

EPOS/EUFOREA update on indication and evaluation of Biologics in Chronic Rhinosinusitis with Nasal Polyps 2023*

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Rhinology **61:** **3**, 194 - 202, 2023

<https://doi.org/10.4193/Rhin22.489>

*Received for publication:

December 22, 2022

Accepted: March 6, 2023

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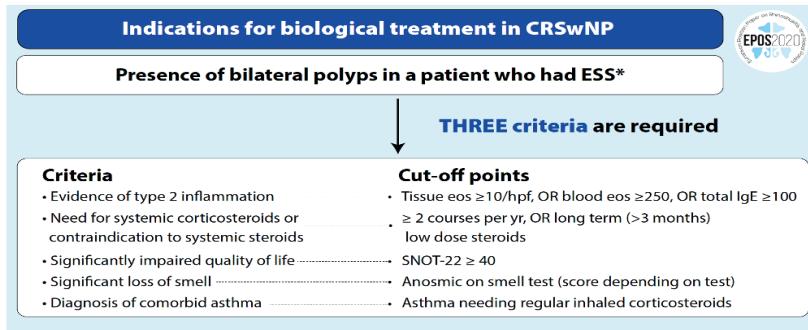
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Abstract

Severe chronic rhinosinusitis with nasal polyps (CRSwNP) is a debilitating disease with a significant impact on the quality of life (QoL). It is typically characterized by a type 2 inflammatory reaction and by comorbidities such as asthma, allergies and NSAID-Exacerbated Respiratory Disease (N-ERD). Here, the European Forum for Research and Education in Allergy and Airway diseases discusses practical guidelines for patients on biologic treatment. Criteria for the selection of patients who would benefit from biologics were updated. Guidelines are proposed concerning the monitoring of the drug effects that provide recognition of responders to the therapy and, subsequently, the decision about continuation, switching or discontinuation of a biologic. Furthermore, gaps in the current knowledge and unmet needs were discussed.

Key words: Chronic rhinosinusitis, nasal polyps, type 2 inflammation, biologics, indication, patient selection, biomarkers, therapeutic response

EPOS2020 criteria



CRS, chronic rhinosinusitis; CRSwNP: chronic rhinosinusitis with nasal polyps; ESS, endoscopic sinus surgery; hpf: high power field (x400); SNOT-22, sino-nasal outcome test-22.

EPOS/EUFOREA 2023 criteria

Criteria	Cut-off points
Evidence of type 2 inflammation	Tissue eos ≥10/hpf, OR blood eos ≥ 150 OR total IgE ≥100
Need for systemic corticosteroids or contraindication to systemic steroids	≥2 courses per Yr OR long term (> 3 months) low dose steroids
Significantly impaired quality of life	SNOT-22 ≥40
Significant loss of smell	Anosmic on smell test (score depending on test)
Diagnosis of comorbid asthma	In case of asthma: regular need for inhaled corticosteroids

* Exceptional circumstances excluded (e.g., not fit for surgery)

Figure 1. Adjustments in EPOS/EUFOREA criteria. The only change is the reduction of blood eosinophils to 150 cells/ μ l.

INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) is present in around 1-2% of the European population⁽¹⁾. It is often characterized by a long-term disease burden and poor quality of life (QoL). Therapy consists of long-term local corticosteroids and short periods of systemic corticosteroids and in severe patients repeated sino-nasal surgery^(1,2). Biological drugs for type 2 immune effectors such as IL-4, IL-13, IL-5 and IgE offer new therapeutic options in managing the patients with this challenging disease⁽³⁻⁹⁾. The European Position paper on Rhinosinusitis and Nasal Polyps, EPOS, is a long-standing initiative of the European Rhinologic Society in creating guidance in the management of patients with CRS. The latest version, EPOS2020, advised on the use of biologics in the treatment of CRSwNP⁽¹⁾. This update on indication and evaluation of biologics in CRSwNP is written in collaboration with the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA). EUFOREA is an international not-for-profit organization with the aim of preventing and improving the burden of chronic respiratory diseases⁽¹⁰⁾. Otorhinolaryngologists, allergists, and pneumologists working in leading EU research institutes are part of EUFOREA as well as patients of the EUFOREA Patient Advisory Board^(10,11). Representatives of the pharmaceutical industry producing biologic drugs were asked to contribute their knowledge but were not involved in any strategic discussions nor decisions on any criteria-related care pathway. The recommendations in this special report are based on the experiences of the experts and the current knowledge of the efficacy of biologics and evidence-based care pathways for the management of uncontrolled severe type 2 CRSwNP with or

