Spanish consensus on the management of chronic rhinosinusitis with nasal polyps (POLIposis NAsal / POLINA 2.0)

Brief running title: Nasal polyps management

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Abstract

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a high prevalent and burdensome disease for individuals and health systems which management involves many specialties: otorhinolaryngology, allergology, pulmonology, primary care, pharmacy, and paediatrics. A multidisciplinary approach and the participation of the patient in decision making are essential, both for the diagnosis and for the therapeutic strategy. The authors of the consensus aim to translate the current knowledge into an easy-to-read practical guide and emphasize those aspects in which there is still discussion or unmet needs due to the lack of proper scientific evidence. An iterative approach for the development of an evidence-based systematic review with recommendations was used, using a standard quality assessment scheme (Scottish Intercollegiate Guidelines Network -SIGN- and National Institute for Health and Care Excellence -NICE-), and a critical evaluation of the guideline has been carried out through the instrument Appraisal of Guidelines for Research and Evaluation (AGREE II) and Recommendation Excellence (AGREE REX). Based on the foregoing, the POLINA has been considered a guideline of good quality by an independent agency.

The POLINA consensus contributes with new schemes for the definition of control, therapeutic management including severity evaluation and surgery, and indications for biologic use and response. Finally, this guideline focuses on the research unmet needs in CRSwNP.

Resumen

La rinosinusitis crónica con pólipos nasales (RSCcPN) es una enfermedad de alta prevalencia y onerosa para las personas y los sistemas de salud cuyo manejo involucra a muchas especialidades: otorrinolaringología, alergología, neumología, atención primaria, farmacia y pediatría. El abordaje multidisciplinar y la participación del paciente en la toma de decisiones son fundamentales, tanto para el diagnóstico como para la estrategia terapéutica. Los autores del consenso pretenden traducir los conocimientos actuales en una guía práctica de fácil lectura y enfatizar aquellos aspectos en los que todavía hay discusión o necesidades no cubiertas por falta de evidencia científica adecuada. Se utilizó un enfoque iterativo para el desarrollo de una revisión sistemática basada en evidencia con recomendaciones, utilizando un esquema de evaluación de calidad estándar (Scottish Intercollegiate Guidelines Network -SIGN- y National Institute for Health and Care Excellence -NICE-), y una evaluación crítica de la directriz se ha llevado a cabo a través del instrumento Evaluación de Directrices para la Investigación y Evaluación (AGREE II) y Recomendación de Excelencia (AGREE REX). Con base en lo anterior, la guía POLINA ha sido considerada una guía de buena calidad por una agencia independiente.

El consenso POLINA aporta nuevos esquemas para la definición de control, manejo terapéutico incluyendo evaluación de gravedad, indicaciones de la cirugía y del uso de biológicos y la respuesta al tratamiento. Finalmente, esta guía se enfoca en las necesidades de investigación insatisfechas en la RSCcPN.

**Introduction**

Chronic rhinosinusitis (CRS) is an inflammatory disease of multifactorial aetiology involving the immune system and epithelial barrier responses and being influenced by the microbiome, the environment, as well as genetic and epigenetic factors [1,2]. CRS affects 11–13% of the general population [3,4] and has a negative impact on quality of life (QoL) [5,6] and it affects sleep quality and increases somnolence and the risk of sleep apnoea [7]. CRS has two main phenotypes, with (CRSwNP) or without (CRSsNP) nasal polyps, the former accounting for 18–20% of all CRS cases [8]. In Europe, annual costs of CRSwNP represent about 7,160€ per patient annually, direct costs being 1,501€, mainly derived from medical consultations and hospitalization, and indirect 5,659€ derived from work productivity loss [9].

CRSwNP is predominantly associated (85%) with type 2 (T2) inflammation in western countries, mainly represented by the production of T2 cytokines such as alarmins, IL-4, IL-5 and IL-13 which results in tissue eosinophilia [10-12].

A 25% of patients with CRS have asthma while 20% of asthmatics have CRS [13]. The asthma that accompanies CRSwNP is usually late-onset, non-atopic, with more severity, worse control, more exacerbations, and reduction in QoL [14,15]. In severe asthma up to 43% may present CRSwNP, with a longer duration of nasal symptoms and an increased number of sinus surgeries [13,16]. NSAID-exacerbated respiratory disease (N-ERD) comorbidity affects up to 26% of CRSwNP patients [15,16], in which sinonasal disease is more severe, has a high risk of postsurgical recurrence and coexists with a more severe and uncontrolled asthma [17,19].
A variety of specialties including otorhinolaryngology, pulmonology, allergology, as well as primary care, pharmacy, and paediatrics may participate in the management of CRSwNP. In consequence, a multidisciplinary approach is considered essential for both diagnostic and therapeutic strategies [20].

CRSwNP is clinically diagnosed by the presence of sinonasal symptoms such as nasal obstruction/congestion, rhinorrhea (anterior or/and posterior), smell dysfunction, and/or facial pressure/pain. Therefore, for the diagnosis of CRS it is required that the patient presents two or more cardinal symptoms, one of them always being nasal congestion or rhinorrhea, lasting for more than 12 weeks without resolution, together with diagnostic signs on nasal endoscopy (mucus secretion or nasal polyps from middle meatus) or on sinonasal CT scan (opacification of paranasal sinuses) (Table 1) [1].

The treatment of CRSwNP is based on three levels: 1) Appropriate/maximal medical treatment, 2) Surgical treatment when there is no optimal response to medical treatment, and 3) biological therapy in severe uncontrolled disease. Since there is a growing consensus that the goal of the treatment is to maintain clinical control of the CRSwNP, identifying the patients with poor control after a regular assessment is necessary to guide the therapeutic response [1]. The existing disease control instruments have however demonstrated a lack of uniformity regarding the controlled criteria and included items [21].

POLINA.1 (POLIposis NAsal), Spanish guideline on CRSwNP management, has been published one decade ago [22]. The main objective of the present document (POLINA.2) is to collect, since POLINA.1, the best scientific evidence for each aspect of the disease (epidemiology, pathophysiology, disease burden, diagnosis, treatment, and short/long term follow-up). The authors aimed to translate the
current knowledge into an easy-to-read practical guide and emphasize those aspects in which there is still discussion or unmet needs due to the lack of proper scientific evidence. New algorithms for CRSwNP treatment from mild to severe disease in the era of biologics are also included. Disease control and criteria for therapeutic indication of and response to the use of biologic agents are also widely discussed. Finally, this guideline focuses on the research unmet needs in CRSwNP.

