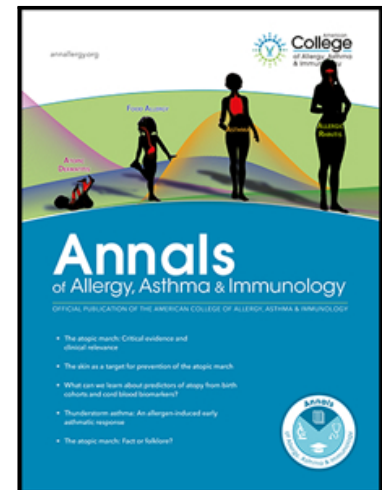


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PII: S1081-1206(22)00300-3
DOI: <https://doi.org/10.1016/j.anai.2022.04.004>
Reference: ANAI 3914



To appear in: *Annals of Allergy, Asthma Immunology*

Received date: 14 October 2021
Revised date: 30 March 2022
Accepted date: 4 April 2022

Please cite this article as: Larry Borish MD , Noam A Cohen MD , Geoffrey Chupp MD ,
Claire Hopkins DM (Oxon) , Martin Wagenmann MD , Ana R Sousa PhD , Steven G Smith PhD ,
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Robert H Chan MD , Wytke Fokkens PhD , Evaluating enrolment and outcome criteria in trials
of biologics for chronic rhinosinusitis with nasal polyps, *Annals of Allergy, Asthma Immunology* (2022),
doi: <https://doi.org/10.1016/j.anai.2022.04.004>

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Conflicts of Interest:

Larry Borish reports having participated in advisory boards and receiving honoraria from Regeneron Pharmaceuticals, DevPro Biopharma, GSK, and AstraZeneca and receiving clinical research grants from GSK and Regeneron Pharmaceuticals.

Noam A Cohen has reported personal fees from Novartis and Sanofi/Regeneron Pharmaceuticals and Licensing of Patent rights namely GeneOne Life Sciences.

Geoffrey Chupp has acted as a consultant for AstraZeneca, Genentech, Boehringer Ingelheim, and Teva, attended a speaker's bureau with AstraZeneca, Genentech, and Circassia, and received research grants from AstraZeneca and institutional grants from AstraZeneca, Genentech, Boehringer Ingelheim, and GSK.

Claire Hopkins has reported personal fees from Sanofi, Chordate, Olympus, Smith and Nephew, and Medtronic.

Martin Wagenmann reports personal fees from ALK-Abelló, Allergopharma, AstraZeneca, Bencard Allergie, Genzyme, HAL Allergie, Infectopharm, LETI Pharma, MEDA Pharma, Novartis, Sanofi Aventis, Stallergenes, and Teva.

Wyske Fokkens reports that the department of otorhinolaryngology of the Amsterdam University Medical Centres, location AMC received grants from GSK, Sanofi, Novartis Chordate, Mylan, ALK, Allergy diagnostics and ZonMW and that she is a consultant for Sanofi and Lyra Therapeutics.

Ana R Sousa, Steven G Smith, Jared Silver, Shibing Yang, Bhabita Mayer, Steven W Yancey, and Robert H Chan are employees of GSK and own stocks/shares.

Author contributions: SWY, RHC, BM, SGS, JS, ARS, and LB were involved in the conception or design of this manuscript. All authors contributed to the analysis or interpretation of data, drafted the work, or revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Funding Source: The SYNAPSE study discussed in this article was funded by GlaxoSmithKline (GSK ID: 205687)

Trial Registration: Not applicable

Key Words: chronic rhinosinusitis with nasal polyps, Phase III trials, disease severity, baseline characteristics, biologic agents, dupilumab, omalizumab, mepolizumab

Abbreviations/Acronyms: AERD, aspirin-exacerbated respiratory disease; CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computed tomography;

HRQoL, health-related quality of life; IgE, immunoglobulin E; IgG, immunoglobulin G; IL, interleukin; INCS, intranasal corticosteroids; LS, least squares; MCID, minimal clinically important difference; NCS, nasal congestion score; NIAID, National Institute of Allergy and Infectious Diseases; NP, nasal polyps; NPS, nasal polyps score; NR, not reported; Q2W, every 2 weeks; Q4W, every 4 weeks; SCS, systemic corticosteroids; SD, standard deviation; SE, standard error; SNOT-22, Sino-Nasal Outcome Test-22; SoC, standard of care; T2, type 2; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog scale.

Word Count: 3,379

Figures: 2

Tables: 4

Abstract

Objective: Treatment for chronic rhinosinusitis with nasal polyps (CRSwNP) generally involves intranasal corticosteroids (INCS) and saline irrigation, followed by short courses of systemic corticosteroids (SCS) and/or surgery with postoperative medical therapy for patients who do not respond to INCS. However, both SCS use and surgery are associated with a range of adverse effects and/or complications, have a high recurrence rate and are unsuitable for some patients. Biologics targeting the underlying pathophysiology are promising treatment alternatives for these patients. Dupilumab, omalizumab, and mepolizumab are approved for use in patients with severe, uncontrolled CRSwNP. However, the lack of a consistent definition of severe CRSwNP makes the decision to initiate biologic treatment particularly complex. Furthermore, the position of each biologic in the overall management of CRSwNP remains to be clarified.

Data Sources: Publications reporting results of Phase III trials of dupilumab, omalizumab, mepolizumab, and benralizumab in the treatment of CRSwNP.

Study Selection: Randomized controlled Phase III trials of biologics approved for CRSwNP.

Results: These trials all utilized different enrollment criteria. We discuss the complexities of assessing CRSwNP disease severity and highlight how these impact comparisons of the populations and outcomes of the Phase III biologic trials.

Conclusion: To position biologic agents appropriately within the existing CRSwNP treatment paradigm, future trials will need to include comparable patient populations and standardized outcome measures. Such trials will help to ensure that biologic treatment is targeted appropriately to support optimal clinical outcomes.

Key Messages

- Phase III clinical trials of biologics for chronic rhinosinusitis with nasal polyps (CRSwNP) have utilized different enrollment criteria.
- The clinical assessment and characterization of CRSwNP is challenging and differences in treatment populations make it difficult to compare outcomes of the Phase III biologic trials.
- Ideally, future studies need to utilize head-to-head comparisons, or, in the absence of this approach, will need to include comparable patient populations and standardized outcome measures.

Introduction

Management of chronic rhinosinusitis with nasal polyps (CRSwNP) is often challenging and frequently involves INCS, SCS, and sinus surgery.¹⁻³ Patients with severe or refractory disease following surgery, who require repeat courses of systemic corticosteroids (SCS), and/or have comorbid inflammatory conditions such as asthma have the highest unmet clinical need and are good candidates for biologic therapies.⁴⁻⁶ Several biologics, including dupilumab, omalizumab and mepolizumab, have been approved in the US and Europe and offer treatment benefit for these refractory patients.⁷⁻¹² Each of these biologics has proven to be effective in patients with CRSwNP and together they represent important therapeutic options for current clinical practice. What is not yet known is how each biologic can be utilized optimally for individual patients. Importantly, study populations, designs and outcome measures among Phase III trials of biologics for CRSwNP varied and confound the indirect comparison of efficacy of each therapy across independent randomized controlled trials (RCTs).