without comorbidities^(1,12,13). The presence of internationally renowned otolaryngology, pulmonology, allergology, and immunology specialists have substantially added to the discussion and decisions. At the Brussels meeting in April 2022, on the first Global CRSwNP awareness day, various topics were discussed point by point until unanimity was reached. A draft of the document was subsequently written and submitted to 3 rounds of review by all authors. In each round of review, the changes made to the proposed algorithms were discussed and refined until they were approved unanimously.

The discussions focused on the following key topics:

- 1) finetuning of the criteria for the indication of biologics,
- 2) expected benefits of biologics,
- 3) duration of biologic care,
- 4) criteria to stop or switch to another biologic, and
- 5) gaps in the current knowledge about the topics and unmet needs were discussed.

1. Who is the right candidate for biologics?

The expert panel discussed the EPOS2020 criteria for biologics⁽¹⁾. EPOS2020 advises considering biologics in patients that are uncontrolled despite appropriate medical treatment and appropriate sinus surgery and fulfil 3 of 5 criteria (presence of type 2 inflammation, regular need for systemic corticosteroids, significant impact on QOL, loss of smell and comorbid asthma (Figure 1)).

The first criterion discussed was the recommendation made in EPOS2020 to reserve biologics for patients who have had sinus

surgery. Three arguments supported this recommendation: first, the positive impact of appropriate medical treatment⁽¹⁴⁾ and sinus surgery in most of the patients with CRSwNP^(15, 16); second, the high price of biologics⁽¹⁷⁾ and lastly, at this moment, we do not know how long biologics must be given and the potential risks of long-term treatment. For that reason, this criterion remained in the updated criteria. There was discussion whether the extent of the surgery needs to be evaluated before considering the choice of a biologic⁽¹⁸⁾. However, because we do not have sufficient data proving that more extensive surgery results in better outcomes in patients with CRSwNP this criterion was not added^(19, 20).

The next suggestion was to make type 2 inflammation a prerequisite instead of one of the 5 criteria. From our clinical experience, we hypothesize that the presence of type 2 inflammation is an important factor determining the success of biologic treatment. However, we also acknowledge that we do not precisely know how to define type 2 inflammation in CRSwNP and to what extent biologics might be helpful in "mixed" inflammation^(21, 22).

Therefore, it was decided not to make type 2 inflammation mandatory.

In alignment with pulmonological literature⁽²³⁾ the blood eosinophils cut-off was reduced to from ≥ 250 cells/ μL to ≥ 150 cells/ μL . There was discussion on the association of other type-2 inflammatory diseases than asthma as a criterion for indication for biologic treatment. Although biologics have been shown to be effective in many forms of type-2 disease^(9, 24), the lack of association between CRSwNP and allergic rhinitis⁽¹⁾ and the inconclusive data on the association between CRSwNP and atopic dermatitis or eosinophilic oesophagitis^(1, 25-28), led to the decision not to include other type-2 inflammatory diseases in the criteria. Once eligibility according to the EPOS/EUFOREA 2023 criteria has been determined, patients' preference for a surgical or non-surgical approach should be considered if funding within the healthcare system allows. The adjustments are indicated in Figure 1.

What biologic can be given to a pregnant woman?