**Literature search and methodology**

An iterative approach for the development of an evidence-based systematic review with recommendations was used, using a standard quality assessment scheme (Scottish Intercollegiate Guidelines Network -SIGN- and National Institute for Health and Care Excellence -NICE-) which are summarized in Supplementary Table 1-2S [23,24].

The guideline has subsequently been externally reviewed by specialists in methodology from the Institute for Health and Clinical Excellence (INPECS) with a double objective, first, to assessing the scientific quality of the POLINA Guideline and its recommendations and, second, to analyse its structure, content, and presentation. This critical evaluation of the POLINA Guideline has been carried out through the instrument Appraisal of Guidelines for Research and Evaluation (AGREE II) [25], through which both the methodological rigor and the transparency during the elaboration process of the guideline and the credibility of the recommendations as well as their possibility of implementation through the AGREE REX instrument were evaluated [26]. Three external reviewers read the POLINA Guideline in an independent manner by applying both instruments, which were completed by responding to different items (23 in the case of AGREE II and 9 in the case of AGREE REX) according to the degree of agreement. The different items were grouped into a series of domains (6 in AGREE II: scope and objective, participation of those involved, rigor in the elaboration, clarity of
presentation, applicability, and editorial independence; and 3 in AGREE REX: clinical applicability, values and references, and implementation) for which an overall score expressed as a percentage of the weighted score of the reviewers who evaluated the document. A higher percentage expressed higher quality of the evaluated domain. Based on the foregoing, the POLINA has been considered a guideline of good quality by the Institute for Clinical and Health Excellence (Table 3-4 supplementary).

**Type 2 inflammation**

In response to tissue damage, cells of the sinonasal epithelium produce alarmins such as thymic stromal lymphopoietin (TSLP), IL-33, and IL-25. TSLP is essential to start T2 immune response through activation of ILC2 and Th2 lymphocytes [27,28]. Once activated, ILC2, Th2 cells, eosinophils, and mast cells are important sources of T2 cytokines (IL-4, IL-5, and IL-13) which participate in the inflammatory response, both innate and adaptive. Stimulation of immunity is produced through the humoral cytokines IL-4 and IL-13 by activating B lymphocytes, which produce polyclonal IgE [29,30].

In CRSwNP, Staphylococcus aureus (SA) produces enterotoxins that act as superantigens, giving rise to an increased response of lymphocytes, which interact with a large proportion of T or B cells through their antigen receptor and producing a polyclonal IgE response [31]. Eosinophils play a very important role in CRSwNP since their recruitment, activation, and survival are regulated, in addition to IL-5, by epithelial cytokines, eicosanoids, and exogenous proteases [32]. Eosinophils are abundantly present in the tissues of the patients with CRSwNP with type 2 inflammation and are considered a biomarker of severe disease and of torpid evolution in these patients [33,34].
Disease control

An increasing number of studies are exploring the different aspects of disease control in patients with CRSwNP. It is important to note that the evaluation parameters of disease control in CRSwNP differ across studies [21]. The primary goal of any therapy, especially in chronic conditions, is to achieve and maintain clinical control, which can be defined as a disease state in which the patient does not have symptoms, or the symptoms are not impacting QoL [1]. Whereas asthma control assessment criteria have been recommended as good clinical practice [35] and poor asthma control has been correlated with high sinus CT scores in CRSwNP [36], CRSwNP disease control is not routinely assessed in daily clinical practice, and a clear consensus on assessment criteria has not yet been achieved.

The European Position Paper on Rhinosinusitis (EPOS) 2020 recently proposed a clinical staging system for disease “control” in CRSwNP [1]. The basis of “control” is defined as a disease state free from bothersome symptoms and having a healthy mucosa. And according to the EUFOREA group Uncontrolled CRSwNP is defined as “persistent or recurring symptoms despite long-term treatment with intranasal corticosteroid (INCS) and having received at least 1 course of systemic corticosteroids in the preceding two years and/or previous sinonasal surgery [37]. However, this initial proposal has been acknowledged to be opinion based and not data driven, and validation studies have shown the disease control assessment by EPOS has slight agreement with patients and a physician [38]. Given the importance of the concept of disease control, from clinical as well as research perspective, there remains a need for a gold standard to assess disease control in CRSwNP.

The POLINA expert committee proposes using the following assessments to define control of CRSwNP: disease severity and loss of smell (VAS 0-10cm), QoL impairment (SNOT-22, 0-110), nasal endoscopic examination (NPS 0-8), use of systemic corticosteroids in the last year, and the need for surgery. Control of the CRSwNP is classified into three categories: controlled, partially controlled, and
uncontrolled (Table 2). Disease control status should be assessed periodically for guiding the stepwise approach to optimizing CRSwNP management.

The results of EPOS 2020 studies and the recommendations for future research described in POLINA can hopefully facilitate this process of validation in the coming years, together with the arrival of mHealth technologies.

**Patient participation in decision making and multidisciplinary approach**

For individual cases, shared decision-making is one of the four cardinal principles of precision medicine at the time of diagnosis, prediction of success of the initiated treatment as well as patient’s participation in decisions regarding the treatment plan can be undertaken [1,39]. Moreover, patient’s involvement is recognized as a key component of clinical practice guideline development with important implications for guideline implementation. It brings together clinicians from many specialties, scientists and above all patients in a collaborative effort to provide the most efficient and effective management. Patient’s participation in POLINA guideline is covered by representatives from the Asociación Española de pacientes con Poliposis Nasal (AEPONA) who were actively involved in the development of the guideline.

Few qualitative studies on the patient’s experiences and perspectives of current management of CRSwNP have been published. These studies identified patient’s frustrations with delayed referral, lack of management of comorbidities, poor communication, inconsistency of advice, incorrect medication use, adherence to INCS, and lack of recognition of the impact of CRS [40,41].