Biologics for the treatment of CRSwNP

In June 2019, dupilumab, a fully human monoclonal antibody inhibitor of IL-4 and IL-13 signaling, was the first biologic agent to be approved by the FDA for CRSwNP following demonstration of efficacy and safety in the Phase III SINUS-24 (NCT02912468) and SINUS-52 (NCT02898454) trials.¹² It is indicated for add-on maintenance treatment in patients whose CRSwNP is inadequately controlled on standard of care (SoC) therapy, with other approved indications including atopic dermatitis and asthma.¹⁰ In December 2020, the indication for omalizumab, an anti-IgE agent already approved for asthma and chronic idiopathic urticaria, was expanded to include add-on maintenance treatment for NP in adults with inadequate response to INCS, based on the results of the Phase III POLYP 1 (NCT03280550) and POLYP 2 (NCT03280537) trials.¹¹ Mepolizumab, a humanized monoclonal antibody that binds to and inactivates IL-5, is approved for the treatment of severe eosinophilic asthma, eosinophilic granulomatosis with polyangiitis, and hypereosinophilic syndrome in multiple regions worldwide.⁷⁻⁹ Additionally, mepolizumab was approved in 2021 in the USA and Europe for add-on maintenance treatment of adult patients with CRSwNP with inadequate response to nasal corticosteroids, following positive data from the Phase III SYNAPSE (NCT03085797) trial.^{7, 8} Benralizumab, a humanized monoclonal antibody directed against the alpha subunit of the IL-5 receptor, has demonstrated efficacy compared to placebo among patients with CRSwNP in the Phase III OSTRO (NCT03401229) trial, but is not approved for use in patients with CRSwNP.¹³ All of these biologic agents have been shown to reduce NP size and improve clinical outcomes significantly more than standard medical therapy alone.^{2, 4, 13-16}

The 2019 National Institute of Allergy and Infectious Diseases (NIAID) workshop

Defining the role of biologics in the overall management of CRSwNP requires consideration of multiple factors beyond efficacy and safety, including disease severity, the risk of recurrence, patient preferences, and cost-effectiveness.⁴ In 2019, the NIAID convened a workshop to describe the current state of CRSwNP management and provide recommendations to optimize future trial designs to help further define the position of biologics within the clinical management framework.³ The report highlighted the broad and varied choice of tools available to assess treatment outcomes in CRSwNP and considered the strengths and limitations of those used in the Phase III trials of biologics in CRSwNP, noting that trials should include outcomes that reflect aspects of CRSwNP that are important to patients, such as impact on daily life.¹⁷ It also emphasized the importance of accurately defining patient baseline characteristics in order to identify predictors of response and compare data across trials.³ These discussions are particularly relevant for clinicians who wish to appraise the benefits of alternative biologic agents across trial populations.

This article discusses the key issues associated with the clinical assessment and characterization of CRSwNP in clinical trials and how these impact on trial design, highlighting how differing trial populations in the six large, pivotal Phase III trials of biologics for CRSwNP confound evaluation of the comparative benefit of biologics across clinical trials in CRSwNP.

Clinical Assessment and Characterization of CRSwNP

Clinical Assessment and characterization of CRSwNP is complex, and several outcome measures, all with associated advantages and drawbacks, may be utilized.¹⁸ Those used in the six pivotal Phase III trials of CRSwNP biologics are shown in **Table 1**. Clinician-rated measures (eg, nasal polyp score [NPS] and Lund-Mackay computed tomography [CT] scores¹⁹) can

provide useful information on the size and stage of polyps (**Table 1**). However, there is often a lack of correlation between polyp size/stage and symptoms experienced by the patient.^{3, 20}

Disease-specific, patient-important outcome measures including patient-reported measures (eg, the 22-item Sino-Nasal Outcomes Test [SNOT-22]²¹ and symptom visual analog scales [VAS] or verbal response symptom scales) and the University of Pennsylvania Smell Identification Test (UPSIT) provide a critical, clinically focused supplement to clinician-rated evaluations of CRSwNP (**Table 1**) as they can characterize the severity of symptoms, the wider health and psychological impact on the individual at a particular time point (eg, at baseline), and any clinically relevant or meaningful changes in disease status over time (eg, following intervention).^{3, 21}

SCS use and the decision to opt for NP surgery may also be used as measures of disease stage given their role in the management of difficult-to-control CRSwNP.^{2, 3} Surgical history is likely to influence scores on other disease measures, particularly loss of sense of smell, which is often seen in patients who have had multiple surgeries.^{22, 23} In addition, patients undergoing revision surgery were found to have higher Lund-Mackay scores and greater bone remodeling compared with patients with NP without prior surgery.²⁴ Furthermore, the extent of post-operative fibrosis has been shown to correlate with pre-operative endoscopic stage.²⁵ In turn, increasing number of prior surgeries and the presence of fibrosis and/or mucosal remodeling have both been associated with poor clinical outcomes in response to surgical treatment^{23, 26-28} and, as such, polyp recurrence (compared with surgically naïve CRSwNP) may present a distinct variable that potentially influences response to treatment. Crucially, the decision to proceed to surgery and/or prescribe further courses of SCS for CRSwNP may be influenced by physician and patient

preference, the presence of comorbidities, or differing treatment algorithms in different geographical locations, rather than treatment failure alone.¹⁴

Phase III Biologic Trials in CRSwNP: Considerations for Disease Characterization

While efficacy versus placebo has been clearly demonstrated for the three FDA-approved biologics and benralizumab, the large, pivotal Phase III trials of these biologics in CRSwNP provide a pertinent example of the complexities of CRSwNP characterization and assessing the response to treatment.

Eligibility criteria and baseline characteristics

The target population for the six pivotal Phase III biologic trials (SINUS-24, SINUS-52, POLYP 1, POLYP 2, SYNAPSE, OSTRO) was severe bilateral CRSwNP; however, details of patient eligibility criteria and the methods used to assess baseline disease characteristics varied between trials. While all eligible patients were required to have an endoscopic nasal polyp score (NPS) ≥ 5 (scale 0–8), with a minimum score of 2 in each nostril, other eligibility criteria used to quantify disease-related symptom severity at trial entry varied across trials, as did requirements relating to prior surgery and corticosteroid use (**Table 2**).

As expected, the differences in eligibility criteria led to differing baseline populations across the trials (**Table 3** and **Figure 1**).¹³⁻¹⁶ The prevalence of comorbid asthma, which is associated with greater severity of disease, worse symptoms, poorer quality of life,⁵ higher risk of revision surgery and severe T2 inflammation,⁴ was higher in SYNAPSE than in the SINUS, POLYP, and OSTRO trials. Blood eosinophil counts were also higher in SINUS, SYNAPSE and OSTRO compared with POLYP.¹⁴⁻¹⁶ Given the association between aspirin-exacerbated respiratory disease (AERD)/asthma/elevated eosinophil counts and T2 inflammation,²⁹⁻³¹ it may also be the

case that higher proportions of patients with these characteristics increase the likelihood of response to T2-targeting biologic therapies. These baseline discrepancies in disease characteristics complicate comparisons between the trial outcomes.