Omalizumab is the only biologic until now that showed no increase in congenital anomalies or adverse outcomes in a registry of pregnant asthmatics treated with omalizumab⁽²⁹⁾. Although there are no indications that the other biologics are teratogenic⁽³⁰⁾, the small sample size and limited studies do not allow firm conclusions^(31, 32). The European Medicines Agency (EMA) states that women have to be counselled that the potential benefit associated with biologic exposure during pregnancy has to be balanced against the risks to the foetus^(31, 32). In line with EMA recommendations, the EUFOREA group advises to counsel the patient and to be very prudent (i.e., stop the therapy unless omalizumab or very strong reasons to continue).

2. How can we define disease modification or remission?

Disease modification or remission can be considered when a treatment leads to the absence of symptoms and prevents disease progression by addressing the underlying pathophysiology of the disease. There is no straightforward definition for disease modification in chronic rhinosinusitis.

On the one hand we can approach it from a histological aspect and investigate barrier remodelling⁽³³⁾, on the other hand, a more functional or clinical point of view can be used⁽³⁴⁾. For example, in asthma, the functional way would be to look at the Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ)^(35, 36). However, in CRSwNP these functional and clinical parameters have not been defined yet, although SNOT-22 and smell tests, but also resolution of nasal polyps (NPS), are potential parameters⁽³⁷⁾.

There is evidence that dupilumab can decrease (self-reported) upper and lower respiratory infection rates in CRS patients⁽³⁸⁾. However, we need more long-term data to define the parameters that can be linked to disease modification.

Can biologics work preventively?

At this moment, there are no data suggesting that biologics can prevent CRS. There have been studies in children with prewheezing/non-asthmatic wheezing who were given omalizumab to investigate whether biologics could prevent additional desensitization or prevent asthma. Here, investigators discovered that biologics could prevent additional desensitization, although they could not prevent the asthma⁽³⁹⁾.

There is no evidence to support use of biologics to prevent the development of CRSwNP, and currently we are unable to reliably identify patients before they develop polyps. Only a minority of patients experience anosmia before the presence of nasal polyps^(40, 41). Also, a minority has eosinophilic CRSsNP^(42, 43). It is unclear whether this group develops nasal polyps and whether that could be prevented.

A preventive strategy that might be more feasible would be the early use of biologics as tertiary prevention, just as the early use of surgery might be beneficial for patients with CRSwNP⁽⁴⁴⁾. Right now, however, the high cost of biologics prevents physicians from prescribing biologics early in the disease.

3. Parameters to evaluate the 'success' of biologics

To evaluate the success of biologics, we need to keep in mind that patients' experience is not always well reflected by clinical measures. Therefore, the EUFOREA expert panel members agreed on the inclusion of both patient and physician reported outcomes in establishing a good sense of overall disease control. Therefore, the panel agrees to measure the following outcome parameters:

