# Indication for biologics in a real-world cohort of dupilumab treated chronic rhinosinusitis with nasal polyps patients according to international recommendations: evidence from the European CRS Outcome Registry (CHRINOSOR)

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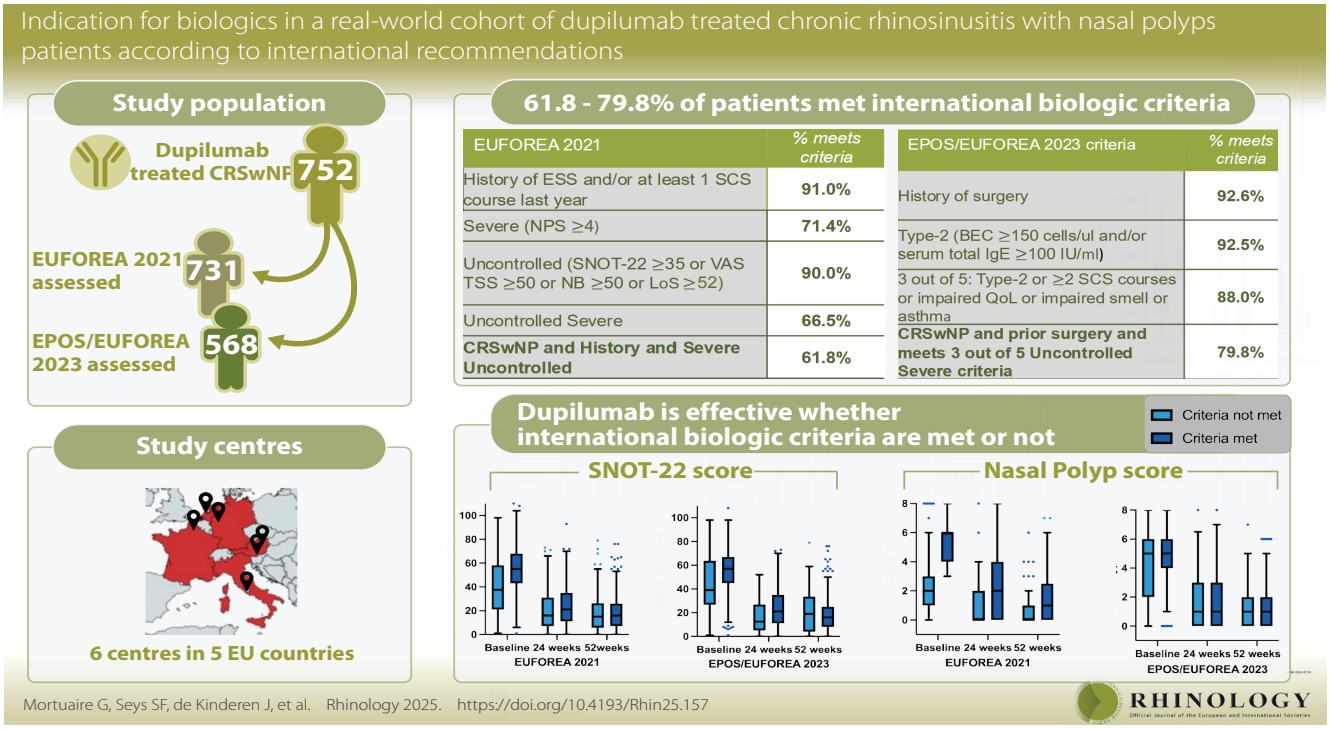


## Abstract

**Background**: Criteria for biologic treatment of uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP) differ across international recommendations and prescription of biologics depends on national reimbursement criteria. CHRINOSOR offers an opportunity to analyse biologic indications in the real-world setting according to international recommendations. **Methods**: CRSwNP patients who received dupilumab treatment in the ENT clinic of 6 tertiary centres (5 countries) were included. Baseline demographic and lifestyle factors, NP score, SinoNasal Outcome Test-22 score, visual analogue scale for sinus symptoms, and Asthma Control Test score were retrieved from the medical records. Indication criteria for biologic treatment according to EUFOREA 2021, and EPOS/EUFOREA 2023 recommendations was applied. Dupilumab effectiveness was assessed at baseline, 24 and 52 weeks in relation to these criteria. **Results**: 61.8% and 79.8% of patients met respectively the EUFOREA 2021 or the EPOS/EUFOREA 2023 indication criteria for biologic treatment. Dupilumab was effective in patients who met or did not meet international criteria for biologic indication. However, patients who met the indication criteria showed overall a more pronounced effect on most of the outcome parameters than patients who did not meet the criteria. **Conclusions**: Real-world management of CRSwNP with biologics does not strictly follow the indication criteria established by international recommendations but depends on management criteria established by local authorities. These vary significantly and are either more or less stringent from one country to another. Dupilumab effectiveness in CRSwNP, whether these criteria are met or not, suggests that a broader CRSwNP population may benefit from dupilumab.

**Key words**: chronic rhinosinusitis, nasal polyps, biologic, indication, dupilumab, real-world evidence

## Introduction

In recent years, the treatment paradigm of chronic rhinosinusitis with nasal polyposis (CRSwNP) has dramatically changed for the subset of patients who have already exhausted traditional therapeutic options, including medical interventions with topical or systemic corticosteroid (SCS) and endoscopic sinus surgery (ESS) [1]. The advent of biologics for type 2 inflammatory disorders offers new approaches for patients with difficult-to-treat disease [2]. Real-world effectiveness of type 2 targeting biologics became apparent because of several studies in the past years [3–10].

In 2019, criteria were developed to identify indication for biologics in CRSwNP patients. A history of prior sinus surgery and three out of five of the following criteria were proposed: evidence of type 2 inflammation, need for SCS, significantly impaired quality of life, significant loss of smell and the presence of comorbid asthma [11].

In 2020, the EPOS steering group made some modifications to these criteria and specified cut-off values for the outcome measures. They concluded that biologics are indicated in patients with bilateral polyps, who underwent previous sinus surgery or who are not fit for surgery and who meet three of the following criteria: evidence of Type 2 inflammation (tissue eosinophils ≥10/high power field and/or blood eosinophils ≥250 cells/µl and/or total IgE ≥100 IU/ml), need for ≥2 courses of SCS per year or long-term (>3 months) low dose corticosteroids, Sino-Nasal Outcome Test-22 (SNOT-22) score ≥40, anosmia confirmed by a smell test and asthma requiring regular inhaled corticosteroids (ICS) [1].

In 2021, EUFOREA introduced the concept of uncontrolled severe CRSwNP to select patients for biologics [2]. Uncontrolled disease was defined as persistent or recurring CRSwNP despite long-term intranasal corticosteroids (INCS), and having received ≥1 course of SCS (minimum of 5 days of SCS at a dose of 0.5-1 mg/kg/day) in the preceding 2 years and/or previous sinonasal surgery (i.e., resection of polyps or conventional ESS); severe disease was defined as bilateral CRSwNP with a bilateral nasal polyp score (NPS) of ≥4 of 8 points and persistent symptoms despite long-term INCS with the need for add-on treatment. Specific cut-off values were proposed for the presence of persistent symptoms: loss of smell (LoS) score (0-3) ≥2, nasal congestion score (0-3) ≥2, SNOT-22 score ≥35, total symptom visual analogue scale (VAS) ≥5mm out of 10. In the subsequent EPOS/EUFOREA 2023 update, EPOS 2020 criteria for biologics were maintained with only one adjustment. The cut-off for blood eosinophil counts was lowered from 250 to 150 cells/µl) to align with asthma literature whereas other cut-off points remained unaltered [12].

Indication criteria proposed by key opinion leaders provide guidance for physicians considering the initiation of biologics in patients with severe and uncontrolled CRSwNP. However, prescribers must prioritize the clinical and/or biological criteria established by the health authorities of each country to obtain reimbursement for biologics. Those criteria for national reimbursement of biologics for CRSwNP vary significantly due to, among others, economic constraints related to healthcare system funding. For instance, specific criteria for assessing disease severity or control levels are not uniformly defined across different countries, cut-off values sometimes differ from international recommendations, or the lack of established cut-off values allows the treating physician to interpret the criteria subjectively. In some countries the governing bodies have pointed to the phase III clinical trials and adopted the inclusion criteria of those (partly or in full). Consequently, the impact of different definitions and regulations on biologic prescriptions in real-world settings, as well as their effect on clinical outcomes and patients' response to biologics, remains unclear.