Measures used to characterize CRSwNP baseline disease and treatment outcomes

CRSwNP characteristics and symptoms were assessed at screening/baseline and throughout the Phase III biologic trials using a broad range of measures.

Clinician-rated measures

All of the Phase III trials incorporated the NPS (**Table 1**) to determine patient eligibility (requiring an endoscopic NPS $\geq 5/8$ for inclusion) and measure treatment efficacy (as change from baseline) as a co-primary endpoint, with endoscopies evaluated by blinded central review.¹³⁻¹⁶ Mean baseline NPS ranged from 5.4–5.6 in SYNAPSE, 5.6–6.3 in SINUS, 6.1–6.2 in OSTRO, and 6.1–6.4 in POLYP, with higher scores indicating larger polyp size (**Figure 1** and **Table 3**).

Baseline Lund-Mackay scores and changes from baseline as an endpoint were only reported in the SINUS and OSTRO trials,^{13, 15} and CT scans were not used in SYNAPSE due to concerns over their limitations, including their inability to accurately identify and quantify nasal polyposis.¹⁴ The SINUS, POLYP, and SYNAPSE trials reported baseline scores on the UPSIT and change from baseline in UPSIT was reported as an outcome in the SINUS and SYNAPSE trials.^{14, 15} Differences in UPSIT score at baseline between the SINUS, POLYP, and SYNAPSE trials were fairly small (**Figure 1** and **Table 3**).

Patient-reported outcome measures

Patient-reported outcome measures were also used across all of the Phase III trials. While baseline differences in total SNOT-22 score were seen between trials, with the highest scores seen in OSTRO, SYNAPSE and POLYP (**Figure 1** and **Table 3**), it is not clear how these differences may reflect differences in overall CRSwNP severity, particularly as SNOT-22 scores include social/emotional measures that may not be directly related to CRSwNP.³² Nonetheless, domains of the SNOT-22, while not unique to impacts of CRSwNP, are a helpful indicator of overall burden of disease experienced by the patient.^{33, 34} Baseline SNOT-22 scores are also likely to be impacted by interventions received in the time period before screening, such as prior surgeries.²⁶

VAS measures were also used to assess symptom severity in both the SINUS trials and SYNAPSE, although the approach to symptom assessment varied substantially across the six trials. The SINUS trials incorporated a 10-point VAS (with >7 indicating severe disease) assessment at baseline and during the trial to assess rhinosinusitis disease severity but used a 4-point categorical (Likert from 0 [not at all] to 3 [severe]) scale to record symptom scores for nasal congestion or obstruction, loss of smell and rhinorrhea, which formed the composite total symptom score.¹⁵ The SYNAPSE trial also used a 10-point continuous VAS (based on a score of 0–100 divided by 10, with higher scores indicating greater severity), to quantify daily symptoms of nasal obstruction, nasal discharge, throat mucus, loss of smell, facial pain, and overall symptoms via an eDiary, which allowed greater granularity in the symptom scores compared with smaller scales.¹⁴ The POLYP trials took a slightly different approach, using an eDiary to record nasal congestion, sense of smell, postnasal drip, and runny nose on a 4-point scale from 0 (not at all) to 3 (severe), with the individual scores summed to provide a total nasal symptom

score of 0–12.¹⁶ The differences in the measures employed makes it difficult to evaluate comparative symptom severity across the trial populations.

Prior SCS use and surgery

A large proportion of patients in SINUS-52 (~80%) had received prior SCS compared with the other trials (**Figure 1** and **Table 3**), but in both SINUS trials this measure was reported for the preceding 2 years, rather than for the previous year only, and prior SCS use (or surgery) during this time was an eligibility requirement (unlike in the POLYP or SYNAPSE trials).¹⁴⁻¹⁶ The proportion of patients with prior SCS use in OSTRO was also relatively high (72–78%). This may reflect the unspecified time period over which history of SCS use (and history of surgery) was reported in OSTRO, in addition to the eligibility requirement for prior SCS use or surgery.¹³ Nevertheless, the high use of SCS in the SINUS and OSTRO trials could be an indicator of the persistency of disease. Notably, all patients in SYNAPSE were required to have had ≥ 1 prior sinonasal surgery during the past 10 years, whereas prior surgery was not an independent eligibility criterion in the SINUS, POLYP, and OSTRO trials.¹³⁻¹⁶ Consequently, a substantial proportion of patients in these trials did not have a history of surgery (26–42%, 37–46%, and 27–27% across treatment arms, respectively).¹³⁻¹⁶ As surgery is typically reserved for patients who have failed to improve on standard therapies such as INCS or SCS and may be associated with fibrosis and remodeling in the mucosa,¹⁻³ the higher proportion of patients with prior surgery in SYNAPSE compared with the other trials may indicate that the SYNAPSE population included more patients with severe and treatment-refractory disease than the other trials. This is supported not only by the need for all patients to have had prior surgery but also by the proportion of patients with ≥ 3 prior surgeries at baseline (30% overall in SYNAPSE, compared with 15% in the SINUS trials; this was not reported in POLYP or OSTRO, but in POLYP 28% had ≥ 2 prior

surgeries [compared with 54% in SYNAPSE]).¹⁴ Time since last surgery is also an important parameter as it reflects severity of disease and has been shown to be a good predictor of future surgical need.³⁵ In SINUS, there was a mean of 7.2 years between prior surgery and study start,¹⁵ and a history of several versus one past surgeries was associated with reduced time since most recent surgery (mean [SD]: 7.16 [6.44] vs 8.12 [7.40] years) and a greater prevalence of comorbid asthma/AERD (70.2% vs 67.3%).³⁵ In POLYP, 72% of patients who had had a prior surgery had received it >5 years prior to the study.¹⁶ In SYNAPSE, all patients were required to have had prior surgery within 10 years of trial initiation but there was a mean of 3.8–4.2 years between prior surgeries and study start.¹⁴ In OSTRO, there was a mean of 6.9 years since prior surgery.¹³ Finally, the type (and quality) of prior surgery was not strictly defined in any of the Phase III trials.¹³⁻¹⁶

Need for additional interventions and treatment outcomes in SoC plus placebo arms

The need for additional interventions for patients in the SoC plus placebo arms during Phase III biologic trials can give further insights into the severity of symptoms in the CRSwNP populations. Surgery and SCS use outcomes are summarized in **Table 4**.