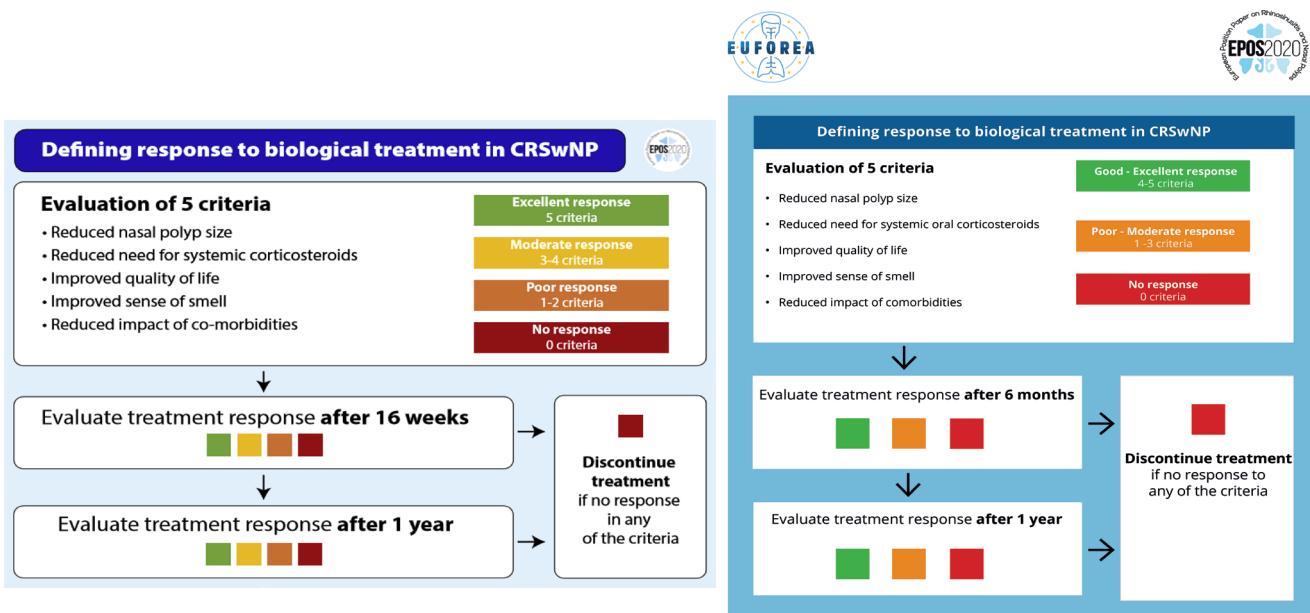


Figure 2. Adjustments in EPOS/EUFOREA response criteria.

- o Significant improvement of patient reported outcomes:
 - SNOT-22
 - Smell loss
 - Congestion scores
 - Benefits on comorbidities (asthma, allergy, middle ear problems)
- o Significant improvement of physician reported outcomes:
 - NP scores
 - CT scan scores
 - Smell tests

The experts acknowledge that physician reported outcomes and impression of disease control do not always correlate well with patient reported outcomes^(45, 46) and have shortcomings related to logistical and interpretational challenges. However, a consensus on the most effective way to grade nasal polyps has not been reached⁽⁴⁶⁾. Moreover, the most appropriate smell test has not been defined yet but should most likely consist of threshold tests and identification tests^(45, 47). In addition, physicians should keep in mind that, while loss of smell and nasal blockage appear to be the most bothersome symptoms for patients, their importance may vary from person to person.

Defining the response to biologic treatment in CRSwNP.

The experts discussed the EPOS2020 criteria to define the response to biologic treatment in CRSwNP (Figure 2)⁽¹⁾.

EPOS2020 defines the response to biologic treatment by the reduction in nasal polyp size, the need for systemic corticosteroids, improvement of QoL and/or sense of smell and the impact on co-morbidities.

The expert panel acknowledged that applying the EPOS 2020

criteria to define a response to biologic treatment had the unwanted effect that a significant portion of patients were not able to achieve an excellent response (e.g., patients who do not have asthma can never have an excellent response), therefore the criteria were simplified into: No response 0 criteria; Poor-Moderate response 1-3 criteria; Good-Excellent response 4-5 criteria. Moreover, the reduced impact of co-morbidities should only be considered if co-morbidities are present. Finally, reduced need for surgery was added as a criterion alongside systemic corticosteroids as both are considered rescue treatments.

In addition, time to evaluation was discussed and, in line with the current literature, 16 weeks was deemed too early to evaluate the response^(12, 48). Therefore, the expert board advises 16 weeks to be adjusted to 6 months. After 1 year, a second evaluation is necessary, and thereafter a yearly evaluation will suffice (Figure 2).

If patients do not have any response to any of the criteria the biologic should be discontinued and/or switched or a revision surgery can be planned.

If there is some improvement (e.g. Poor-moderate response) different strategies can be applied keeping in mind the patient's preference. As suggested by Bachert et al. in the previous EUFOREA expert board meeting on biologics in CRSwNP in 2021: if the patient finds the improvement acceptable at 6 months the biologic can be continued, and the treatment response should be re-evaluated at 12 months as some biologics tend to need more time than 6 months to reach their full potential⁽⁴⁹⁾. If however, the improvement is not deemed significant enough to neither physician nor patient, the biologic should be either switched or other options such as salvage surgery under biologic

protection or an additional short course of systemic glucocorticosteroids could be considered⁽¹²⁾.