A multidisciplinary team collaboration, in particular the improvement of communication between healthcare professionals, the inclusion of CRSwNP in asthma/pulmonology/allergology guidelines, and the introduction of a “United Airway Disease” committee in hospitals may help to promote a
holistic and multidisciplinary patient’s approach [20,39]. Since patients demand for more independence in disease management, this empowerment can be achieved both by implementing mobile health apps, organizing patient training on the correct use of medications and customizing the legislation regarding prescriptions for chronically ill patients [42,43].

**CRSwNP treatment (Figure 1)**

**Appropriate Medical Treatment**

The long-lasting use of INCS is recommended as the first line of treatment in CRSwNP due to its efficacy and safety, since it improves clinical parameters, reduces nasal polyp size and prevents recurrences after surgery [1,19,44]. No differences have been demonstrated among different INCS molecules or different administration device [45-47]. Besides, poor adherence of INCS in patients with CRSwNP has been described [48].

Short courses of systemic corticosteroids (SCS) can be used in the treatment of CRSwNP exacerbations, although its effect is transitory. Since SCS can have significant adverse effects, it is recommended to balance short-term benefit versus their impact bone metabolism (bone mass modification) [49].

Isotonic and hypertonic saline nasal rinsing are effective in CRSwNP, improving both patient’s symptoms and QoL, while the use of large volumes is recommended over nasal saline spraying. The addition of xylitol or sodium hyaluronate to irrigation with nasal saline may have an additional positive effect [1,50,51].

Treatment with antihistamines is only recommended as an option in patients with CRSwNP associated with allergic rhinitis [52]. The use of short-term antibiotics (oral or intranasal) in CRSwNP patients is not recommended while evidence is still lacking for the long-term efficacy and safety of macrolides
at low doses. The use of low-dose macrolides could be useful in selected CRS patients [1], mainly those with CRSsNP. The use of antileukotrienes is not recommended in CRSwNP patients [53,54]. Based on the available data, the use of mucoactive agents, probiotics, phototherapy, proton pump inhibitors, verapamil, furosemide, or herbal medicines in CRSwNP should be avoided [1]. Table 3 summarizes POLINA recommendations.

**Surgical treatment**

Surgery is an option after appropriate medical therapy has failed but there is still a strong debate over the appropriate extent of surgery [55]. The main goals of endoscopic sinus surgery (ESS) are relieving sinonasal symptoms, debriding inflamed tissue, and providing the best access for topical intranasal therapy to paranasal sinuses [56].

ESS can be categorized as limited (simple excision of nasal polyps or polypectomy), functional, or radical. Regarding the extent of ESS, some studies advocate ‘full house’ surgery, which includes a complete sphenoidotomy and a Draf IIA frontal sinusotomy rather than excising only the affected sinuses. This statement is based in the reduced need for revision surgery and greater improvement of nasal symptoms reported in patients undergoing more extensive surgery [57-58]. Table 4 provides POLINA recommendations on surgical treatment.

**Biological therapy**

Biologics constitute a therapeutic choice for patients with type 2 severe CRSwNP when classical treatment approaches do not provide symptom ad disease control. Biologics are drugs produced from living organisms that target specific molecular pathways involved in the pathogenesis of respiratory inflammatory diseases, including asthma and CRSwNP. A nasal biopsy under local anaesthesia would
allow to exclude a tumour and to pheno-endotype CRSwNP by identifying the degree of tissue eosinophilia and other potential type 2 inflammatory biomarkers [59].

1. Efficacy and safety of biologics in treatment of severe CRSwNP

The efficacy and safety of biologics in the treatment of severe CRSwNP has been tested in several pivotal clinical trials with dupilumab (SINUS) [60], omalizumab (POLYP) [61], mepolizumab (SYNAPSE) [62] and benralizumab (OSTRO) [63] (Table 5). The baseline characteristics of the studied populations and the main treatment outcomes from the biologic phase 3 studies are shown in Tables 6 and 7.

1.1. Anti-IgE monoclonal antibodies (omalizumab). Omalizumab is a humanized monoclonal antibody that binds to free IgE and decreases expression of IgE receptors on mast cells, basophils, and dendritic cells, interfering with their activation (Figure 2A) [64]. Omalizumab demonstrated an improvement in nasal (including loss of smell) and pulmonary symptoms, nasal polyps size (NPS), QoL (SNOT-22, SF-36, Asthma Quality of Life Questionnaire (AQLQ)) and reduction of the need for ESS with a very favourable safety profile [61.65].

1.2. Anti-IL-5/IL-5Rα monoclonal antibodies (mepolizumab, benralizumab, reslizumab). Reslizumab and mepolizumab are humanized monoclonal antibody against free IL-5 while benralizumab is an antagonist of the IL-5 receptor alpha subunit (IL-5Rα) (Figure 2B). Reslizumab did not demonstrate differences in the efficacy on sinonasal symptoms [66] and it is not further developed for the treatment of CRSwNP. Patients treated with mepolizumab had an improvement in nasal symptoms, including loss of smell, disease severity, NPS, sinus opacification, quality of life (SNOT-22), and reduction of serum inflammatory biomarkers (eosinophils, eosinophilic cationic protein [ECP], and IL-5 receptor), the use of SCS and the need for ESS but low improvement of the sense of smell measured by the University of Pennsylvania Smell Identification Test (UPSIT)
Benralizumab caused a late improvement of nasal symptoms, including loss of smell, NPS, and SNOT-22. However, no improvement in sense of smell by UPSIT, sinus opacification, time to first ESS or the use of SCS were observed [63,69,70]. Clinical studies of anti-IL-5 monoclonal antibodies have shown an excellent safety profile [71].

1.3. Anti-IL-4Rα monoclonal antibodies (Dupilumab). Dupilumab is a human monoclonal antibody that blocks the subunit of the IL-4Rα receptor while inhibiting the activity of IL-4 and IL-13 pathways (Figure 2C) [72]. Dupilumab produced an improvement in nasal symptoms, with a fast and persistent effect on the loss of smell, NPS, SNOT-22, disease severity, rapid and sustained improvement in the sense of smell by UPSIT, sinus opacification, asthma control and lung function in asthmatics as well as reduction of the use of SCS and need of ESS [60,73-76]. Dupilumab, in patients with N-ERD, showed a greater degree of improvement in the SNOT-22 score, nasal congestion, total symptom score, and peak nasal inspiratory flow compared to patients without N-ERD [77]. Frequency of adverse effects were similar in the dupilumab and placebo groups [60].