In the SINUS trials, a prespecified pooled analysis showed that 34% (n=97) of patients in the SoC plus placebo arm required rescue with SCS or nasal polyp surgery (8% [n=22]; actual or planned) during the treatment period.¹⁵ In the POLYP trials, a pooled analysis showed that the percentage of patients requiring rescue therapy with SCS for >3 consecutive days by Week 24 was very low (6% [n=8]) with SoC plus placebo; no sinus surgeries or polypectomies were recorded.¹⁶ The proportion of patients with nasal surgery until week 52 (time-to-first nasal surgery) was a key secondary endpoint of SYNAPSE, and the proportion of patients requiring SCS for NP until week 52 was an additional secondary endpoint. A total of 23% (n=46) and 37%

(n=74) of patients in the SoC plus placebo arm required nasal surgery and SCS, respectively, during the study. In OSTRO, the proportion of patients with NP surgery (time-to-first NP surgery) and the proportion of patients with NP surgery and/or SCS use (time-to-first NP surgery and/or SCS use) were both key secondary endpoints. During the study, 33% of patients in the SoC plus placebo arm required SCS and 18% (n=37) required nasal surgery.¹³ Notably, 15% of patients in the SoC plus placebo arm in SYNAPSE had ≥ 2 courses of SCS and endpoint measurement continued after SCS use,¹⁴ whereas in the other trials endpoint measurement stopped after one (SINUS and OSTRO) or two (POLYP) courses of SCS.^{15, 16} However, there were no defined criteria and therefore no standardization across trials as to how or why SCS were initiated, the SCS dose and duration prescribed, or indeed how the decision to perform surgery was made.¹³⁻¹⁶ Moreover, study duration (24 weeks for SINUS-24, POLYP 1, and POLYP 2, 52 weeks for SINUS-52 and SYNAPSE, and 56 weeks for OSTRO) is likely to have impacted whether or not patients were offered surgery or SCS treatment.

Systematic reviews and indirect treatment comparisons

A recent systematic review and network meta-analysis attempted to compare the efficacy of mAbs for CRSwNP, including dupilumab, omalizumab, mepolizumab and benralizumab, using data from all published controlled trials meeting the inclusion criteria.³⁶ Whilst this analysis supported the numerous benefits in patient-important outcome measures seen in Phase III studies of these biologics and is a valuable contribution to the field, this and other similar studies, remain limited by the considerations we have set out when comparing across clinical trials. Indeed, while the meta-analysis included random-effects models and supplemental subgroup analyses, the similar but not identical nature of the study populations remains a limitation as noted in the discussion of the systematic review and network meta-analysis.³⁶ Another recent

systematic review and indirect treatment comparison compared the effect sizes of treatment with dupilumab, omalizumab and mepolizumab in Phase II and III trials, and similarly concluded that results support treatment benefits of all three treatments.³⁷ However the authors highlighted the limitations of such an indirect comparison, including the heterogeneity in inclusion criteria, treatment period, dosage and outcome measures.³⁷

Conclusion

Summary and recommendations for future clinical trials with biologics

Accurate and clinically meaningful characterization of baseline CRSwNP is key to identifying patients in most need of biologic treatments.² The differences in enrollment criteria and therefore patient populations, as well as differences in study design, the limitations of the outcome measures used and how such measures may be influenced by patient population characteristics should be carefully considered in the interpretation of efficacy data from different clinical trials (**Figure 2**).

SINUS, POLYP, SYNAPSE, and OSTRO all enrolled patients with severe CRSwNP and an NPS score ≥ 5 , but eligibility criteria were not directly comparable, particularly with regard to symptom measures. In addition, the rate of surgery and SCS use during the trials differed between the SoC plus placebo arms of SINUS, POLYP, SYNAPSE, and OSTRO suggesting that the underlying cohorts did not have comparable symptom burden (**Table 4**).

As dupilumab, omalizumab, mepolizumab, and benralizumab all target facets of T2 inflammation and have all shown efficacy compared with SoC in Phase III trials,¹³⁻¹⁶ any differentiation in efficacy between biologic agents is likely to be small and difficult to identify. To further define the position of biologic agents within the existing CRSwNP treatment paradigm, head-to-head trials comparing the efficacy of the available biologics would be

beneficial.^{2, 37} As highlighted in the NIAID guidance, the establishment of comparative efficacy between biologic therapies in CRSwNP may be best examined in trials with cross-over or adaptive designs.³ In a cross-over trial design patients would sequentially receive two or more biologics allowing response to be directly compared. This may be useful in determining the best treatment for a given patient endophenotype but would be limited by the length of time required and the need for accurate biomarkers.³⁸ Adaptive design can improve on a standard crossover trial design.³⁹ As per the 2019 FDA guidance,⁴⁰ an adaptive trial allows for prospectively planned modifications to one or more aspects of the design based on accumulating data. These data may include both baseline and outcome data and in the context of a sequential, multiple assignment, randomized trial (SMART) design would allow the possibility of multi-arm trials in which treatment could be tailored to individuals based on the emerging data on biomarkers or disease profile.³ Such an approach would allow investigation of the response to biologic treatment in a range of endophenotypes and, as such, would more accurately reflect the intended use of biologics in clinical practice² than the comparatively rigid design of the current Phase III CRSwNP biologic trials. We have highlighted the lack of consistency across Phase III trials in eligibility criteria and clinical outcome measures. In the future, the use of validated biomarkers to facilitate clinical endotyping may help to identify patients most likely to respond to a particular biologic.^{2, 38, 41} This has been essential in the positioning of biologics for severe asthma and is an important area of future research that will help to determine the relative position of individual biologics in CRSwNP management.^{38, 42} Nevertheless, these FDA-approved agents have demonstrated efficacy across a number of patient-important endpoints and should therefore be readily used in eligible patients to optimize clinical outcomes.

Acknowledgments:

Editorial support was provided by Alice Rees, PhD, at Fishawack Indicia Ltd, UK, part of Fishawack Health, under the direction of the authors, and was funded by GlaxoSmithKline (GSK).

References

1. Akdis CA, Bachert C, Cingi C, et al. Endotypes and phenotypes of chronic rhinosinusitis: A PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. *Journal of Allergy and Clinical Immunology*. 2013;131:1479-1490.
2. Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology*. 2020;58:1-464.
3. Naclerio R, Baroody F, Bachert C, et al. Clinical Research Needs for the Management of Chronic Rhinosinusitis with Nasal Polyps in the New Era of Biologics: A National Institute of Allergy and Infectious Diseases Workshop. *The Journal of Allergy and Clinical Immunology: In Practice*. 2020;8:1532-1549.e1531.
4. Patel GB, Peters AT. The Role of Biologics in Chronic Rhinosinusitis With Nasal Polyps. *Ear, Nose & Throat Journal*. 2021;100:44-47.
5. Bachert C, Han JK, Wagenmann M, et al. EUFOREA expert board meeting on uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP) and biologics: Definitions and management. *J Allergy Clin Immunol*. 2021;147:29-36.
6. Agache I, Song Y, Alonso-Coello P, et al. Efficacy and safety of treatment with biologics for severe chronic rhinosinusitis with nasal polyps: A systematic review for the EAACI guidelines. *Allergy*. 2021;76:2337-2353.
7. EMA. Nucala (mepolizumab) summary of product characteristics 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/nucala-epar-product-information_en.pdf. Accessed December, 2021.