In the current study, we compared clinical and biological characteristics of patients who were treated with dupilumab for severe uncontrolled CRSwNP in real-world settings with respect to the indication criteria as defined by EUFOREA 2021 and EUFOREA/EPOS 2023 international recommendations. In addition, we also aimed to determine whether the therapeutic response to biologics is dependent on adherence to the selection criteria proposed by these recommendations. Finally, we compared the reimbursement criteria for initiating biologic treatments across the countries included in this real-world cohort study.

## Materials and methods

### Study design and population

This was an observational, retrospective, multicentre study conducted in 6 tertiary ENT centres from 5 European countries: Austria (2 centres), Germany, Italy, France, and The Netherlands. Data of CRSwNP patients treated with dupilumab was retrieved from local (electronic) health records. This retrospective cohort has previously been described by Seys et al. [4]. The study was approved by the local institutional review boards, except for The Netherlands for which it was not required according to the Dutch Medical Research Involving Human Subject Act. The study was registered at clinicaltrials.gov (NCT04670172).

### Inclusion criteria

Patients who received dupilumab treatment for the primary indication of CRSwNP enrolled in CHRINOSOR and previously reported by Seys et al. [4] were analysed. The clinical and/or paraclinical criteria for initiating dupilumab were determined at the discretion of the treating physicians in line with national reimbursement criteria (Table S1).

### Data collection and outcome measures

Per included patient a health profile of demographic characteristics (age, gender, body mass index (BMI), smoking history), disease history (number of courses of systemic corticosteroids

Table 1. Criteria for biologic indication in CRSwNP patients based on international recommendations.

| EUFOREA 2021 | Real-world measured |
|---|---|
| Chronic rhinosinusitis | Physician-diagnosed |
| Bilateral nasal polyps | Physician-diagnosed |
| At least 1 course of SCS in the past 2 years | Number of SCS courses in the past year |
| Previous sinonasal surgery | History of endoscopic sinus surgery |
| Nasal polyp score ≥4 | Nasal polyp score ≥4 |
| Loss of smell score ≥2 | VAS LoS ≥52 mm |
| Nasal congestion score ≥2 | VAS NB ≥50 mm |
| Total symptom VAS ≥50 mm | VAS total sinus symptoms ≥50 mm |
| SNOT-22 score ≥35 | SNOT-22 score ≥35 |
| **EPOS/EUFOREA 2023** | **Real-world measured** |
| Chronic rhinosinusitis | Physician-diagnosed |
| Bilateral nasal polyps | Physician-diagnosed |
| Previous sinonasal surgery | History of endoscopic sinus surgery |
| Evidence of Type 2 inflammation (BEC ≥150 cells/uL and/or serum total IgE ≥100 IU/mL) | BEC ≥150 cells/uL and/or serum total IgE ≥100 IU/mL |
| At least 2 courses of SCS in the past year | Number of SCS courses in the past year |
| SNOT-22 score ≥40 | SNOT-22 score ≥40 |
| Anosmic on a smell test | VAS LoS ≥52 mm |
| Asthma requiring ICS | Physician-diagnosed |

EUFOREA 2021 criteria from Bachert et al. [2] and EPOS/EUFOREA 2023 criteria from Fokkens et al. [12]. Since not all of the criteria were measured in the real-world setting, surrogate measurements have been proposed. *: Adapted cutoff value in line with Alobid et al. and Otten et al. [35,36]. SCS: systemic corticosteroids, SNOT-22: sinonasal outcome test-22, ICS: inhaled corticosteroids. SCS: systemic corticosteroids, VAS: visual analogue scale; LoS: loss of smell; NB: nasal blockage; SNOT-22: sinonasal outcome test-22; BEC: blood eosinophil count; ICS: inhaled corticosteroid.

(SCS) in the past year, number of ESS in the past year), presence of comorbidities (NSAID-exacerbated respiratory disease (N-ERD), asthma, allergy) was established. Specific CRS-related symptoms were collected by visual analogue scale (VAS) (from 0 "no burdensome symptoms" to 100 "extremely burdensome symptoms"): total sinus symptoms (TSS), loss of smell (LoS), nasal blockage (NB). Disease-specific health-related questionnaires (SNOT-22) (on a total score of 110), NPS: 0-4 on every side, total score 0-8), blood eosinophil counts (BEC), and serum total IgE levels were also collected. VAS scores, SNOT-22 and NPS were measured at three time points to assess dupilumab effective-

Table 2. Biologic indication according to EUFOREA 2021 criteria.

| EUFOREA 2021 CRITERIA | | | |
|---|---|---|---|
| History | History of ESS | **92.6%** | (626/676) |
| | At least 1 SCS course last year | **58.2%** | (435/748) |
| | History of ESS and/or at least 1 SCS course last year | **91.0%** | (684/752) |
| Severe | NPS ≥4 | **71.4%** | (510/714) |
| Uncontrolled | SNOT-22 ≥35 | **76.8%** | (525/684) |
| | VAS TSS ≥so | **57.7%** | (329/570) |
| | VAS NB ≥so | **68.1%** | (401/589) |
| | VAS Los ≥52 | **76.5%** | (450/588) |
| | Meets the SNOT-22 criteria and/or any of the 3 VAS criteria | **90.0%** | (668/742) |
| Severe Uncontrolled | NPS ≥4 and meets at least one Uncontrolled criteria | **66.5%** | (475/714) |
| **Criteria met** | **CRSwNP plus History plus Severe Uncontrolled** | **61.8%** | **(452/731)** |

CRSwNP: chronic rhinosinusitis with nasal polyps; ESS: endoscopic sinus surgery; SCS: systemic corticosteroids, NPS: nasal polyp score; VAS: visual analogue scale; TSS: total sinus symptoms; LoS: loss of smell; NB: nasal blockage; SNOT-22: sinonasal outcome test-22.

Table 3. Biologic indication according to EPOS/EUFOREA 2023 criteria.

| EPOS/EUFOREA2023 CRITERIA | | | |
|---|---|---|---|
| History | History of surgery | **92.6%** | (626/676) |
| Blood values | BEC >150 | **89.8%** | (544/606) |
| | Serum total IgE >100 | **53.5%** | (329/615) |
| | Type-2 (BEC >150 cells/ul and/or serum total IgE >100 IU/ml) | **92.5%** | (604/653) |
| | At least 2 SCS courses last year | **29.6%** | (204/690) |
| | Impaired QoI measured by SNOT-22 score >40 | **70.5%** | (482/684) |
| | Impaired Smell measured by VAS Los >52 | **76.5%** | (450/588) |
| | Asthma (self-reported) | **69.7%** | (507/727) |
| Meets at least 3 out of the following 5: Type-2 and/or >2 SCS courses and/or impaired QoI and/or impaired smell and/or asthma | | **88.0%** | (505/574) |
| **Criteria met** | **CRSwNP and prior surgery and meets 3 out of 5 severe uncontrolled criteria** | **79.8%** | (453/568) |

CRSwNP: chronic rhinosinusitis with nasal polyps; ESS: endoscopic sinus surgery; SCS: systemic corticosteroids, NPS: nasal polyp score; VAS: visual analogue scale; TSS: total sinus symptoms; LoS: loss of smell; NB: nasal blockage; SNOT-22: sinonasal outcome test-22.

| Cohort | Indication status | History of ESS | At least 1 SCS course last year | History of ESS and/or at least 1 SCS course last year | NPS ≥4 | SNOT-22 ≥35 | VAS TSS ≥50 | VAS NB ≥50 | VAS LoS ≥50 | Meets the SNOT-22 criteria and/or any of the 3 VAS criteria | NPS ≥4 and meets at least one Uncontrolled criteria | CRSwNP plus History plus Severe Uncontrolled |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Selected criteria met** | Indicated | 419 | 295 | 452 | 452 | 377 | 238 | 278 | 290 | 452 | 452 | 452 |
| | Not indicated | 189 | 131 | 211 | 56 | 134 | 86 | 115 | 150 | 197 | 23 | |
| **Selected criteria not met** | Indicated | 20 | 155 | | | 54 | 104 | 72 | 62 | | | |
| | Not indicated | 28 | 146 | 68 | 204 | 102 | 131 | 111 | 73 | 74 | 234 | 279 |