2. Meta-analyses and indirect treatment comparisons of biologics in CRSwNP

Several network meta-analyses have been published in patients with severe CRSwNP by assessing direct comparisons between several biologics (omalizumab, mepolizumab, dupilumab, and benralizumab) and placebo as well as indirect comparisons between the different biologics [78-81]. All these meta-analysis show superiority of biologics over placebo in the reduction of NPS, need for ESS, and the use of SCS, as well as improvement of nasal obstruction, loss of smell, and quality of life (SNOT-22). The three biologics approved for treatment of the CRSwNP (dupilumab, mepolizumab and omalizumab) demonstrated an improvement of smell loss compared to placebo. In addition, dupilumab is associated with an early and sustained improvement in smell [78-81].
Indirect comparisons have suggested that dupilumab could present a greater effect in some efficacy outcomes, with a faster and persistent improvement of the loss of smell [78-81]. However, these are still exploratory analyses based on a limited number of studies and with a high percentage of discontinuations and missing data, as well as heterogeneity both in the studied populations and used methodology. Head-to-head clinical trials are needed to comparing efficacy and safety among different biologics in severe CRSwNP to conclusively establish whether or not there are significant differences between them in both efficacy and safety.

3. Treatments with biologics (real life studies) (Table 7)

3.1. Omalizumab. A study conducted in patients with severe asthma and CRSwNP treated with omalizumab reported an improvement in nasal symptoms, disease severity, asthma exacerbations, and sinus opacification, while no significant reduction of NPS was observed [82].

3.2. Mepolizumab. A study in severe asthma and CRSwNP treated with mepolizumab showed improvement in NPS, SNOT-22, and a reduction in blood and tissue eosinophils. However, no reduction of FeNO was reported [83].

3.3. Benralizumab. A study conducted in severe asthma and CRSwNP treated with benralizumab found a reduction in SNOT-22. The study showed a 31% reduction of patients with anosmia (total loss of smell) [84].

3.4. Dupilumab. A study conducted in patients with CRSwNP treated with dupilumab reported an improvement of nasal symptoms, including anosmia [85]. In another study, the authors found an improvement in all efficacy outcomes, including sense of smell. According to the EPOS 2020 control criteria, no patient was considered controlled with 94% being partially controlled and 6% uncontrolled [86].
4. Other comparisons among biologics.

A study carried out in patients with severe asthma and CRSwNP treated with anti-IgE, anti-IL-5Rα, and anti-IL-4Rα biologics observed an improvement in SNOT-22 which was higher in the group treated with anti-IL-4Rα than in the anti-IgE and anti-IL-5Rα treated groups [87]. Nasal and total symptoms improved with anti-IL-5Rα and anti-IL-4Rα, but not with anti-IgE. The conclusion was that efficacy improvement was higher in the anti-IL-4Rα treated group.

Another study conducted in CRSwNP patients treated with omalizumab, mepolizumab, or benralizumab, patients treated with mepolizumab showed the best success rates (79%), followed by omalizumab (50%), and benralizumab (50%) [88] (Meier 2021). A strong improvement in the sense of smell was observed in patients treated with mepolizumab (29%), followed by benralizumab (17%) and omalizumab (13%).

Finally, a study conducted in severe asthma and CRSwNP treated with omalizumab, mepolizumab, reslizumab, or benralizumab showed that 2 out of every 5 patients presented a subjective improvement in the sense of smell, although anosmia was maintained in 60% of patients, without significant differences between biologics [89].

5. Indication criteria for biologics use

Different consensus guidelines (EUFOREA 2019/2021 and EPOS 2020) have been published on the indication of and response to biologics in the treatment of severe CRSwNP [1,37,90]. Following these international consensuses, the current POLINA guideline is proposing modified criteria for the indication of biologics in severe CRSwNP (Figure 3). Biologicals would be indicated in “severe bilateral CRSwPN with at least 1 previous ESS” (ESS >6 months) with one additional criterion being: presence...
of type 2 inflammation (high tissue or/and blood eosinophilia, or high serum total IgE), severe loss of smell (by smell test or VAS), need for SCS (≥2 short courses from 5 days at a dose of 0.5-1 mg/kg/day) in the last year or contraindicated SCS, or concomitant asthma and/or N-ERD treated with inhaled therapy. In this framework, severe CRSwNP was defined as VAS >7cm and/or SNOT-22 >50, while ESS should include the opening of the paranasal sinuses (not only nasal polypectomy).

6. Response criteria for biologic use

The current POLINA guideline recommends assessment of response to biological treatment at both 6 and 12 months. Biologic treatment of CRSwNP should be continued if the disease is controlled or partially controlled and accepted by the patient. When the physician and/or the patient consider the disease is uncontrolled, biologic should be discontinued and a short course of SCS or even ESS/revision surgery is recommended. In addition, the swift from one to another biologic based on control criteria could be evaluated according to pheno-endototyping and agreed by physician and patient (decision-making) (Figure 4).

Unmet needs in CRSwNP

- To define clinical predictors of poor disease control and how this affects treatment decisions regarding biologics or surgery.
- To conduct direct comparative studies on the efficacy and safety of the different biologics.
- To determine the accuracy of biomarkers to assessing response to biologics.
- To conduct studies to determine criteria to stop the use of or the swift between biologics.
Conclusions

Patients with CRSwNP and comorbid asthma/N-ERD, as well as those with high corticosteroid use and/or history of sinus surgical, have more severe disease and associated sinonasal symptom burden while representing a difficult-to-treat population under the existing management paradigm.

Shared clinician-patient decision making and communication, patient education, and multidisciplinary strategy may all provide solutions to this major unmet need in CRSwNP.

The role of biologics in the treatment paradigm requires consideration of multiple factors that have yet to be clearly established. This includes identifying patients most appropriate for biologic therapy while considering long-term safety and cost-effectiveness in the context of patient preferences and goals.