8. GlaxoSmithKline. NUCALA (mepolizumab) prescribing information. Available at:
https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL-IFU-COMBINED.PDF. Accessed August, 2021.
9. GlaxoSmithKline. Nucala (mepolizumab) prescribing information, Japan. Available at:
<https://gskpro.com/ja-jp/products-info/nucala/index/>. Accessed July, 2021.
10. Regeneron. Dupixent (dupilumab) prescribing information. Available at:
https://www.regeneron.com/downloads/dupixent_fpi.pdf. Accessed July, 2021.
11. Roche. FDA approves Xolair (omalizumab) for adults with nasal polyps. Available at:
<https://www.roche.com/investors/updates/inv-update-2020-12-01b.htm>. Accessed July 21, 2021.
12. Sanofi. FDA approves Dupixent (dupilumab) for chronic rhinosinusitis with nasal polyposis. Available at: <https://www.sanofi.com/-/media/Project/One-Sanofi-Web/Websites/Global/Sanofi-COM/Home/media-room/press-releases/2019/2019-06-26-19-30-00-1874771-en.pdf>. Accessed July 21, 2021.
13. Bachert C, Han JK, Desrosiers MY, et al. Efficacy and safety of benralizumab in chronic rhinosinusitis with nasal polyps: A randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2021;doi.org/10.1016/j.jaci.2021.08.030.
14. Han JK, Bachert C, Fokkens W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Respiratory medicine*. 2021;doi.org/10.1016/s2213-2600(21)00097-7.
15. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet (London, England)*. 2019;394:1638-1650.
16. Gevaert P, Omachi TA, Corren J, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *J Allergy Clin Immunol*. 2020;146:595-605.
17. Vennik J, Eyles C, Thomas M, et al. Chronic rhinosinusitis: a qualitative study of patient views and experiences of current management in primary and secondary care. *BMJ open*. 2019;9:e022644.
18. Hopkins C, Lee SE, Klimek L, et al. Clinical Assessment of Chronic Rhinosinusitis. *J Allergy Clin Immunol Pract*. 2022;doi.org/10.1016/j.jaip.2022.02.008.

19. Lund VJ, Mackay IS. Staging in rhinosinusitis. *Rhinology*. 1993;31:183-184.
20. Wabnitz DA, Nair S, Wormald PJ. Correlation between preoperative symptom scores, quality-of-life questionnaires, and staging with computed tomography in patients with chronic rhinosinusitis. *Am J Rhinol*. 2005;19:91-96.
21. Toma S, Hopkins C. Stratification of SNOT-22 scores into mild, moderate or severe and relationship with other subjective instruments. *Rhinology*. 2016;54:129-133.
22. Nguyen DT, Bey A, Arous F, et al. Can surgeons predict the olfactory outcomes after endoscopic surgery for nasal polyposis? *Laryngoscope*. 2015;125:1535-1540.
23. Seys SF, De Bont S, Fokkens WJ, et al. Real-life assessment of chronic rhinosinusitis patients using mobile technology: The mySinusitisCoach project by EUFOREA. *Allergy*. 2020;75:2867-2878.
24. Cho SH, Shin KS, Lee YS, et al. Impact of chronic rhinosinusitis and endoscopic sinus surgery on bone remodeling of the paranasal sinuses. *Am J Rhinol*. 2008;22:537-541.
25. Ragab A, El-Rasheedy AL, Samaka RM, et al. Assessment of fibroproliferative healing after functional endoscopic sinus surgery. *Menoufia Med J*. 2014;27:16-22.
26. Marino MJ, Garcia JO, Zarka M, et al. A structured histopathology-based analysis of surgical outcomes in chronic rhinosinusitis with and without nasal polyps. *Laryngoscope Investig Otolaryngol*. 2019;4:497-503.
27. Do TQ, Barham HP, Earls P, et al. Clinical implications of mucosal remodeling from chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2016;6:835-840.
28. Wang F, Yang Y, Wu Q, et al. Histopathologic analysis in chronic rhinosinusitis: Impact on quality of life outcomes. *Am J Otolaryngol*. 2019;40:423-426.
29. Bachert C, Gevaert P, Holtappels G, et al. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. *J Allergy Clin Immunol*. 2001;107:607-614.
30. Stevens WW, Peters AT, Tan BK, et al. Associations Between Inflammatory Endotypes and Clinical Presentations in Chronic Rhinosinusitis. *J Allergy Clin Immunol Pract*. 2019;7:2812-2820 e2813.
31. Tomassen P, Vandeplas G, Van Zele T, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol*. 2016;137:1449-1456 e1444.

32. Hopkins C, Gillett S, Slack R, et al. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol*. 2009;34:447-454.
33. Phillips KM, Hoehle LP, Caradonna DS, et al. Minimal clinically important difference for the 22-item Sinonasal Outcome Test in medically managed patients with chronic rhinosinusitis. *Clin Otolaryngol*. 2018;43:1328-1334.
34. Phillips KM, Hoehle LP, Caradonna DS, et al. Determinants of noticeable symptom improvement despite sub-MCID change in SNOT-22 score after treatment for chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2019;9:508-513.
35. Hopkins C, Wagenmann M, Bachert C, et al. Efficacy of dupilumab in patients with a history of prior sinus surgery for chronic rhinosinusitis with nasal polyps. *Int Forum Allergy Rhinol*. 2021;11:1087-1101.
36. Oykhman P, Paramo FA, Bousquet J, et al. Comparative efficacy and safety of monoclonal antibodies and aspirin desensitization for chronic rhinosinusitis with nasal polyposis: A systematic review and network meta-analysis. *J Allergy Clin Immunol*. 2021;doi.org/10.1016/j.jaci.2021.09.009.
37. Hellings PW, Verhoeven E, Fokkens WJ. State-of-the-art overview on biological treatment for CRSwNP. *Rhinology*. 2021;59:151-163.
38. Workman AD, Kohanski MA, Cohen NA. Biomarkers in Chronic Rhinosinusitis with Nasal Polyps. *Immunology and allergy clinics of North America*. 2018;38:679-692.
39. Pallmann P, Bedding AW, Choodari-Oskoei B, et al. Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Med*. 2018;16:29.
40. FDA. Adaptive designs for clinical trials of drugs and biologics: Guidance for industry. 2019. Available at: <https://www.fda.gov/media/78495/download>. Accessed July, 2021.
41. Orlandi RR, Kingdom TT, Smith TL, et al. International consensus statement on allergy and rhinology: rhinosinusitis 2021. *Int Forum Allergy Rhinol*. 2021;11:213-739.
42. Yancey SW, Keene ON, Albers FC, et al. Biomarkers for severe eosinophilic asthma. *Journal of Allergy and Clinical Immunology*. 2017;140:1509-1518.
43. Lou H, Meng Y, Piao Y, et al. Predictive significance of tissue eosinophilia for nasal polyp recurrence in the Chinese population. *Am J Rhinol Allergy*. 2015;29:350-356.

44. Prazma CM, Bel EH, Price RG, et al. Oral corticosteroid dose changes and impact on peripheral blood eosinophil counts in patients with severe eosinophilic asthma: a post hoc analysis. *Respir Res.* 2019;20:83.
45. Doty RL, Frye RE, Agrawal U. Internal consistency reliability of the fractionated and whole University of Pennsylvania Smell Identification Test. *Percept Psychophys.* 1989;45:381-384.
46. Washington University School of Medicine. Sino-nasal Outcome Test (SNOT-22). Available at: <https://www.canvasc.ca/pdf/SNOT22.pdf>. Accessed July 21, 2021.
47. Tabberer M, Trigg A, Busse W, et al. Mepolizumab reduces disease symptoms for Patients with Chronic Rhinosinusitis with Nasal Polyps: Data from the SYNAPSE study. *Journal of Allergy and Clinical Immunology.* 2021;147:AB126.