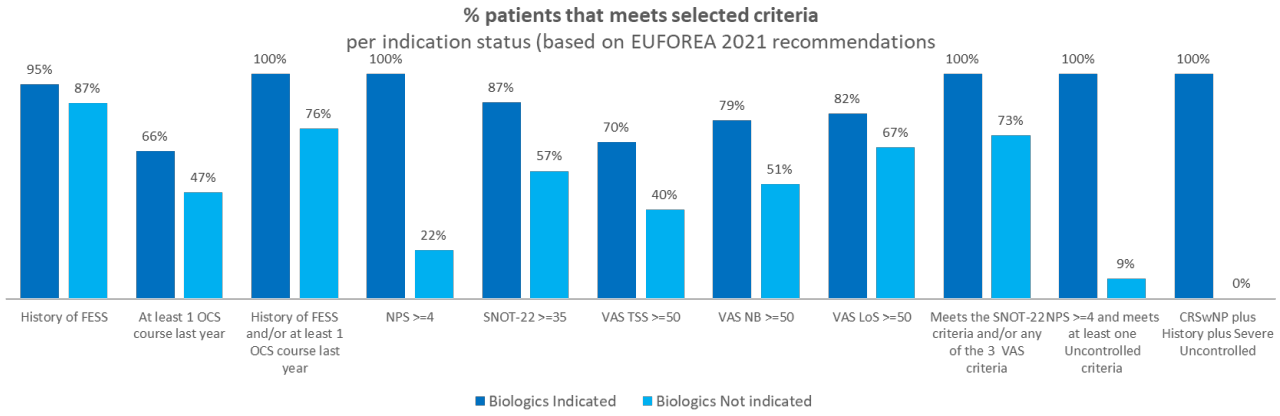


Figure 1. Biologic indication according to EUFOREA 2021 criteria per individual criterium. CRSwNP: chronic rhinosinusitis with nasal polyps; ESS: endoscopic sinus surgery; SCS: systemic corticosteroids, NPS: nasal polyp score; VAS: visual analogue scale; TSS: total sinus symptoms; LoS: loss of smell; NB: nasal blockage; SNOT-22: sinonasal outcome test-22.

ness: at the start of dupilumab (up to one month preceding biologic initiation for both clinical and biological criteria), after 24 and 52 weeks of treatment.

### Evaluation of indication for biologic therapy

Both the EUFOREA 2021 criteria [2] and the EPOS/EUFOREA 2023 criteria [12] were applied to assess whether included patients were indicated for treatment with biologics. For some parameters, criteria as defined in the recommendations were not measured in the real-world setting. For this reason, available surrogate real-world variables were proposed and assessed (Table 1).

### Statistics

Data are presented as Tukey box-whisker plots. Between-group comparison of the outcome parameters in the stratified subgroups was performed by mixed-effects model and Dunnett's multiple comparisons test. The number of patients with available data was reported for each measured outcome in the text and/or figure legends. Statistical analysis was performed using Graphpad Prism 9 software (Boston, MA, USA). A p-value of less than 0.05, two-sided, was considered statistically significant.

## Results

### Patient characteristics

*a) applying the EUFOREA 2021 criteria*

752 CRSwNP patients who received dupilumab treatment were analysed (Figure 1, Table 2). Of these patients, 90.0% (684/752 received ≥1 course of SCS during the year prior to the initiation of dupilumab (58.2%, 434/748) and/or previous ESS (92.6%, 626/676). 66.5% (475/714) of CRSwNP patients have severe disease based on have a NPS ≥4 (71.4%, 510/714, 71.4%) and persistent symptoms based on VAS LoS ≥52mm 76.5%, (450/588), VAS NB ≥50mm (68.1%, 401/589), VAS total sinus symptoms ≥50mm (57,7%, 329/570) or SNOT-22 ≥35 (76.8%, 525/684). For 21 patients, not all data were available to define the disease status (731 out of 752 with required data). Therefore, 61.8% (452/731) of CRSwNP patients met EUFOREA 2021 criteria for uncontrolled, severe disease.

Applying EUFOREA 2021 criteria to the individual site level can be found in Table S2.

*b) applying the EPOS/EUFOREA 2023 criteria*

Of 752 CRSwNP patients treated with dupilumab (Figure 2, Table 3), 92.6% (626/676) had a history of ESS (which is a criterion in both recommendations). Five other criteria determine whether a patient may be indicated for a biologic treatment: 1. presence of Type 2 inflammation (92.5%, 604/653), 2. at least 2 courses of SCS in the past year (29.6%, 204/690), 3. SNOT-22 ≥40 (70.5%, 482/684), 4. VAS LoS ≥52mm (76.5%, 450/588), and 5. presence

| Cohort | Indication status | History of surgery | BEC ≥150 | Total IgE ≥100 | Type-2 (BEC ≥150 and/or Total IgE ≥ 100) | At least 2 SCS courses last year | Impaired QoL mesaured by SNOT-22 ≥40 | Impaired Smell measured by VAS LoS ≥52 | Asthma (self-reported) | 3 out of the following 5: Type-2 and/or ≥2 SCS courses and/or impaired QoL and/or impaired smell and/or Asthma | CRSwNP and prior surgery and meets 3 out of 5 severe uncontrolled criteria |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Selected criteria met** | Indicated | 419 | 397 | 234 | 432 | 177 | 377 | 321 | 367 | 453 | 453 |
| | Not indicated | 189 | 71 | 47 | 84 | 18 | 52 | 56 | 56 | 37 | |
| **Selected criteria not met** | Indicated | 20 | 25 | 187 | 12 | 227 | 64 | 42 | 84 | | |
| | Not indicated | 28 | 19 | 49 | 23 | 93 | 59 | 52 | 57 | 69 | 115 |

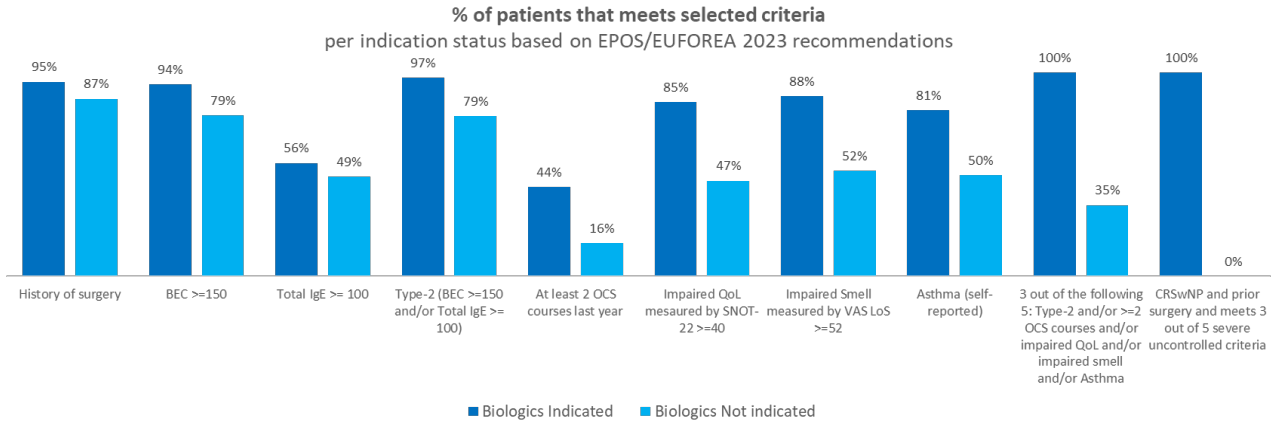


Figure 2. Biologic indication according to EPOS/EUFOREA 2023 criteria per individual criterium. CRSwNP: chronic rhinosinusitis with nasal polyps; ESS: endoscopic sinus surgery; SCS: systemic corticosteroids, NPS: nasal polyp score; VAS: visual analogue scale; TSS: total sinus symptoms; LoS: loss of smell; NB: nasal blockage; SNOT-22: sinonasal outcome test-22.

of comorbid asthma (69.7%, 507/727). 88.0% (505/574) patients had a history of ESS and reached 3 out of 5 of the above criteria. For 184 patients, not all required data were available to determine the disease status (overall, 568 patients with required data). Therefore, 79.8% (453/568) of patients met EPOS/EUFOREA 2023 criteria for indication for biologic treatment.
Applying EUFOREA 2021 criteria to the individual site level can be found in Table S3.

*c) applying both EUFOREA 2021 and EPOS/EUFOREA 2023 criteria*
Among the 557 patients with available data to assess both criteria, 60.0% met criteria of both recommendations whereas 10.6% did not meet them. Discordance was observed in 29.4% of patients.