CRSwNP is a burdensome condition with a high percentage of patients with uncontrolled disease, especially those with comorbid asthma/N-ERD. These patients usually need high corticosteroid use and/or sinus surgery, have more severe disease and represent a difficult-to-treat population under the existing management paradigm.

Shared decision-making, good patient–clinician communication, patient education, multidisciplinary strategy, may all provide solutions to this major unmet need in CRSwNP.

The role of biologics in the treatment paradigm requires consideration of multiple factors that have yet to be clearly established and includes identifying patients most appropriate for biologic therapy while considering long-term safety and cost-effectiveness in the context of patient preferences and goals.

The POLINA consensus is an evidence-based clinical guideline, which have been externally evaluated as having good quality, and may be useful to assists clinicians to improve CRSwNP management.
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Conflicts of interest
I. Alobid has received honoraria for consultancy and conferences from Viatris, Roche, Sanofi, GSK, MSD, Menarini, Salvat, Galensus Health, Olympus, and Novartis.

C. Colás has received honoraria for consultancy and conferences from Novartis, GSK, Sanofi, Viatris, Chiesi, MSD, Takeda, Roxall, and ThermoFisher.

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E. Arismendi has received honoraria for consultancy and conferences from AstraZeneca, GSK, MSD, Novartis, and Sanofi-Genzyme.

J. Sastre has received honoraria for consultancy and conferences from Sanofi, GSK, MSD, Mundipharma, ALK and Novartis.

A. del Cuvillo has received honoraria for consultancy and conferences from MSD, SANOFI, GSK, Menarini, FAES Pharma, Alk Abello, Astra Zeneca, Novartis, Viatris, Uriach, UCB Pharma and TEVA.

J. Mullol is a member of national or international advisory boards and has received speaker fees or funding for clinical trials and research projects from AstraZeneca, Genentech, GSK, Glenmark, Menarini, Mitsubishi-Tanabe, MSD, NOUCOR/Uriach Group, Novartis, Proctor & Gamble, Regeneron Pharmaceuticals Inc., Sanofi-Genzyme, UCB Pharma, and Viatris/MEDA Pharma.

A. Gómez-Outes declares no conflict of interest.
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Figure 1. Therapeutic steps for the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP). NSAIDs: non-steroidal anti-inflammatory drugs; N-ERD, NSAID-exacerbated respiratory disease; VAS: visual analogue scale; SNOT-22: sino-nasal outcome test 22. a Spray, drops or rinsing; b Rinsing with isotonic saline solution or lactated Ringer's; c See POLINA criteria for the control of CRSwNP (Table 2); d Short courses from 5 days at a dose of 0.5-1 mg/kg/day; e Opening of affected paranasal sinuses; f Possible choice according to endotype; g Evaluate more radical/extended surgery according to consensus between surgeon and patient.
Figure 2. Mechanisms of action of biologics in CRSwPN. A: humanized anti-IgE monoclonal antibody (omalizumab); B: humanized anti-IL-5 (mepolizumab and reslizumab) and anti-IL-5Rα (benralizumab) monoclonal antibodies, C: human anti-IL-4Rα monoclonal antibody (dupilumab).
**Figure 3.** POLINA criteria for the use of biologicals. 

\(^a\) VAS >7cm and/or SNOT-22 >50, \(^b\) Opening of affected paranasal sinuses > 6 months; \(^c\) Short courses from 5 days at a dose of 0.5-1 mg/kg/day. HPF: high power field; N-ERD, NSAID-exacerbated anti-inflammatory drugs; VAS: visual analogue score.
**Figure 4.** Evaluation of biological treatment for chronic rhinosinusitis with nasal polyps (CRSwNP) at 6 and 12 months. a See control criteria (Table 2); b ESS: Endoscopic sinus surgery with opening of affected paranasal sinuses; c OCS: oral corticosteroids for 5 days at a dose of 0.5-1 mg/kg/day.
**Table 1.** POLINA recommendations on diagnosis of chronic rhinosinusitis with nasal polyps.

| Diagnosis is based on sinonasal symptoms and the presence of bilateral nasal polyps by nasal endoscopy. | A |
| Nasal symptoms should be assessed subjectively using Likert or visual analogue scale (VAS). | B |
| To establish the endotype, blood eosinophil count and total IgE show the association with type 2 inflammation. Skin tests and/or determination of serum specific IgE serve to confirm patient sensitivities to common allergens. | B |
| It is recommended to carry out a pheno-endotyping for the histopathological study of nasal polyps (biopsy) and rule out other pathologies (benign or malignant). | B |
| The assessment of sense of smell should be done with validated olfactometry. | B |
| Since it is very complex to predict the improvement of smell after surgery, it is currently not recommended to use this isolated symptom as indication for surgery. | B |
Table 2. POLINA criteria for the control of chronic rhinosinusitis with nasal polyps.

<table>
<thead>
<tr>
<th></th>
<th>Controlled (all of the following)</th>
<th>Partially controlled (at least 1 present)</th>
<th>Uncontrolled (3 or more present)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity of disease</strong></td>
<td>0-3</td>
<td>&gt; 3-7</td>
<td>&gt; 7-10</td>
</tr>
<tr>
<td>VAS (0-10 cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Loss of smell</strong></td>
<td>0-3</td>
<td>&gt; 3-7</td>
<td>&gt; 7-10</td>
</tr>
<tr>
<td>VAS (0-10 cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quality of life (SNOT-22)</strong></td>
<td>8-20</td>
<td>&gt;20-50</td>
<td>&gt;50</td>
</tr>
<tr>
<td>(0-110)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Endoscopic nasal polyp</strong></td>
<td>Maximum of 1 in each nasal cavity</td>
<td>Total score &lt; 5</td>
<td>Total score ≥ 5</td>
</tr>
<tr>
<td>score (0-8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Use of SCS in the last year</strong></td>
<td>No</td>
<td>1-2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt; 2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>(Short courses)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Needs for surgery</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

VAS: visual analogue scale; SCS: systemic corticosteroids; SNOT-22: Sino-Nasal Outcome Test 22.

<sup>a</sup>: Short course from 5 days at a dose of 0.5-1 mg/kg/day.