Figure Legend

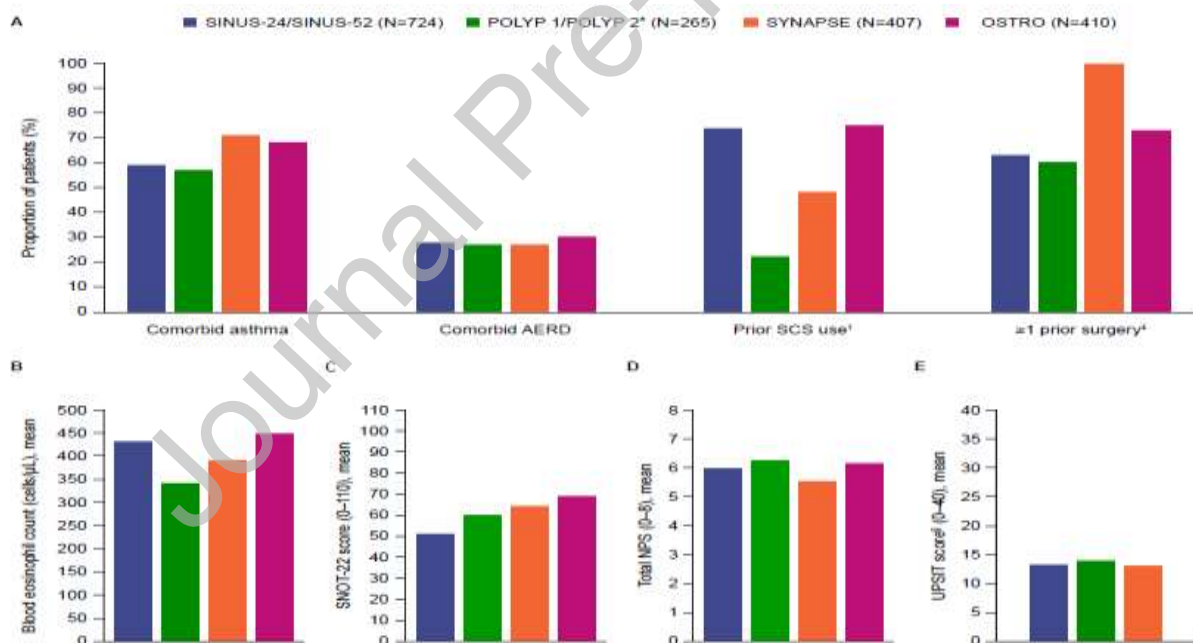


Figure 1. Selected comorbidities, baseline treatment history and baseline disease characteristics among patients in the SINUS, POLYP, SYNAPSE, and OSTRO trials.

A. Proportion of patients with asthma, AERD, prior SCS use and ≥ 1 prior surgery; B. mean blood eosinophil count; C. mean SNOT-22 score; D. mean total NPS; E. mean UPSIT score.

Studies are not directly comparable due to differences in study design, patient populations (eligibility criteria).

*In B–E, POLYP 1/POLYP 2 data are presented as weighted means calculated from means of the individual treatment arms; [†]in the previous 12 months in POLYP 1/POLYP 2 and SYNAPSE and in the previous 24 months for SINUS-24/SINUS-52, period not specified in OSTRO; [‡]during the previous 10 years for SYNAPSE; [§]in SYNAPSE, UPSIT was evaluated at sites in UK, USA, and Canada only (n=108).

AERD, aspirin-exacerbated respiratory disease; CI, confidence interval; NPS, nasal polyp score; SCS, systemic corticosteroids; SD, standard deviation; SNOT-22, Sino-Nasal Outcome Test-22; UPSIT, University of Pennsylvania Smell Identification Test.

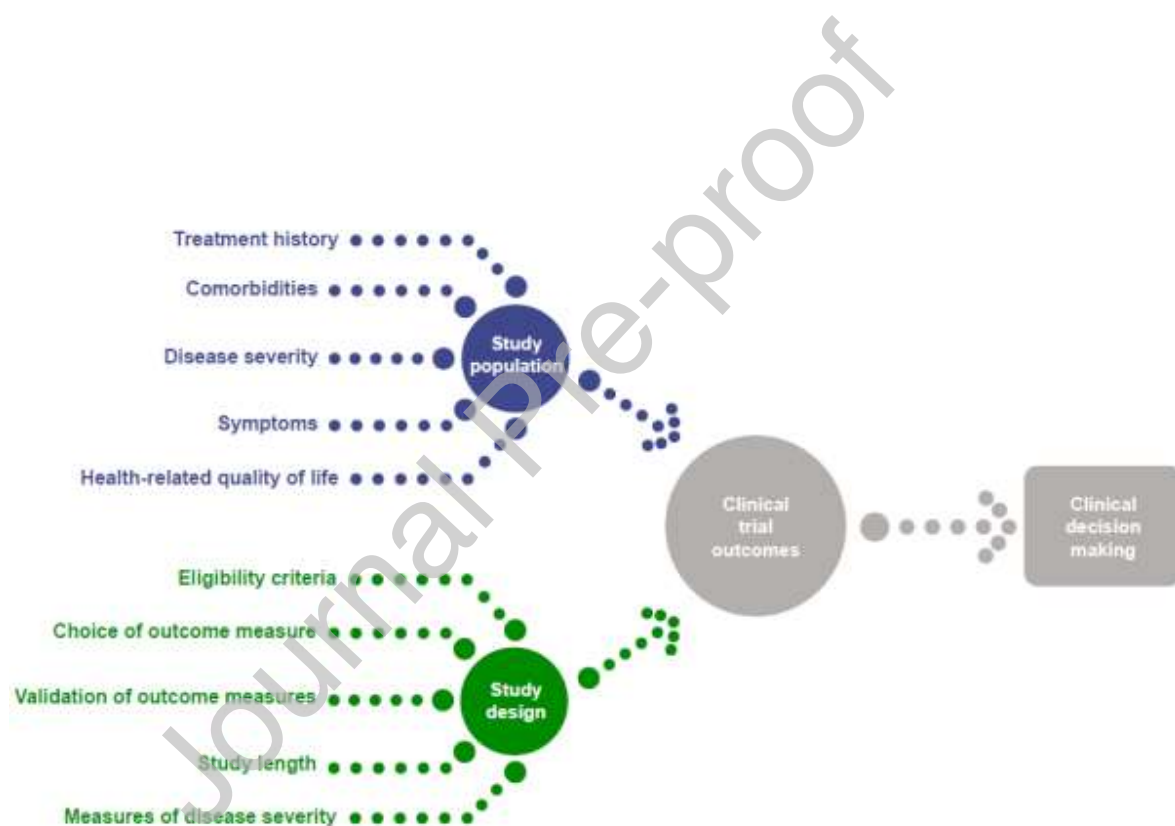


Figure 2. Considerations for clinical decision making in CRSwNP: factors influencing biologic trial outcomes.

CRSwNP, chronic rhinosinusitis with nasal polyp

Tables

Table 1. Tools for CRSwNP disease assessment used in the six Phase III biologic trials.