In addition, considering that the most bothersome symptoms can differ significantly between patients, it might be beneficial for future government guidelines to consider letting physicians choose between a list of symptoms on which they base their decision to prescribe a biologic on. However, data to show the value of this approach are missing.

3. Expected effect of biologics beyond ocs/ess

What can we expect of the effectiveness of biologics?

In general, biologics have a success rate of 60% regarding improvement in the sense of smell depending on the biologic⁽⁵⁰⁾. However, currently we are not able to predict the time until improvement. It typically takes 4 weeks for the effect to appear, however it can vary from days to months^(51, 52). Interestingly, there is no correlation between polyp size (NPS) and improvement of the sense of smell⁽⁵³⁾. Once the sense of smell improves, it is advised to start smell training to reactivate the neurogenic pathways responsible for smell function, that were inactive during the period of anosmia although more mechanistic data on smell recovery is needed^(54, 55).

In addition, the expert panel expects that the effect of biologics in real life might be better than the results in clinical trials. Two arguments were put forward. The first being that in the clinical trials type 2 inflammation was not a prerequisite, whereas in the clinic, physicians try to select patients who are more likely to have a type 2 inflammation. The second argument is that in the trials patients did not fulfil the EPOS2020 criteria, e.g., were not operated and have probably less severe disease than the patients chosen in real life for treatment with a biologic. It is important to gather real-life data from patients on biologics in order to back up these claims with the proper data^(50, 56, 57). Moreover, better data on objective and cost-effective measurement of type 2 inflammation are needed^(12, 58).

4. Reasons to switch/decrease/stop biologics

When to switch biologics?

Although for the last decades, the united airways hypothesis emphasized the similarities between the upper and lower airways^(59, 60), the use of biologics now also points to significant differences in the treatment effect of biologics aiming at different points in the type 2 inflammatory cascade⁽⁶¹⁾. In a minority of patients, some biologics work better for asthma than for CRSwNP or vice versa. Recently, some first suggestions for an algorithm for choosing the most appropriate biologic to start with in severe asthma and the first choice to switch have been published but data are still incomplete⁽⁶²⁾.

The panellists describe case reports from patients that benefit from different biologics for upper and/or lower airways which in some patients lead to the need to either switch or combine bio-

logics. This small group of patients need multidisciplinary care in specialized centres. It is important to register from which biologic these patients benefit as there is a definite need to properly investigate biomarkers that can predict a good response to a specific biologic. For the moment, we do not yet have evidence-based criteria on when to switch from one biologic to another, and which biologic should be preferred. Therefore, our goal is to set up different real-life data registries to gather information necessary to define biomarkers, which can predict a favourable response, and gather necessary data to define guidelines for switching.

Reasons to decrease/stop biologics

Side effects are seldom a reason to stop treatment with biologics. Transient hypereosinophilia is a known phenomenon of treatment with anti-IL4ralpha treatment, usually occurring between 2 and 6 months of treatment^(22, 24). However, when it persists usually in combination with symptoms, it can cause organ damage⁽⁶³⁻⁶⁵⁾. Therefore, the panel advises measuring the blood eosinophil levels at one and three months after biologic initiation in every patient, and when needed more often in patients with high baseline eosinophils (>500/ μ L) and in patients that were on chronic systemic corticosteroids before treatment with a biologic. Moreover, it is advised to do a careful history of symptoms/signs of vasculitis/hypereosinophilia at every visit. After three months the frequency can be adjusted according to the blood eosinophil count. At the moment, there are insufficient data to advise on the frequency of monitoring, though once every 2-4 weeks when blood eosinophils are high (over 1500 cells/ μ L) seems prudent. If a rise in blood eosinophils over 3000 is seen, temporization of the dose (to every four weeks) or treatment with a short course of systemic corticosteroids can be considered. Persistent high blood eosinophils or symptoms related to vasculitis are reasons to consult an immunologist⁽⁶⁴⁾. Data concerning biomarkers other than blood eosinophil levels, that would be useful to screen for hypereosinophilic syndrome, are lacking. Therefore, further research is required.

