95% CI] 0.238 [0.156–0.364]; nominal $P < 0.0001$ (**Figure 4**)
  - Dupilumab 300 mg q2w vs placebo reduced the proportion of patients requiring SCS by 74.6% (HR [95% CI] 0.254 [0.166–0.391]; nominal $P < 0.0001$) and the proportion of patients requiring NP surgery by 89.4% (HR [95% CI] 0.106 [0.024–0.475]; nominal $P = 0.0033$)
- In patients with comorbid asthma (59.6%), dupilumab significantly increased FEV_1 and reduced ACQ-6 by Week 4, with results sustained up to Week 24 ($P < 0.0001$ vs placebo for both at all time points) (**Figure 5A** and **B**)

Figure 4. Dupilumab treatment (300 mg q2w pooled) vs placebo reduced the need for SCS use and/or NP surgery in the ITT population over the 52-week treatment period.



Dupilumab treatment group here is dupilumab treatment Arms A+B pooled (first 24 weeks only for Arm B).

Figure 5. Dupilumab treatment (300 mg q2w and 300 mg q2w–q4w) improved lung function (A) and asthma control (B) in the ITT population, vs placebo, from baseline to Week 24.



***P < 0.001, **P < 0.001, ***P < 0.0001, dupilumab 300 mg q2w, 300 mg q2w–q4w, and both treatment groups pooled vs placebo.

***P < 0.0001 for dupilumab (pooled treatment groups) vs placebo. $P < 0.001$ for dupilumab 300 mg q2w and 300 mg q2w–q4w vs placebo at all time points. Difference > 0.5 are considered clinically relevant.

SAFETY

- The most common TEAE occurring at higher frequency in dupilumab-treated vs placebo-treated patients was injection-site reactions (**Table 2**)
- The most common TEAE in all treatment groups was nasopharyngitis (**Table 2**)
- Overall safety profile was comparable between the two dupilumab regimens. However, TEAEs of worsening of nasal polyps, asthma and sinusitis occurred with a higher cumulative incidence in patients who switched at Week 24 from dupilumab 300 mg q2w to q4w dosing compared with those who remained on 300 mg q2w for the full 52 weeks

Table 2. Treatment-emergent adverse events.

Patients with TEAEs,[a] n (%)	Placebo (n = 150)	Dupilumab 300 mg q2w (n = 149)	Dupilumab 300 mg q2w–q4w (n = 148)
Any TEAE	136 (90.7)	124 (83.2)	132 (89.2)
Any serious TEAE	15 (10.0)	8 (5.4)	10 (6.8)
Any TEAE leading to death	0	0	1 (0.7)
Any TEAE leading to permanent treatment discontinuation	17 (11.3)	6 (4.0)	2 (1.4)
TEAEs occurring in ≥ 5% of patients (MedDRA PT)			
Nasopharyngitis	36 (24.0)	30 (20.1)	31 (20.9)
Upper respiratory tract infection	19 (12.7)	10 (6.7)	8 (5.4)
Bronchitis	8 (5.3)	9 (6.0)	9 (6.1)
Sinusitis	17 (11.3)	8 (5.4)	13 (8.8)
Headache	18 (12.0)	14 (9.4)	16 (10.8)
Nasal polyps	25 (16.7)	8 (5.4)	15 (10.1)
Epistaxis	20 (13.3)	13 (8.7)	7 (4.7)
Cough	8 (5.3)	9 (6.0)	9 (6.1)
Asthma	19 (12.7)	6 (4.0)	13 (8.8)
Injection-site erythema	11 (7.3)	11 (7.4)	10 (6.8)
Injection-site reaction	3 (2.0)	5 (3.4)	8 (5.4)

[a]Defined as events occurring from the first administration of study medication to the end of the post-treatment period by Medical Dictionary for Regulatory Activities Preferred Term (MedDRA PT).