	Description	Advantages	Disadvantages
Clinician-rated measures			
NPS ^{3,18}	Sizes NP based on video recordings of the endoscopic evaluations made by trial investigators (scale 0–8)	• Useful measure of polyp size • Reproducible • Responsive to change	• Unavailable in clinics that do not routinely conduct endoscopy procedures • Categorical rather than continuous • Only measures 2-dimensional polyp size • No demonstrable correlation between NPS and symptoms • No validated MCID
Lund-Mackay CT score ^{3,18, 19}	Stages CRSwNP based on the degree of scarring, crusting, edema, polyps, and discharge using CT images (scale 0–24)	• Uses CT scans, which are the standard for assessing burden of disease in the paranasal sinuses • Semiquantitative	• Scores do not correlate well with symptoms • Widely thought to be challenging to meaningfully demonstrate improvement as an equivalent score is given to modest mucosal hypertrophy and severe near complete opacification of a given sinus • Exposure to ionizing radiation
Biomarkers			
Eosinophil count ^{3, 14}	A biomarker of T2 inflammation used to assess eligibility for and response to biologic treatment in severe asthma	• Can be measured in peripheral blood • Well-established biomarker in severe asthma • Elevated tissue levels shown to predict risk of recurrence after treatment⁴³	• Role in predicting response to biologic treatment in CRSwNP currently unclear • Tissue biopsy required to determine levels in the tissue • May be suppressed by recent OCS use⁴⁴
Measures of olfactory function			

UPSIT ^{3, 45}	A 40-item measure of loss of smell resulting from CRSwNP widely used in clinical trials and sometimes in clinical practice (scale 1–40)	• High consistency and reliability	• No validated MCID • Measures discrimination but not threshold • Unfamiliarity with odors may affect score
Patient-reported outcome measures			
SNOT-22 ^{18, 21, 32-34, 46}	Assesses health-related quality of life. Incorporates 22 items rated on a scale of 0–5 (0=no problem; 5=as bad as it can be), which cover symptoms relevant to CRSwNP (including nasal and ear/facial discomfort subdomains) and more general symptoms (sleep and emotional subdomains) (scale 0–22)	• Disease-specific • Validated • Correlates well with symptom severity (mild/moderate/severe) in patients with CRS • A MCID of 8.9 has been reported, though an MCID of 12 has been suggested for medically managed CRS • Used routinely in clinical practice for CRS	
VAS ^{3, 14}	Assesses symptom severity based on a 10 cm scale. Common in clinical trials of patients with CRSwNP (scale 0–10)	• Possible to use a 100-point scale (divided by 10 to give a score on the 10-point scale), which allows greater granularity than scales with a smaller range	• Not validated for use in CRSwNP • Preliminary MCIDs based on SYNPASE study data⁴⁷
Total symptom score ¹⁵	A composite severity score consisting of the sum of daily symptoms of nasal congestion, loss of smell, and anterior or posterior rhinorrhea	• A composite score encompassing a range of symptoms	• No validated MCID

CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computed tomography; MCID, minimal clinically important difference (ie, the change in score over time that is noticeable by the patient); NPS, Nasal Polyps Score; SNOT-22, Sino-Nasal Outcomes Test-22; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog scale.

Table 2. Inclusion criteria for the Phase III trials of biologic agents in patients with CRSwNP.

[illegible]

					posterior)				patients with prior surgery
Omalizumab ¹⁶	POLY P 1	18 – 75 years	Persistent, bilateral NP	Total NPS of ≥ 5 (≥ 2 per nostril) at screening and after 4 weeks of INCS (200 µg mometasone twice daily) during run-in	NCS of ≥ 2 (with additional symptoms of postnasal drip, runny nose, and/or loss of sense of smell) at screening. Weekly mean NCS ≥ 1 at randomization	≥ 4 weeks of INCS therapy prior to screening	None	None	Weight (30–50 kg) and serum IgG level (30–1500 IU/mL) permitting omalizumab dosing Impaired HRQoL Current and former smokers included
	POLY P 2								
					SNOT-22 score of ≥ 20 at screening and randomization				

Mepolizumab ¹⁴	SYNA PSE	≥18 years	Bilateral NP as diagnosed by endoscopy or historical CT scan	See surgery column	Nasal obstruction symptom VAS score of >5 ≥2 different symptoms for ≥12 weeks prior to screening (including nasal blockage, obstruction, and congestion, or nasal discharge), with ≥1 symptom of nasal discharge, facial pain or pressure, or reduction or loss of smell	INCS for ≥8 weeks prior to screening	≥1 nasal surgery* in the past 10 years Eligible for repeat nasal surgery (overall symptoms VAS score >7 and endoscopic NPS of ≥5 [≥2 per nostril])	None	Body weight ≥40 kg Current smokers and those who had smoked in the prior 6 months were excluded
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Benralizumab ¹³	OSTRO	18 – 75 years	Bilateral sinonasal polyposis	See surgery column	SNOT-22 score ≥ 30 at screening and randomization Biweekly mean NBS ≥ 2 at randomization	Stable INCS (with $\geq 70\%$ compliance) for ≥ 4 weeks prior to screening	Prior treatment with SCS or prior NP surgery Eligible for surgery (NPS ≥ 5 [≥ 2 per nostril], symptoms for ≥ 12 weeks prior to screening, patient-reported moderate-to-severe nasal blockage [score: $\geq 2/3$] for 2 weeks prior to screening)	Body weight ≥ 40 kg Evaluable diary data for ≥ 8 days in the 14 days prior to randomization
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*Nasal surgery was defined as any procedure involving instruments with resulting incision of the paranasal sinuses and removal of polyp tissue from the nasal cavity (polypectomy) and the sinuses. For the purposes of inclusion into this study any procedure involving instrumentation in the nasal cavity resulting in dilatation of the nasal passage such as balloon sinuplasty, insertion of coated stents or direct injection of corticosteroids or other medication without any removal of NP tissue was not accepted.

CT, computed tomography; HRQoL, health-related quality of life; IgG, immunoglobulin G; INCS, intranasal corticosteroids; NBS, nasal blockage score; NCS, nasal congestion score; NP, nasal polyps; NPS, nasal polyps score; SCS, systemic corticosteroids; SNOT-22, Sino-Nasal Outcome Test-22; VAS, visual analog scale.

Table 3. Baseline disease characteristics of patients with CRSwNP in Phase III trials of biologic agents.