### Dupilumab effectiveness stratified according to indication status

Significant decreases were observed for SNOT-22 score and NPS at 24 and 52 weeks compared to baseline in patients independent of meeting as well as not meeting EUFOREA 2021 or EPOS/EUFOREA 2023 criteria (p<0.0001; Figure 3). Also, significant effectiveness of dupilumab was observed at both time points in terms of improved VAS LoS VAS NB for patients regardless of whether or not meeting the EUFOREA 2021 or EPOS/EUFOREA 2023 criteria (p<0.0001; Figure 4), except for the ACT score where patients not meeting the criteria did not show a significant improvement at 24 weeks (p=0.21 and p=0.41; Figure 4). The change in SNOT-22 score at 24 and 52 weeks compared to the baseline value was more pronounced in patients meeting the indication criteria of EUFOREA 2021 compared to those not meeting these criteria (p<0.0001; Figure S1), however for EPOS/EUFOREA 2023 this only reached significance at 52 weeks. The change to baseline for NPS was more pronounced for patients meeting EUFOREA 2021 compared to patients not meeting the criteria at both time points (p<0.0001; Figure S1), whereas there were no differences between patients meeting or not meeting EPOS/EUFOREA 2023 (p=0.82 and p=0.81; Figure S1). For the VAS for LoS, the VAS for nasal blockage and the ACT score, patients meeting EUFOREA 2021 or EPOS/EUFOREA 2023 showed again more pronounced effects compared to patients not meeting the criteria, except for ACT score at 24 weeks (EUFOREA 2021 and EPOS/EUFOREA 2023) and VAS for LoS and VAS for NB at 52 weeks (EPOS/EUFOREA 2023) (Figures S2-3).

### National reimbursement criteria per market

Type 2 directed biologics are available in each of the studied countries for adults with CRSwNP (Table S1). Severity status was based on objective criteria only for The Netherlands and Italy (SNOT-22 and/or NPS). Failure of medical treatment with at least two courses of SCS over the last year is a criterion in The

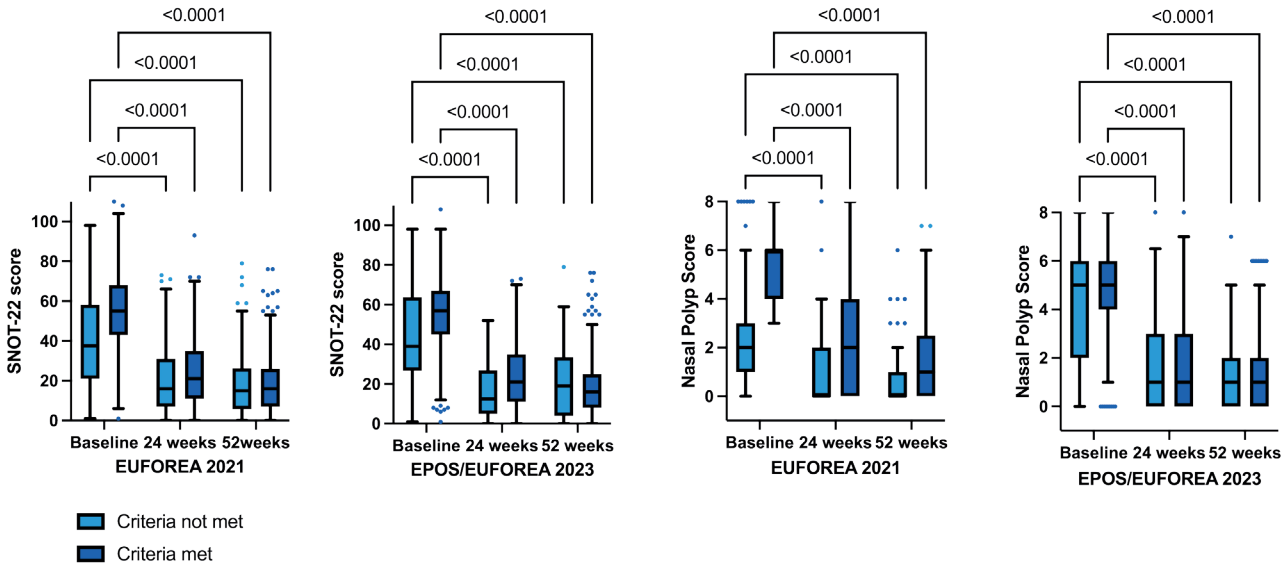


Figure 3. Dupilumab effectiveness for SNOT-22 and NPS stratified by biologic indication status. Data are presented as Tukey box-whisker plots. Between-group comparison of the outcome parameters in the stratified subgroups was performed by two-way ANOVA and Dunnett's multiple comparisons test. SNOT-22: sinonasal outcome test-22; NPS: nasal polyp score. Patients with SNOT-22: EUF2021 criteria met (baseline, 24w, 52w): 359, 303, 233, EUF2021 criteria not met: 162, 139, 98, EPOS/EUF2023 criteria met: 352, 309, 245, EPOS/EUF2023 criteria not met: 82, 58, 45. Patients with NPS: EUF2021 criteria met (baseline, 24w, 52w): 371, 323, 253 EUF2021 criteria not met: 178, 145, 99, EPOS/EUF2023 criteria met: 358, 324, 263, EPOS/EUF2023 criteria not met: 81, 61, 44.

Netherlands, Italy and France. Failure of surgery is only mandatory in France for biologics reimbursement. In Austria, patients with severe, uncontrolled CRSwNP with ongoing INCS treatment and failure of previous sinus surgery as well as failure of medical treatment with SCS or medical contraindication to SCS are indicated for dupilumab treatment Reduction of ≥ 2 points in NPS score within the first 6 month of treatment has to be observed for further reimbursement in Austria (Table S1). The differences observed among the five countries participating in this registry reflect the prescribing criteria imposed by the regulatory authorities responsible for approving reimbursement of biologic therapies. The scientific committees advising these authorities vary in composition across countries and establish clinical and/or biological eligibility criteria based on their interpretation of the literature and the budgetary limitations set by their respective national health insurance systems.

## Discussion

### Summary of results

This real-world study in dupilumab treated patients for the primary indication of CRSwNP, aimed to compare the application of indication criteria for biologics as defined by international recommendations. Clinical and biological data from 5 European countries gathered through the Chronic RhINOSinusitis Outcome Registry (CHRINOSOR) showed a significant disparity in adherence to the criteria for biologics indication. Nevertheless, non-compliance with these criteria did not seem to impact therapeutic effectiveness on clinical quality of life measures (SNOT-22), CRS symptom control including olfaction, or comorbid asthma control.

International recommendations and their use in clinical practice

The recommendations proposed by EPOS and EUFOREA aim at defining the indication for biologics in clinical practice. The results from randomized controlled trials have shown efficacy of biologics targeting the type 2 inflammatory pathway, with rapid improvement in quality of life and symptoms, especially in cases of olfactory impairment that have been difficult to manage, or causing a temporary effect, with medical treatment and/or endoscopic sinus surgery. The economic burden of biologics necessitated defining a prescription framework, given that medical treatment with corticosteroids and/or surgery manages to ensure satisfactory symptom control in more than two third of patients [13,14]. The authors of these recommendations relied on the endpoints used in randomized controlled trials to establish indication criteria (SNOT-22, nasal congestion score, anosmia measurement, nasal polyp score). The thresholds chosen for these various criteria are based on specific cutoff values defined for research purpose and statistically validated stratification of the SNOT-22 score [15]. Therapeutic criteria used to define patients with difficult-to-treat CRSwNP (at least two courses of SCS in the last year) were also included [1]. Finally, in response