End of treatment with biologics

The maximum treatment duration with biologics in trials for CRSwNP has been 12 months. In these trials, there was recurrent disease after stopping the biologic at 6 months^(22, 66). However, reducing dose of dupilumab to once every four weeks did not show relevant difference compared to 300 mg once every two weeks⁽²²⁾. There is an urgent need to define an end of treatment schedule for biologics, when CRSwNP patients' symptoms are under control.

Until these studies have been performed, data from asthma trials can give some indications.

The Xolair Persistence Of Response After Long-Term Therapy (XPORT) study, a 52-week multicentre randomized double-blind

Table 1. Unmet needs in the field of biologics for CRSwNP and asthma.

Unmet needs	Plan to address
Educate patients on the use of biologicals and what they can expect from treatment	<ul style="list-style-type: none"> • Webinar on what to expect from what treatment (practical, financial, and medical aspects) • Patient community chat box, with possibility to exchange experiences and information • Prepare a leaflet for patients explaining the role of biologics
Standardise use of biologicals in clinical practice by educating physicians to correctly diagnose and treat CRSwNP	<ul style="list-style-type: none"> • Publish guidelines with treatment algorithms and a screening tool to provide a clear overview when to choose treatment with a biological and how to embed in general CRSwNP management
Assess (long-term) efficacy/disease-modifying effect of biologicals in severe chronic rhinosinusitis (after treatment cessation)	<ul style="list-style-type: none"> • Mechanistic studies (at a single-cell level) • Well-designed RCT and real-life data studies focusing on real-life efficacy
Identification of clinically relevant biomarkers to select responders to current available biologicals	Identify biomarkers related to disease activity of CRSwNP
Positioning of biologicals in the treatment pathway of patients with known severe CRSwNP (such as N-ERD, severe asthma comorbidity): surgery vs biologics; combination therapy (surgery and biologics)	Well-designed RCT and/or real-life data studies
Duration of therapy	Well-designed RCT and/or real-life data studies
Pregnancy data for Dupilumab and mepolizumab.	Real world data and registries
Adverse effects with long term use	Real world data and registries
Definition of remission	Real world data and registries
Criteria for switching	Real world data and registries
Feasibility of dosing interval prolongation (along with duration of therapy)	Real world data and registries
Mechanistic data on smell recovery is needed	In vivo and in vitro evaluation of inflammation
Role of smell training during biologic treatment on smell recovery	Well-designed RCT and/or real-life data studies

study, evaluated the effects of discontinuing omalizumab in patients with severe asthma⁽⁶⁷⁾. They observed that nearly half the patients in the discontinuation group remained well-controlled in the year after stopping the treatment, despite having a higher rate of exacerbations by 20%. Another, open prospective study with omalizumab among 49 patients with severe asthma showed that the effect of long-term use of omalizumab persisted for at least 4 years after treatment discontinuation in 60% of patients⁽⁶⁸⁾. Interestingly, the failure group (patients who experienced exacerbations after discontinuation) tended ($p=0.09$) to have CRSwNP and/or N-ERD more often than the success group. This might indicate that the presence of comorbidities could be a potential predictor of failure after discontinuation. The COMET- study, a randomized double-blind placebo-controlled discontinuation trial⁽⁶⁹⁾, in patients with severe eosinophilic asthma on ≥ 3 years of mepolizumab, reported a small increase (14%) in asthma exacerbations in the year after discontinuation of mepolizumab, however severe exacerbations (leading to ED visits or hospitalizations), were not increased in the discontinuation group. Asthma symptoms and pulmonary function did not deteriorate 1-year post-discontinuation.

Considering the results of these studies, discontinuing biologics could be a feasible strategy in suitable patients, however the presence of co-morbidities might be a risk factor for failure⁽⁷⁰⁾.