	SINUS-24		SINUS-52			POLYP 1		POLYP 2		SYNAPSE		OSTRO	
	SoC + plac ebo (n=133)	SoC + dupilu mab Q2W (n=143)	SoC + plac ebo (n=153)	SoC + dupilu mab Q2W– Q4W (n=145)	SoC + dupilu mab Q2W (n=150)	SoC + plac ebo (n=66)	SoC + omaliz umab (n=72)	SoC + plac ebo (n=65)	SoC + omaliz umab (n=62)	SoC + plac ebo (n=201)	SoC + mepoliz umab (n=206)	SoC + plac ebo (n=203)	SoC + benraliz umab Q4W– Q8W (n=207)
Durat ion of NP diseas e, years, mean (SD)	10.8 (8.6)	11.4 (9.7)	10.9 (9.4)	10.7 (9.1)	11.3 (10.4)	NR	NR	NR	NR	11.5 (8.3)	11.4 (8.5)	NR	NR
Como rbid asthm a, n (%)	79 (59)	82 (57)	91 (59)	91 (63)	85 (57)	32 (49)	42 (58)	39 (60)	38 (61)	149 (74)	140 (68)	136 (67)	142 (69)
Como rbid AER D, n (%)	38 (29)	46 (32)	44 (29)	41 (28)	35 (23)	11 (17)	16 (22)	21 (32)	24 (39)	63 (31)	45 (22)	59 (29)	62 (30)
Blood eosin ophil count, cells/ μL, mean (SD)	440 (310)	440 (350)	450 (360)	400 (300)	450 (390)	359 (305.2)	334 (264.7)	357 (196.2)	311 (176.6)	400 (0.91)*	390 (0.88)*	446 (245.1)	448 (364.6)
Total NPS, mean (SD), scale 0–8	5.9 (1.3)	5.6 (1.2)	6.0 (1.2)	6.3 (1.2)	6.1 (1.2)	6.3 (0.9)	6.2 (1.0)	6.1 (0.9)	6.4 (0.9)	5.6 (1.4)	5.4 (1.2)	6.1 (1.1)	6.2 (1.2)
SNO T-22	50.9 (20.)	48.0 (20.2)	53.5 (21.)	51.9 (21.1)	50.2 (19.7)	60.5 (15.)	59.8 (19.7)	59.8 (18.)	59.2 (20.5)	64.4 (19.)	63.7 (17.6)		

total score, mean (SD), scale 0–110	2)		9)			3)		2)		0)		69.0 (19.0)	69.3 (19.8)
UPSI T score, mean (SD), scale 0–40[†]	14.4 (8.3)	14.7 (8.7)	13.8 (8.3)	13.6 (7.6)	13.5 (8.2)	13.9 (7.4)	12.8 (7.9)	13.1 (7.3)	12.8 (7.6)	13.4 (7.5)	13.0 (6.8)	NR	NR
Prior SCS use, n (%)[‡]	87 (65)	92 (64)	122 (80)	116 (80)	121 (81)	8 (12)	18 (25)	15 (23)	18 (29)	91 (45)	106 (51)	146 (72)	161 (78)
Number of previous NP surgeries, %[§]													
0 surgeries	34 (26) 	44 (31) 	65 (42) 	60 (41) 	62 (41) 	26 (39) **	33 (46) **	25 (38) **	23 (37) **	0	0	NR	NR
≥1 surgery^{††}	99 (74)	99 (69)	88 (58)	85 (59)	88 (59)	24 (36)	23 (32)	15 (23)	22 (36)	201 (100)	206 (100)	NR	NR
≥2 surgeries	NR	NR	NR	NR	NR	16 (24)	16 (22)	25 (39)	17 (27)	120 (60)	98 (48)	NR	NR
≥3 surgeries	29 (22)	33 (23)	18 (12)	9 (6)	22 (15)	NR	NR	NR	NR	73 (36)	51 (25)	NR	NR
Time since previous NP surgery, years													
>12 months–5 years, n (%)	NR	NR	NR	NR	NR	13 (33)	9 (23)	12 (30)	9 (24)	NR	NR	NR	NR
>5 years, n (%)	NR	NR	NR	NR	NR	27 (68)	30 (77)	28 (70)	28 (76)	NR	NR	NR	NR
Mean (SD)	5.5 (5.1)	5.9 (5.6)	8.8 (7.2)	8.4 (6.8)	7.5 (7.0)	NR	NR	NR	NR	3.8 (2.7)	4.2 (2.7)	7.0 (5.5)	6.9 (6.5)

*Geometric mean (coefficient of variation); [†]in SYNAPSE UPSIT was evaluated at sites in UK, USA, and Canada only (n=54 for both SoC plus placebo and mepolizumab); [‡]during previous 2 years in SINUS-24 and SINUS-52 and previous year in POLYP 1, POLYP 2, and SYNAPSE; [§]during the previous 10 years in SYNAPSE; ||remaining patients who were not in the ≥1 surgery

category; **remaining patients who were not in the 1 or ≥ 2 surgery category; $\dagger\dagger$ only 1 surgery in POLYP 1 and POLYP 2.

AERD, aspirin-exacerbated respiratory disease; CRSwNP, chronic rhinosinusitis with nasal polyps; NP, nasal polyps; NPS, nasal polyp score; NR, not reported; Q2W, every 2 weeks; Q4W, every 4 weeks; SCS, systemic corticosteroids; SD, standard deviation; SNOT-22, Sino-Nasal Outcome Test-22; SoC, standard of care; UPSIT, University of Pennsylvania Smell Identification Test.

Table 4. SCS, surgery, and other outcomes in SoC plus placebo arms of Phase III trials of biologic agents for CRSwNP.

		SINUS- 24	SINUS- 52	POLYP 1	POLYP 2	SYNAPSE	OSTRO
SCS and surgery outcomes							
Patients requiring rescue with SCS or nasal polyp surgery, n/N (%)	SoC + placebo	97/286 (34)		NR		NR	91/203 (45)
Patients requiring rescue with SCS, n/N (%)	SoC + placebo	88/286 (31)		8/129 (6)		74/201 (37)	(33)
Patients requiring rescue with nasal polyp surgery, n/N (%)	SoC + placebo	22/286 (8)		0/129 (0)		46/201 (23)	37/203 (18)
Other outcomes							
Change from baseline in total endoscopic	SoC + placebo	0.2 (0.2)*	0.2 (0.2)*	0.1 (0.2) [‡]	-0.3 (0.2) [‡]	-0.1 (1.5)*	0.2 (NR)*

NPS (scale 0–8)							
Change from baseline in nasal obstruction VAS score (scale 0–10)	SoC + placebo	NR	NR	NR	NR	-2.5 (3.2) [‡]	NR
Change from baseline in nasal congestion, nasal obstruction or nasal blockage score (scale 0–3)	SoC + placebo	-0.5 (0.1)*	-0.4 (0.1)*	-0.4 (0.1) [†]	-0.2 (0.1) [†]	NR	-0.4 (NR)*
Change from baseline in SNOT-22 total score (scale 0–110)	SoC + placebo	-9.3 (1.6)*	-8.9 (1.6)*	-8.6 (2.1) [†]	-6.6 (2.2) [†]	-15.7 (24.0) [‡]	-11.0
Change from baseline in UPSIT score (scale 0–40)	SoC + placebo	0.7 (0.7)*	-0.8 (0.7)*	0.6 (0.9) [†]	0.4 (0.8) [†]	0.4 (8.6) [‡]	NR

*LS mean (SE); [†]adjusted (for baseline covariates) mean (SE); [‡]mean (SD);

CRSwNP, chronic rhinosinusitis with nasal polyps; LS, least squares; NP, nasal polyps; NPS, nasal polyps score; NR, not reported; SCS, systemic corticosteroids; SD, standard deviation; SE, standard error; SNOT-22, Sino-Nasal Outcome Test-22; SoC, standard of care; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog scale.