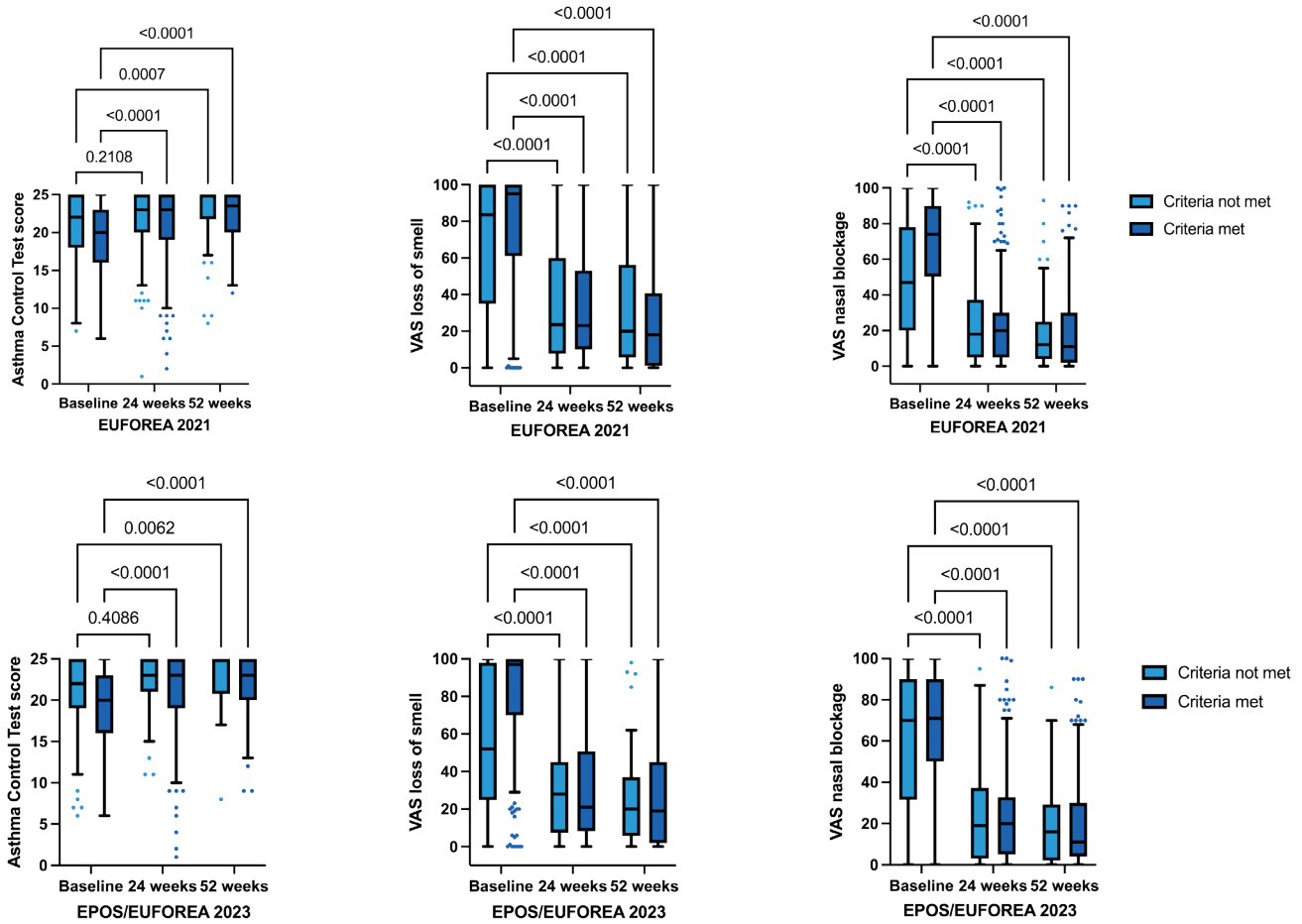


Figure 4. Dupilumab effectiveness for ACT and CRS symptoms stratified by biologic indication status. Data are presented as Tukey box-whisker plots. Between-group comparison of the outcome parameters in the stratified subgroups was performed by two-way ANOVA and Dunnett's multiple comparisons test. VAS: visual analogue scale. Patients with ACT: EUF2021 criteria met (baseline, 24w, 52w): 236, 142, 118 EUF2021 criteria not met: 119, 81, 58, EPOS/EUF2023 criteria met: 247, 158, 135, EPOS/EUF2023 criteria not met: 46, 27, 18. Patients with VAS LoS EUF2021 criteria met (baseline, 24w, 52w): 263, 241, 174, EUF2021 criteria not met: 148, 122, 822, EPOS/EUF2023 criteria met: 278, 248, 179, EPOS/EUF2023 criteria not met: 82, 64, 46. Patients with VAS NB EUF2021 criteria met (baseline, 24w, 52w): 276, 243, 173, EUF2021 criteria not met: 147, 122, 81, EPOS/EUF2023 criteria met: 277, 248, 180, EPOS/EUF2023 criteria not met: 77, 66, 46.

to the pathophysiological characteristics associated with the type 2 inflammatory pattern, biologic criteria based on baseline blood eosinophil counts and serum total IgE levels were introduced in the recommendations. The biomarker thresholds were established in harmony with those used in pulmonology to characterize type 2 eosinophilic asthma, although there are no data supporting cutoffs for serum total IgE [16,17]. In fact, BEC drive the compliance with the type 2 criterion in almost all patients [18]. Since 2019 and the initial recommendations of EPOS, adjustments have been made to arrive at the latest consensus of EPOS/EUFOREA 2023. These latest recommendations are specific regarding the definition of the type 2 inflammatory profile, the minimum threshold for SNOT-22, and the definition of treatment failure under SCS. In contrast to the EUFOREA 2021 criteria, no measurable data were proposed for symptomatic VAS, NPS, or olfactory function loss. The EPOS/EUFOREA 2023 recommendations condition the use of biologics on the failure of endoscopic sinus surgery, whereas this surgical criterion is optional in the EUFOREA 2021 recommendations. By applying EPOS 2020 criteria to initiate biologics in a cohort of 98 patients with uncontrolled CRSwNP, Van der Lans et al. showed a therapeutic effect comparable or slightly better compared to the preceding LIBERTY NP SINUS-24 and -52 [19,20].

In our study, 60.0% of patients treated with dupilumab met both the EUFOREA 2021 and EPOS/EUFOREA 2023 criteria. Variation in adherence to recommendation criteria is also observed in other studies. A recent literature review reported results from 15 real-life studies of dupilumab in CRSwNP. Only one study provided data on nasal congestion, and three reported on VAS for smell loss; baseline blood eosinophil count was not avai-

lable in seven studies, and baseline IgE in ten studies [21]. In a retrospective US cohort of 121 patients who were prescribed dupilumab for CRSwNP indication, Schmale et al. reported that 29 % did not meet EPOS 2020 indications for biologic initiation whereas an overall improvement of symptoms was observed [22]. In a multicentric observational cohort study carried out in Sicily in three University Hospitals including 170 patients treated with dupilumab, 17.6% did not receive SCS in the last year and 21.9% did not undergo ESS before biologic initiation [23].

In real-world situations, clinicians may have fewer constraints imposed by regulatory authorities when prescribing treatments, which may explain the lack of compliance with the international recommendations. This also helps to explain the extent of missing data regarding variables considered as prescribing criteria for biologics, particularly considering the 2023 EPOS/EUFOREA recommendations.

Clinicians primarily rely on the failure of medical and/or surgical treatment to define the loss of control of CRSwNP. The need for SCS, as defined in both recommendations (at least 1 or 2 courses of SCS in the last 1 or 2 years), was among the least respected criteria for initiating biologics. The concept of severity remains mostly subjective, based on clinical experience. For many, utilizing patient-reported outcome measures in daily patient management is still not common practice. The impact of NPS on patient management in the real-world practice is also debated. NPS was found to be the most limiting factor in EUFOREA 2021 recommendations. Its clinical applicability is hampered by an inherent measurement error, impact of SCS, problematic scoring after ESS and poor correlation with SNOT-22. The lack of correlation between NPS and patient-reported symptoms has been documented before. In a meta-analysis assessing the correlation between NP grading systems and patient-reported outcome measures from 55 studies, Jeong et al. demonstrated that current NP endoscopic scoring systems were not associated with subjective measures [24]. Hence, NPS and patient-reported scores may provide complementary information about the patient's disease status.

Local guidelines for biologic prescription and reimbursement

Some discrepancies between international recommendations and local guidelines need to be stressed. The initiation criteria for biologics in CRSwNP defined by national scientific societies are mainly designed by expert panels consisting of both university centers and field hospital centers. Their responses often reflect their clinical practice habits.

The reimbursement criteria proposed by health organizations are constrained by medical-economic imperatives. They are mainly guided by the marketing authorization wording for biologics in in each country. The European Medicines Agency indication states that dupilumab is indicated "as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery does not provide adequate disease control" [25]. As stated in the Summary of Products Characteristics, the definition of 'adequate disease control' remains very vague and does not provide a framework to specify the therapeutic burden, medical or surgical, resulting in treatment failure, nor the timeframe from which biologic therapy should be discussed. The loss of therapeutic control is the primary criterion upheld by most countries. The failure of surgery is even mandated by some reimbursement bodies [26]. The definition of severity is, however, more arbitrary. Some countries impose strict, measurable criteria, like in Netherlands and Italy [3,19]. Others allow practitioners more interpretative freedom [27]. This heterogeneity can be attributed to different governance structures, more or less restrictive reimbursement authorization procedures, and varying policies guiding the best allocation of limited healthcare resources.

**Perspectives of future recommendations for biologics in CRSwNP**

We observed in our study that non-compliance with recommendations regarding disease severity for initiating a biologic in CRSwNP did not impact the therapeutic effectiveness of dupilumab. This result may suggest a broader use of biologics in the management of CRSwNP. However, the medico-economic impact of these treatments must be considered when making therapeutic decisions. Appropriately used topical and systemic corticosteroids, along with tailored surgical interventions, allow disease control in a large proportion of patients, with relatively low costs and manageable morbidity [28,29]. Therefore, the positioning of biologics into treatment algorithms should be guided by a comprehensive assessment of individual patient needs, disease severity, and the broader medico-economic implications [11]. It is the responsibility of each practitioner to consider the cost of biologics when comparing with surgical management [30] and to avoid burdening the healthcare system with broad and uncontrolled prescribing [31].