CONCLUSIONS

- **In patients with severe uncontrolled CRSwNP, dupilumab as add-on to MFNS significantly improved all disease components tested (nasal polyp size, sinus opacification, rhinosinusitis symptoms), reduced anosmia, and improved HRQoL**
  - **Improvements in all outcome measures were noted early in treatment (a the first assessment time point) and continued to improve across the 52-week treatment period**
- **Dupilumab reduced systemic steroid use and the need for NP surgery**
- **Dupilumab improved lung function and asthma control in CRSwNP patients with comorbid asthma, a difficult-to-treat patient population**
- **Overall, the 300 mg q2w regimen had better sustained improvements in the objective measures of NPS and LMK-CT scan score and fewer breakthrough TEAEs of worsening of nasal polyps, asthma, and sinusitis than the 300 mg q2w–q4w regimen**
- **Dupilumab was well tolerated**

References

1. Fokkens W, et al. Rhinol Suppl. 2007;20:1-136. 2. Nat A. Allergol Int. 2015;64:121-30. 3. Macdonald LE, et al. Proc Natl Acad Sci U S A. 2014;111:5167-72. 4. Murphy AJ, et al. Proc Natl Acad Sci U S A. 2014;111:5153-8. 5. Gandhi NA, et al. Expert Rev Clin Immunol. 2017;13:425-37. 6. Rabe KF, et al. N Engl J Med. 2018;378:2475-85. 7. Gandhi N, et al. Expert Rev Clin Immunol. 2017;13:425-37. 8. Murphy K, et al. J Allergy Clin Immunol Pract. 2017;5:1572-81. 9. Thaçi D, et al. Lancet. 2016;387:40-52. 10. Wenzel S, et al. Lancet. 2016;388:31-44. 11. Castro M, et al. N Engl J Med. 2018;378:2486-96. 12. Bachert C, et al. JAMA. 2016;315:469-79.

Acknowledgments

Research sponsored by Sanofi and Regeneron Pharmaceuticals, Inc. ClinicalTrials.gov Identifier: NCT02898454. Medical writing/editorial assistance provided by Sinéad Holland, PhD, of Excerpta Medica, funded by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc.

Disclosures

Bachert C:ALK, ASIT Biotech, AstraZeneca, Intrexon Actobiotics, Novartis, Sanofi, Stallergenes Greer –advisory boards. **Desrosiers M:** AstraZeneca, GSK, Protonivose Therapies, Sanofi – clinical trial funding; Regeneron Pharmaceuticals, Inc., Sanofi – advisory boards; Protonivose Therapies – equity. **Mullol J:** Regeneron Pharmaceuticals Inc., Sanofi – clinical trial funding, advisory boards. **Hellings PW:** No conflicts of interest to disclose. **Cervin A:** Intrexon Actobiotics – advisory boards. **Sher L:** Aimmune, Optinose, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme – advisory boards; Regeneron Pharmaceuticals, Inc., Sanofi Genzyme – speaker fees; Aimmune, Amgen, AstraZeneca, Circassia, DBV, Galderma, GSK, Lupin, Merck, Mylan, Novartis, Novo Nordisk, Optinose, Pearl, Pfizer, Pulmagen, Roxane, Sanofi, Spirometrix, Teva, Vectura, Watson – clinical trial funding. **Bosso JV:** Cumberland Pharma, Sanofi – clinical trial funding; Novartis/Genentech, Optinose – consultant. **Lee SE:** Allakos, AstraZeneca, Kiniqo Biosciences, Sanofi – clinical trial funding; Novartis, Regeneron Pharmaceuticals, Inc., Sanofi – advisory boards. **Maspero JF:** AstraZeneca, GSK, Novartis, Sanofi, Teva, – consultant; Boehringer Ingelheim, Menarini, Novartis, Uriach – speaker fees; AstraZeneca, Novartis, Sanofi – research grants. **Fujieda S:** Kyowa Hakko Kirin, Sanofi – advisory boards; Kyorin – speaker fees. **Matsune S:** Kyorin, Meiji Seika Pharma, Sanofi, Taiho, Torii – speaker fees. **Lu X, 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.

Disclaimer

Note: Dupilumab is in clinical development for treatment of chronic rhinosinusitis with nasal polyps and currently has no marketing authorization for this indication.

Presented at the 2019 Annual Meeting of the American Academy of Allergy, Asthma & Immunology (AAAAI): San Francisco, CA, USA; February 22–25, 2019.