<sup>b</sup>: Endoscopic sinus surgery with opening of the affected sinuses.
Table 3. POLINA recommendations on medical treatment of chronic rhinosinusitis with nasal polyps.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal saline rinsing and INCS are recommended as the first line of treatment.</td>
<td>A</td>
</tr>
<tr>
<td>No differences have been demonstrated between different INCS molecules, nor higher doses or according to the administration device</td>
<td>A</td>
</tr>
<tr>
<td>The use of INCS after surgery is recommended to prevent recurrences.</td>
<td>A</td>
</tr>
<tr>
<td>Short-course systemic corticosteroids can be used, although their effect is transitory, and safety is low.</td>
<td>A</td>
</tr>
<tr>
<td>The use of short- and long-term antibiotics courses are not recommended.</td>
<td>B</td>
</tr>
<tr>
<td>The use antileukotrienes are not recommended.</td>
<td>B</td>
</tr>
<tr>
<td>Despite the efficacy of aspirin desensitization in N-ERD patients, it’s use in clinical practice is not common due to high risk/benefit ratio.</td>
<td>B</td>
</tr>
<tr>
<td>Aspirin treatment after desensitization is not recommended for N-ERD patients.</td>
<td>B</td>
</tr>
<tr>
<td>The use of mucoactive agents, probiotics, phototherapy, pump inhibitors protons, verapamil, furosemide or medicinal herbs is not recommended.</td>
<td>B</td>
</tr>
</tbody>
</table>
Table 4. POLINA recommendations on surgical treatment of chronic rhinosinusitis with nasal polyps.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic sinus surgery should be considered as the preferred option</td>
<td>B</td>
</tr>
<tr>
<td>when adequate medical treatment is no longer effective, mainly when the first</td>
<td></td>
</tr>
<tr>
<td>surgery is considered.</td>
<td></td>
</tr>
<tr>
<td>In the case of a first intervention, functional surgery is recommended.</td>
<td>D</td>
</tr>
<tr>
<td>Reboot surgery ± Draf III is recommended in patients with high risk of recurrence (with multimorbid asthma and/or N-ERD).</td>
<td>C</td>
</tr>
</tbody>
</table>
### Table 5. Efficacy and safety of biologics in treatment of severe chronic rhinosinusitis with nasal polyps.