Although variable and adaptable, the current recommendations facilitate transdisciplinary discussions with colleagues in allergy/immunology, dermatology, and pulmonology, as well as regulators, to ensure that all appropriate treatment options for CRSwNP are discussed before opening the gate to a potentially excessive use of biologics. Multidisciplinary consultations are also essential for the appropriate use of biologics, especially in cases of severe asthma or atopic dermatitis. Finally, the recommendations define measurable therapeutic effectiveness criteria primarily to be assessed at 6 months of treatment, or at the latest by 12 months if a more gradual improvement in symptoms is observed [2,12]. These algorithms assist the practitioner in their management strategy, particularly when a switch of biologic or a tapering of treatment currently off-label needs to be discussed [32,33].

**Limitations of our study**

Our study has certain limitations. Although it uses clinical data from 5 European countries, our cohort does not fully reflect the prescribing practices proposed in CRSwNP. Some other European countries are constrained by strict prescription criteria (Finland, Switzerland), closely aligning with the EUFOREA 2021 recommendations or there is no reimbursement at all like in United Kingdom. The size of the patient populations managed, along with the specifics of care pathways, including some organizations having prescriptions limited to tertiary centers, can also influence the quality of the data collected. In a global perspective, the mode of health system financing also plays a significant role in the ability to use biologics. For instance, in the United States, funded insurance such as Medicaid, Medicare, and Veterans Affairs, along with numerous private insurances, are involved. Here, the social coverage system determines therapeutic choices more than the severity and control characteristics of CRSwNP. According to the Swiss Federal Office of Health, reimbursement for dupilumab is conditional on a SNOT-22 score ≥50, with a nasal congestion score of at least 2/3, alongside confirmed olfactory impairment with an UPSIT score ≤25 or an STT with at least 16 items ≤ 10 points [34]. Continued reimbursement is assured only if the therapeutic effectiveness of dupilumab is observed at 16 weeks of treatment according to threshold values for SNOT-22 and NPS, with a cumulative annual dose of SCS not exceeding 250 mg/year.

Our real-world cohort also relies on clinical data reported by the patient or medical doctors. Not all information was available to the investigators at the time of data collection. Thus, we did not have all the data required to determine whether the EUFOREA 2021 and EPOS/EUFOREA 2023 criteria were met for 21 patients and 184 patients, respectively. As mentioned before, for some variables, surrogate outcome measures that are routinely measured in the real-world setting were applied. Validated psychophysical olfactory tests are not systematically used in routine clinical practice across all centers to assess smell loss. Furthermore, the diagnostic thresholds for anosmia vary depending on the test utilized, leading to potential inconsistencies in patient evaluation. In this context, the use of a VAS, applying the threshold (≥52mm) recently validated in 2 independent studies [35,36], appeared necessary to harmonize the assessment of olfactory loss across participating centers. Also, we cannot rule out that the presence of type 2 inflammation may have been missed because of the lack of information on tissue eosinophils or in patients who recently took systemic corticosteroids.

This registry includes only patients treated with dupilumab, as it was the first biologic approved and widely accessible for prescription across the five participating countries. Given their academic roles in teaching and clinical research, prescribing physicians inevitably had interactions with the pharmaceutical company manufacturing dupilumab. However, as the study focuses on a single biologic in patients eligible according to national reimbursement criteria, potential conflicts of interest are unlikely to have influenced the quality of the data collected.

## Conclusions

Our results confirm the significant effectiveness of dupilumab in CRSwNP in a real-world setting regardless of whether patients met or did not meet international biologic indication criteria. By defining criteria for biologic initiation in uncontrolled severe CRSwNP, the currently proposed recommendations help to prevent a harmful prescription drift that is scientifically unfounded and irresponsible for the sustainability of healthcare systems. The growing experience provided by real-world data collected through clinical follow-up registries will refine these recommendations. The arrival of new biologics targeting other type 1 and type 3 inflammatory patterns, the variety of responder profiles, and therapeutic strategies combining endoscopic sinus surgery and biologics present future challenges to expert committees responsible for these recommendations.

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## Authorship contribution

SFS, GMa, CB designed the study. GMo, CC, SR, SS, PVT, MW, AC, WJF, MdV, CH and SM recruited patients for the study. GMo, SFS, JdK and GB contributed to data analysis. GMo, SFS and JdK prepared the first draft of the manuscript. All authors critically revised the manuscript.

## Conflict of interest

CB: reports grants or contracts from GSK, Sanofi, Novartis, Galenus Health. GB: an employee of Galenus Health. CC: reports consulting fees from GSK, Sanofi, Novartis, Astra Zeneca, participation on advisory board from GSK, Sanofi, Novartis. ZD: reports consulting fees and/or payment for lectures from Antabio, Arcede, Biosion, EUFOREA, Foresee Pharmaceuticals, Galenus Health, GSK, Hippo-Dx, Pleuran, QPS-NL, Sanofi-Genzyme; leadership role in EUFOREA (asthma expert panel chair 2020-2024) and associate editorships at Allergy (2019-2023), Springer (MedNet) and Respiratory Medicine. JED: reports grants (institution) from Astra Zeneca, Novartis, payment for lectures from Allergopharma, participation on advisory board from GSK, Astra Zeneca, Bencard.

WF: reports grants (institution: AMC) from GSK, Novartis, Sanofi, consulting fees from Dianosic, Sanofi, GSK, Novartis, payment for lectures from Sanofi, GSK, Novartis, participation on advisory board from Lyra and Leadership roles in ERS (Secretary General), Rhinology (Editor in chief), Allergy (Associate Editor).

MdV: No relevant conflict of interest to disclose. CH: Clemens

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KS: No relevant conflict of interest to disclose. SFS: is an employee of Galenus Health, reports payment for lectures from Teva Pharmaceutical. SS: Sven Schneider reports grants, payment for lectures and participation on advisory board from Sanofi, Novartis. PVT: No relevant conflict of interest to disclose. MW: reports grants from ALK-Abello, GSK, Regeneron, Astra Zeneca, Novartis, Sanofi, Takeda, consulting fees from ALK, Genzyme, Novartis, Stallergenes, Astra Zeneca, GSK, Sanofi, payment for lectures from ALK-Abello, Astra Zeneca, GSK, Leti Pharma, Sanofi, Allergopharma, Bencard Allergie, Infectopharm, Novartis, Stallergenes, Leadership role in DGAKI (executive committee).

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**This manuscript contains online supplementary material**