<table>
<thead>
<tr>
<th>Study</th>
<th>CRSwNP</th>
<th>Treatment</th>
<th>Variables</th>
<th>Results</th>
</tr>
</thead>
</table>
| Gevaert et al. 202061  | POLYP 1: N = 138  
POLYP 2: N = 127  | Omalizumab each 2 or 4 weeks for 24 weeks SC, dose depends on blood IgE levels and weight  
(N = 134) Placebo (N = 131) | • NPS  
• Nasal congestion  
• SNOT-22  
• UPSIT  
• Nasal symptoms  
• AQLQ  
• ESS  
• Adverse events | • Improvement NPS and nasal congestion  
• Improvement SNOT-22, UPSIT, hyposmia and rhinorrhoea  
• Improvement AQLQ  
• ESS reduction  
• Equal adverse events |
| Anti-IgE               |        |                                                                           |                                                                           |                                                                         |
| Gevaert et al. 201365  | N = 24  | Omalizumab each 2 or 4 weeks for 16 weeks SC, dose depends on blood IgE levels and weight  
(N = 16) Placebo (N = 8) | • RSOM-31, AQLQ, SF-36  
• Symptoms  
• NPS  
• LMS (CT)  
• Spirometry  
• Blood and nasal biomarkers  
• Adverse events | • Improvement AQLQ, SF-36 (physical summary), some domains RSOM-31  
• Improvement: nasal congestion, anterior rhinorrhoea, hyposmia, and wheezing / dyspnea  
• Reduction NPS and LMK  
• Reduction total IgE and ECP only in nose  
• More common cold, one case of lymphoblastic lymphoma |
| Tiotiu et al. 202082   | N = 24  | Omalizumab each 2 or 4 weeks for 24 weeks SC, dose depends on blood IgE levels and weight 6 months | • NPS  
• Sinonasal symptoms  
• LMS (CT) | • No Improvement NPS  
• Improvement: sinonasal symptoms  
• Improvement LMS (CT) |
| Anti-IL-5/5Ra e - IL-5 |        |                                                                           |                                                                           |                                                                         |
| Han et al. 202162      | SYNAPSE: N = 407 Severe CRSwNP (1 or more previous ESS) | Mepolizumab 100 mg SC each 4 weeks for 52 weeks (N = 206) Placebo (N = 201) | • NPS  
• Nasal congestion  
• Smell loss (VAS)  
• Sinonasal symptoms  
• VAS-CRS  
• SNOT-22  
• ESS  
• ACQ-5  
• OCS use | • Improvement NPS  
• Improvement sinonasal symptoms, nasal congestion, smell loss  
• Improvement SNOT-22  
• Improvement VAS-CRS  
• Reduction ESS  
• Improvement ACQ-5  
• Reduction OCS use  
• Reduction blood eosinophils |
<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Sample</th>
<th>Treatment</th>
<th>Outcomes</th>
<th>Biomarkers: Blood eosinophils</th>
<th>Additional Outcomes</th>
</tr>
</thead>
</table>
| Bachert et al. 2017<sup>68</sup> RCT | N = 105      | Mepolizumab 750 mg IV each 4 weeks for 6 weeks (N = 54) Placebo (N = 53) | • ESS indication  
• VAS-CRS  
• NPS  
• Sinonasal symptoms  
• UPSIT  
• SNOT-22, EQ-5D  
• PFIN  
• Eosinophils  
• FEV<sub>1</sub>/FVC | • ESS reduction  
• Improvement Sinonasal symptoms (smell loss), NPS, SNOT-22, PFIN and VAS-CRS  
• Eosinophils reduction  
• No significant differences in UPSIT, EQ-5Q or lung function |
| Gevaert et al. 2011<sup>67</sup> RCT | N = 30 severe or recurrent CRSwNP | Mepolizumab 750 mg IV each 4 weeks 2 doses (N = 20) Placebo (N = 10) | • NPS  
• CT (worse, better, without changes)  
• PFIN  
• Sinonasal symptoms  
• Biomarkers: eosinophils, ECP, IL-5Rα, IL5, IgE | • No change on sinonasal symptoms  
• Improvement NPS and PFIN  
• No reduction: ECP, IL5 Rα, IgE |
| Detoraki et al. 2021<sup>69</sup> Real life | N = 44      | Mepolizumab (100 mg each 4 week) 1 year | • NPS  
• SNOT-22 | • Improvement NPS  
• Improvement SNOT-22 |
| Gevaert et al. 2006<sup>66</sup> RCT | N = 24      | Reslizumab 3 mg/kg IV 1 dose (N = 8) Reslizumab 1 mg/kg IV 1 dose (N = 8) Placebo (n = 8) | • NPS  
• Sinonasal symptoms  
• PFIN  
• Eosinophils, ECP, eotaxin, IL-5 | • No improvement NPS, PFIN, sinonasal symptoms  
• Reduction of NPS only for 1 mg/kg  
• Reduction Eos, ECP and IL-5 |
| Bachert et al. 2022<sup>63</sup> RCT | OSTRO: N = 413 | Benralizumab 30 mg every 4 weeks for first 3 doses and every 8 weeks thereafter for 56 weeks (N = 207) Placebo (N = 206) | • NPS  
• Nasal congestion  
• SNOT-22  
• UPSIT  
• Smell loss  
• Time to first surgery | • Improvement NPS, nasal congestion  
• Late improvement smell loss and SNOT-22  
• No improvement: surgery, LMS (CT), OCS use  
• Improvement ACQ-6  
• No differences adverse events |
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Tversky et al. 2021<sup>69</sup> RCT | N = 24 CRSwNP Previous polypectomy | Benralizumab 30 mg every 4 weeks for 20 weeks (N = 12) Placebo (N = 12) | • OCS use  
• LMS (CT)  
• ACQ-6  
• Adverse events  
• Biomarkers: Blood eosinophils | • Reduction blood eosinophils  
• Improvement NPS, nasal congestion, SNOT-22 and LMS (CT)  
• No improvement UPSIT  
• No differences adverse events |
| Canonica et al. 2022<sup>70</sup> RCT | ANDHI: N = 153, asma y CRSwNP | Benralizumab 30 mg every 4 weeks for 24 weeks (N = 96) Placebo (N = 57) | • NPS  
• Nasal congestion  
• SNOT-22  
• Smell loss  
• UPSIT  
• LMS (CT)  
• Adverse events | • Improvement SNOT-22  
• Improvement of asthma parameters |
| Bagnasco et al. 2020<sup>84</sup> Real life | N = 34 | Benralizumab 30 mg every 4 weeks for 24 weeks | • SNOT-22  
• ACT  
• OCS use  
• Anosmia  
• Biomarkers: Blood eosinophils | • Improvement SNOT-22 and ACT  
• Reduction OCS use  
• Improvement anosmia in 31% of patients  
• Reduction blood eosinophils |
| Bachert C et al. 2019<sup>60</sup> RCT | SINUS 24: N = 276  
SINUS 52: N = 448 | SINUS 24: 24 weeks  
• Dupilumab 300 mg SC each 2 weeks (N = 143)  
• Placebo (N = 133)  
SINUS 52:  
• Dupilumab 300 mg SC each 2 weeks, for 52 weeks (N = 150) | • NPS  
• Nasal congestion  
• Smell loss  
• SNOT-22  
• VAS-CRS  
• UPSIT  
• LMS (CT)  
• ACQ-6  
• FEV<sub>1</sub>  
• OCS use  
• ESS indication  
• Blood biomarkers  
• Nasal biomarkers | • Improvement both studies (week 24 and 52):  
• NPS  
• Nasal congestion  
• Smell loss  
• SNOT-22  
• VAS-CRS  
• UPSIT  
• LMS (CT)  
• ACQ-6  
• FEV<sub>1</sub>  
• ESS reduction  
• Reduction OCS use  
• Reduction blood biomarkers: total IgE, TARC, eotaxin 3, periostin (NO eosinophils) |
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Groups</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bachert et al. 2016</strong>&lt;sup&gt;73&lt;/sup&gt; RCT</td>
<td></td>
<td>Dupilumab 600 mg SC + 300 mg SC each week for 15 weeks (N = 60) placebo (N = 60)</td>
<td>- NPS&lt;br&gt;- Nasal congestion&lt;br&gt;- Smell loss&lt;br&gt;- SNOT-22&lt;br&gt;- VAS-CRS&lt;br&gt;- UPSIT&lt;br&gt;- LMS (CT)&lt;br&gt;- ACQ-6, FEV&lt;sub&gt;1&lt;/sub&gt;&lt;br&gt;- Blood biomarkers: eosinophils, total IgE, eotaxin 3, TARC</td>
</tr>
<tr>
<td><strong>Nowsheed et al. 2021</strong>&lt;sup&gt;85&lt;/sup&gt; Real life</td>
<td>N = 29</td>
<td>Dupilumab 300 mg each 2 weeks for 11 months (3-20 months)</td>
<td>- NPS&lt;br&gt;- Nasal congestion&lt;br&gt;- Smell loss&lt;br&gt;- SNOT-22&lt;br&gt;- Sniffin-Stick&lt;br&gt;- LMS (CT)&lt;br&gt;- PNIF&lt;br&gt;- ACT</td>
</tr>
<tr>
<td><strong>Lans et al. 2022</strong>&lt;sup&gt;86&lt;/sup&gt; Real life</td>
<td>Baseline: N = 131&lt;br&gt;48 weeks: N = 26</td>
<td>Dupilumab 300 mg each 2 weeks for 28 weeks</td>
<td>- NPS&lt;br&gt;- Smell loss&lt;br&gt;- SNOT-22&lt;br&gt;- Sniffin-Stick&lt;br&gt;- LMS (CT)&lt;br&gt;- PNIF&lt;br&gt;- ACT</td>
</tr>
</tbody>
</table>

Improvement:
- NPS<br>- Nasal congestion<br>- Smell loss<br>- SNOT-22<br>- Sniffin-Stick<br>- PNIF<br>- ACT