## SUPPLEMENTARY MATERIAL

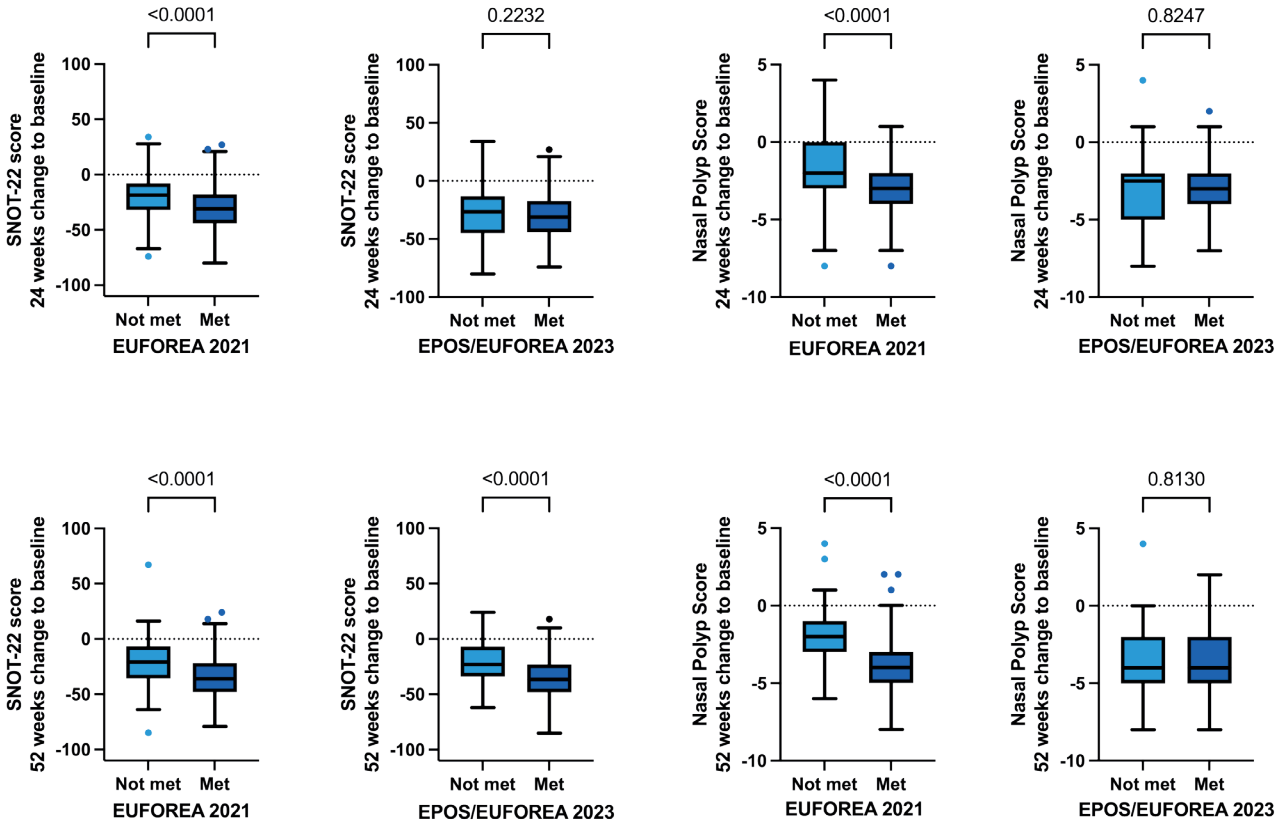


Figure S1. Change to baseline in SNOT-22 and NPS at 24 and 52 weeks of dupilumab stratified by biologic indication status.

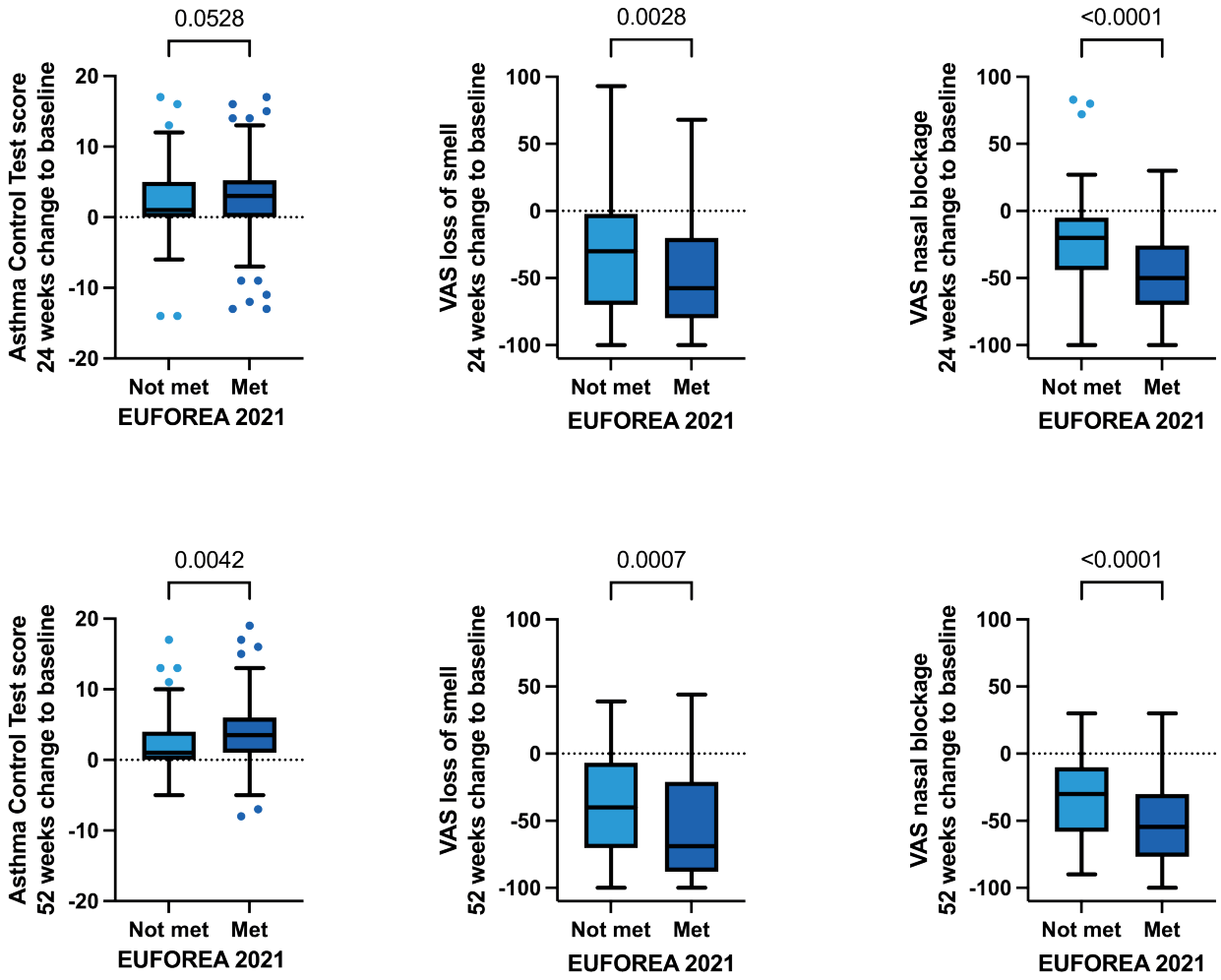


Figure S2. Change to baseline in ACT, VAS LoS and NB at 24 and 52 weeks of dupilumab stratified by biologic indication status.

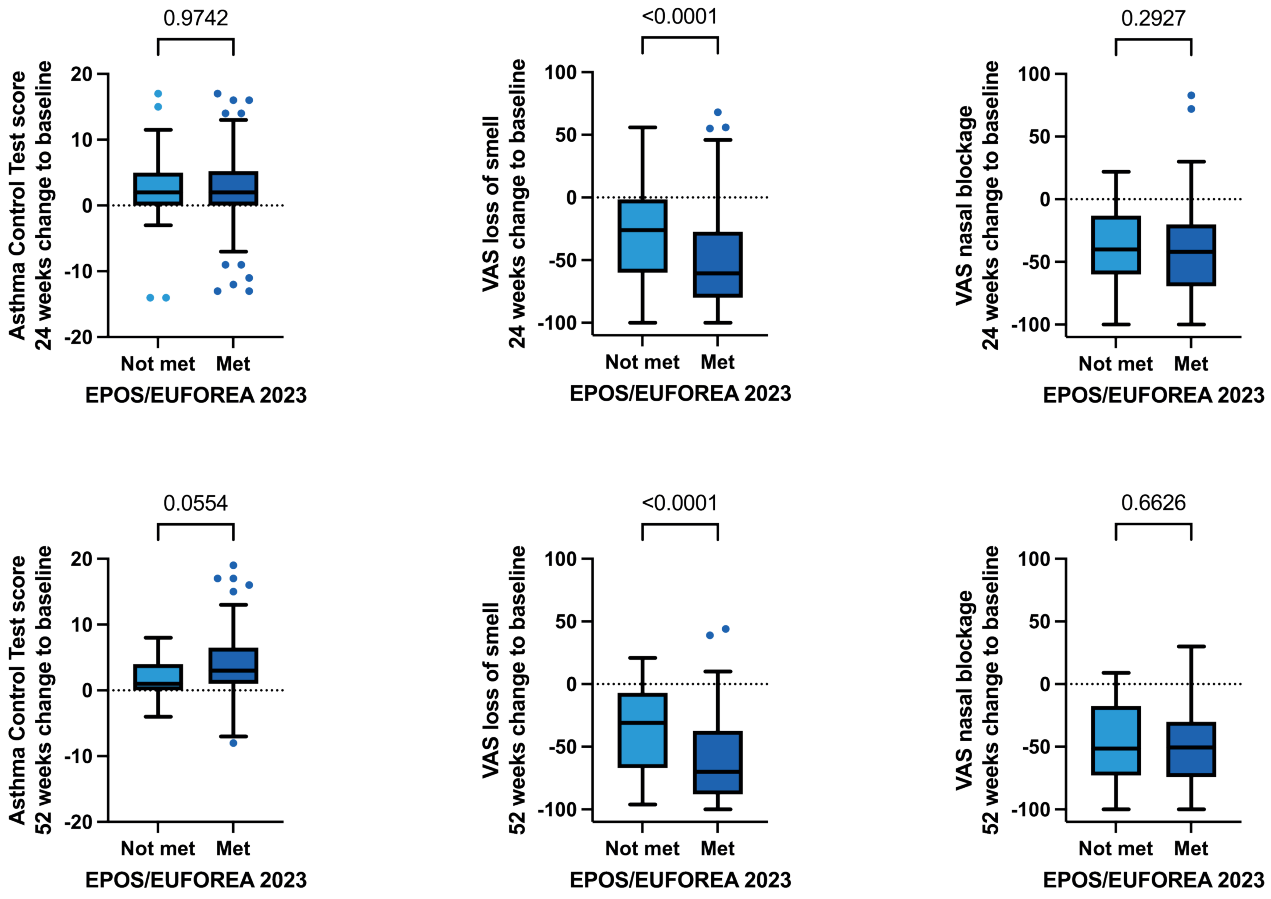


Figure S3. Change to baseline in ACT, VAS LoS and NB at 24 and 52 weeks of dupilumab stratified by biologic indication status.