EPOS 2020 control:
- Controlled: 0%
- Partial control: 94%
- No control: 6%
Table 6. Characteristics of the baseline population in pivotal trials with biologics in the treatment of chronic rhinosinusitis with nasal polyps.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Benralizumab (OSTRO)</th>
<th>Dupilumab (SINUS)</th>
<th>Mepolizumab (SYNAPSE)</th>
<th>Omalizumab (POLYP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>410</td>
<td>724</td>
<td>407</td>
<td>265</td>
</tr>
<tr>
<td>Gender (female) N (%)</td>
<td>147 (36)</td>
<td>287 (40)</td>
<td>143 (35)</td>
<td>94 (35)</td>
</tr>
<tr>
<td>NPS (0-8), mean</td>
<td>6.1</td>
<td>5.9</td>
<td>5.5</td>
<td>6.2</td>
</tr>
<tr>
<td>Nasal congestion (0-3)</td>
<td>&gt; 2</td>
<td>&gt; 2</td>
<td>9 (0-10)</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>Smell loss (0-3)</td>
<td>&gt; 2</td>
<td>&gt; 2</td>
<td>&gt; 9 (0-10)</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>UPSIT (0-40), mean</td>
<td>83% with &lt;18*</td>
<td>14.0</td>
<td>NA</td>
<td>13.1</td>
</tr>
<tr>
<td>VAS-CRSwNP Severity, mean</td>
<td>ND</td>
<td>7.8 (0-10 cm)</td>
<td>9.1 (0-10)</td>
<td>ND</td>
</tr>
<tr>
<td>SNOT-22 (0-110), mean</td>
<td>69</td>
<td>50.9</td>
<td>64</td>
<td>60</td>
</tr>
<tr>
<td>LMS (0-24) mean</td>
<td>ND</td>
<td>18.3</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>≥ 1 previous ESS, N (%)</td>
<td>300 (73)</td>
<td>459 (63)</td>
<td>407 (100)</td>
<td>158 (60)</td>
</tr>
<tr>
<td>OCS Use N (%)</td>
<td>307 (75)</td>
<td>538 (74)</td>
<td>197 (48)</td>
<td>59 (22)</td>
</tr>
<tr>
<td>Blood eosinophils, cell/µl, mean</td>
<td>447</td>
<td>430</td>
<td>395</td>
<td>340</td>
</tr>
<tr>
<td>Total IgE, KU/l, mean</td>
<td>232</td>
<td>229</td>
<td>NA</td>
<td>175</td>
</tr>
<tr>
<td>N-ERD, N (%)</td>
<td>121 (30)</td>
<td>204 (28)</td>
<td>108 (26)</td>
<td>72 (27)</td>
</tr>
<tr>
<td>Asthma, N (%)</td>
<td>278 (68)</td>
<td>428 (59)</td>
<td>289 (71)</td>
<td>151 (57)</td>
</tr>
</tbody>
</table>

* In the OSTRO study, anosmia (UPSIT < 18) was observed in 83% of patients.

ESS: endoscopic sinus surgery; LMS: Lund-Mackay Score by CT scan; NA: not available; N-ERD: NSAID-exacerbated respiratory disease; NPS: nasal polyp score; OCS: oral corticosteroids; SNOT-22: Sinonasal Outcome Test 22; UPSIT: University of Pennsylvania Smell Identification Test; VAS: visual analogue score; VAS-CRSwNP: VAS chronic rhinosinusitis with nasal polyps.
Table 7. Efficacy of biological therapy on the variables of chronic rhinosinusitis with nasal polyps and level of evidence-based medicine.

<table>
<thead>
<tr>
<th></th>
<th>Omalizumab 24 weeks&lt;sup&gt;61&lt;/sup&gt;</th>
<th>Dupilumab 52 weeks&lt;sup&gt;60&lt;/sup&gt;</th>
<th>Mepolizumab 52 weeks&lt;sup&gt;62&lt;/sup&gt;</th>
<th>Benralizumab 40 weeks&lt;sup&gt;63&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of nasal polyp size (0-8), mean</td>
<td>-1.3</td>
<td>-2.3</td>
<td>-0.7</td>
<td>-0.6</td>
</tr>
<tr>
<td>Reduction of nasal congestion (0-3), mean</td>
<td>-0.5</td>
<td>-0.9</td>
<td>-3.1 cm (0-10)</td>
<td>-0.7</td>
</tr>
<tr>
<td>Reduction of total sinonasal symptoms (0-9), mean</td>
<td>-2.0 (0-12)</td>
<td>-2.4 (0-9)</td>
<td>3.1 (0-10)</td>
<td>NA</td>
</tr>
<tr>
<td>Reduction of smell loss (0-3), mean</td>
<td>-0.4</td>
<td>-1.0</td>
<td>-0.4 (0-10)</td>
<td>-0.2</td>
</tr>
<tr>
<td>UPSIT improvement (0-40), mean</td>
<td>+3.8</td>
<td>+10.5</td>
<td>+0.4</td>
<td>NS</td>
</tr>
<tr>
<td>SNOT-22* improvement (0-110), mean</td>
<td>-15.6</td>
<td>-19.1</td>
<td>-16.5</td>
<td>-5.2 (NS)</td>
</tr>
<tr>
<td>LMS reduction (0-24), mean</td>
<td>-0.2</td>
<td>-7.0</td>
<td>N/A</td>
<td>-0.9 (NS)</td>
</tr>
<tr>
<td>ESS reduction (%)</td>
<td>-84</td>
<td>-83</td>
<td>-57</td>
<td>-10</td>
</tr>
<tr>
<td>OCS reduction (%)</td>
<td>-63</td>
<td>-74</td>
<td>-42</td>
<td>NA</td>
</tr>
<tr>
<td>Adverse events vs placebo</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Level of evidence-based medicine</td>
<td>Ia</td>
<td>Ia</td>
<td>Ia</td>
<td>Ia</td>
</tr>
</tbody>
</table>

* SNOT-22: minimal clinically important difference > 8.9.

ESS: endoscopic sinus surgery; LMS: Lund-Mackay Score by CT scan; NA: not available; NPS: nasal polyp score; OCS: oral corticosteroids; SNOT-22: Sinonasal Outcome Test 22; UPSIT: University of Pennsylvania Smell Identification Test; VAS: visual analogue score.