| Country | Germany | The Netherlands | Austria | Italy | France |
|---|---|---|---|---|---|
| Centres (cities) | Düsseldorf | Amsterdam | Graz, Vienna | Rome | Lille |
| Mandatory criteria (all need to be met) | • ≥18years<br>• CRSwNP (confirmation by objective methods)<br>• Severe<br>• Inadequate control with continuous INCS<br>• Systemic corticosteroids, and/or previous ESS | • ≥18years<br>• Diffuse CRSwNP confirmed by endoscopy and CT | • ≥18years<br>• CRSwNP<br>• Severe<br>• Inadequate symptom control with INCS | • ≥18years<br>• Diffuse CRSwNP confirmed by endoscopy and CT<br>• Inadequate symptom control with INCS<br>• At least two cycles of systemic corticosteroid over the last year and/or<br>• previous ESS | • ≥18years<br>• CRSwNP confirmed by endoscopy and CT<br>• Impaired quality of life<br>• Inadequate symptom control with INCS<br>• At least two to three courses of systemic corticosteroid (7 to 10 days, 1mg/kg/day) over the last year<br>• Adequate previous ESS |
| Optional criteria (some need to be met) | | Needs to meet at least 3 out of 5 numbered criteria:<br>1.SNOT-22 ≥ 40 and/or<br>2.At least two cycles of systemic corticosteroids over the last year<br>3.Anosmia measured with a validated smell test with accompanying cut-off (via sniffin' sticks)<br>4.Presence, defined by BEC ≥150 cells/ul, and/or Total IgE ≥100 IU/ml<br>5.Maintenance CS | Needs to meet at least 1 out of 2 numbered criteria:<br>1.Systemic corticosteroids<br>2.previous ESS | Needs to meet at least 1 out of 2 numbered criteria:<br>1.NPS ≥ 5<br>2.SNOT-22 ≥ 50 | |
| Additional criteria applied locally | | • At least full ethmoidectomy<br>• No current smoker | | | |

**Table S1. National reimbursement criteria biologics for CRSwNP patients.**

- Hard criteria (method, metric, and cut-off value / dose / frequency value defined)
- Semi-hard criteria (method and metric, but no cut-off value / dose / frequency defined)
- Semi-soft criteria (optional method and metric, but no cut-off value / dose / frequency defined)
- Soft criteria (no method, metric, or cut-off value / dose / frequency defined)

| | | Vienna | Amsterdam | Graz | Rome | Lille | Düsseldorf | Total |
|---|---|---|---|---|---|---|---|---|
| History | History of FESS | 85,1% (183/215) | 99,3% (135/136) | 96,8% (61/63) | 88,4% (61/69) | 100,0% (56/56) | 94,9% (130/137) | 92,6% (626/676) |
| | At least 1 SCS course last year | 46,9% (136/290) | 58,2% (78/134) | 63,5% (40/63) | 100,0% (68/68) | 92,9% (52/56) | 44,5% (61/137) | 58,2% (435/748) |
| | History of FESS and/or at least 1 SCS course last year | 77,9% (226/290) | 99,3% (136/137) | 100,0% (63/63) | 100,0% (69/69) | 100,0% (56/56) | 97,8% (134/137) | 91,0% (684/752) |
| Severe | NPS >=4 | 59,5% (157/264) | 83,0% (112/135) | 93,1% (54/58) | 87,0% (60/69) | 57,1% (32/56) | 72,0% (95/132) | 71,4% (510/714) |
| Uncontrolled | SNOT-22 >=35 | 61,0% (136/223) | 80,1% (109/136) | 79,4% (50/63) | 87,0% (60/69) | 94,6% (53/56) | 85,4% (117/137) | 76,8% (525/684) |
| | VAS TSS >=50 | 29,5% (75/254) | 75,7% (53/70) | N/A | 97,1% (67/69) | 89,3% (50/56) | 69,4% (84/121) | 57,7% (329/570) |
| | VAS NB >=50 | 59,0% (157/266) | 62,3% (48/77) | N/A | 89,9% (62/69) | 82,1% (46/56) | 72,7% (88/121) | 68,1% (401/589) |
| | VAS LoS >=52 | 74,2% (198/267) | 60,5% (46/76) | N/A | 85,5% (59/69) | 85,7% (48/56) | 82,5% (99/120) | 76,5% (450/588) |
| | Meets the SNOT-22 criteria and/or any of the 3 VAS criteria | 86,1% (241/280) | 92,7% (127/137) | 79,4% (50/63) | 100,0% (69/69) | 98,2% (55/56) | 92,0% (126/137) | 90,0% (668/742) |
| Uncontrolled Severe | NPS >=4 and meets at least one Uncontrolled criteria | 54,4% (143/263) | 79,3% (107/135) | 72,9% (43/59) | 87,0% (60/69) | 57,1% (32/56) | 68,2% (90/132) | 66,5% (475/714) |
| **Criteria met** | **CRSwNP plus History plus Uncontrolled Severe** | 43,2% (121/280) | 79,3% (107/135) | 72,9% (43/59) | 87,0% (60/69) | 57,1% (32/56) | 67,4% (89/132) | 61,8% (452/731) |

**Table S2. Biologic indication per site according to EUFOREA 2021 criteria.**
N/A: not assessed.

| EPOS/EUFOREA 2023 CRITERIA | | Vienna | Amsterdam | Graz | Rome | Lille | Düsseldorf | Total |
|---|---|---|---|---|---|---|---|---|
| History | History of ESS | 85,1% (183/215) | 99,3% (135/136) | 96,8% (61/63) | 88,4% (61/69) | 100,0% (56/56) | 94,9% (130/137) | 92,6% (626/676) |
| Blood values | BEC >=150 | 83,3% (130/156) | 93,7% (118/126) | 96,8% (61/63) | 95,7% (66/69) | 92,9% (52/56) | 86,0% (117/136) | 89,8% (544/606) |
| | Total IgE >= 100 | 52,1% (101/194) | 54,7% (70/128) | 58,7% (37/63) | 54,7% (35/64) | 53,6% (30/56) | 50,9% (56/110) | 53,5% (329/615) |
| Must meet 3 out of 5 criteria for Uncontrolled Severe | Type-2 (BEC >=150 and/or Total IgE >= 100) | 87,0% (174/200) | 97,7% (126/129) | 98,4% (62/63) | 95,7% (66/69) | 96,4% (54/56) | 89,7% (122/136) | 92,5% (604/653) |
| | At least 2 SCS courses last year | N/A | 44,5% (61/137) | 36,5% (23/63) | 100,0% (68/68) | 92,9% (52/56) | N/A | 29,6% (204/690) |
| | Impaired QoL mesaured by SNOT-22 >=40 | 54,7% (122/223) | 75,7% (103/136) | 76,2% (48/63) | 75,4% (52/69) | 91,1% (51/56) | 77,4% (106/137) | 70,5% (482/684) |
| | Impaired Smell measured by VAS LoS >=52 | 74,2% (198/267) | 60,5% (46/76) | N/A | 85,5% (59/69) | 85,7% (48/56) | 82,5% (99/120) | 76,5% (450/588) |
| | Asthma (self-reported) | 68,3% (181/265) | 78,8% (108/137) | 60,3% (38/63) | 46,4% (32/69) | 82,1% (46/56) | 74,5% (102/137) | 69,7% (507/727) |
| | Meets at least 3 out of the following 5: Type-2 and/or >=2 SCS courses and/or impaired QoL and/or impaired smell and/or Asthma | 78,8% (134/170) | 90,6% (106/117) | 100,0% (39/39) | 91,3% (63/69) | 96,4% (54/56) | 88,6% (109/123) | 88,0% (505/574) |
| **Criteria met** | **CRSwNP and prior surgery and meets 3 out of 5 Uncontrolled Severe criteria** | 61,2% (101/165) | 89,7% (104/116) | 94,9% (37/39) | 79,7% (55/69) | 96,4% (54/56) | 82,9% (102/123) | 79,8% (453/568) |

**Table S3. Biologic indication per site according to EPOS/EUFOREA 2023 criteria.**
N/A: not assessed.