Currently, we cannot give clear guidelines on this subject yet as we lack evidence-based data in CRSwNP patients.

5. Unmet needs in the field of biologics for CRSwNP and asthma

The expert panel proposed several key areas of interest for both clinicians and basic researchers, from a healthcare point of view in Table 1. Unmet needs have been assessed from the perspectives of different stakeholders.

Authorship contribution

All authors contributed to the discussion that was the base for this document and approved the content.

Conflict of interest

W.J. Fokkens: The department of Otorhinolaryngology of the Amsterdam University Medical centre, location AMC received grants for research in Rhinology from: ALK, AllergyTherapeutics, Chordate, Novartis, EU, GSK, MYLAN, Sanofi-Aventis, and Zon-MW. Prof. dr. Wytske Fokkens received consultation and/or speaker fees from Bioinspire, GSK, Novartis and Sanofi-Aventis/Regeneron. An-Sofie Viskens: No conflict of interest to declare. Vibeke Backer: I have worked as advisor, supervisor, investigator of pharmaceutical studies, unrestricted grants, and others with:

AstraZeneca, GSK, MSD & Shering Plough, ALK-Abello; Chiesi, Novartis, Pharmaxis, Pfizer, Boehringer Ingelheim, Aerocrine, Teva, Sanofi, Birk NPC as; Diego Conti: No conflict of interest to declare. Eugenio de Corso: Speaker activity and Advisory boards participation for: Sanofi, Novartis, GSK, AstraZeneca; Philippe Gevaert: PG has participated in advisory boards and received speaker fees from ALK-Abelló, Argenx, AstraZeneca, Genentech, GSK, Novartis, Regeneron, Roche, Sanofi Genzyme, and Stallergenes-Greer. Glenis K. Scadding: Honoraria for articles, speaker, and advisory boards: ALK, AstraZeneca, Britannia Pharmaceuticals, Capnia, Church & Dwight, Circassia, Grupo Uriach, GSK, Meda/Mylan/Viatris, Merck, MSD, Ono Pharmaceuticals, Oxford Therapeutics, Sanofi-Aventis, Stallergenes, UCB. Travel funding: ALK, Bayer, GSK, Meda. Lead for BSACI Rhinitis guidelines. Past Chair of EAACI Ethics Committee. Scientific Chief Editor, Rhinology Section, Frontiers in Allergy. Board Member, Lead for Allergic Rhinitis, EUFOREA. Chair of Data Monitoring Board for Paediatric AR trials of HDM SLIT. Martin Wagemann: Fees for lectures and / or participation in scientific advisory boards: ALK-Abelló, AstraZeneca, Genzyme, GSK, Infectopharma, LETI Pharma, Novartis, Regeneron, Sanofi, Stallergenes Grants (to institution): ALK-Abelló, AstraZeneca, GlaxoSmithKline, Novartis, Regeneron, Sanofi-Aventis, Takeda. Manuel Bernal Sprekelsen: Speaker honorarium from: Olympus Europe, Sanofi Spain, Viatris Spain. Adam Chaker: Dr. Chaker reports grants, speaker honoraria, consultancy or advisory fees and/or research support and other all via Technical University of Munich from Allergopharma, ALK Abello, Bencard / Allergen Therapeutics, GSK, Novartis, LETI, Roche, Zeller, Sanofi Genzyme/Regeneron,

European Institute of Technology, AstraZeneca, Immunotek, all outside the submitted work; In addition, Dr. Chaker has a patent A ratio of immune cells as prognostic indicator of therapeutic success in allergen-specific immunotherapy: 17 177 681.8 licensed to none, and a patent pending. Enrico Heffler: Speaker activity and Advisory boards participation for: Sanofi, Regeneron, Novartis, GSK, AstraZeneca, Circassia, Valeas, Stallergenes-Greer, Nestlé Purina. Joseph K. Han: Research consultant for Sanofi Regeneron, GSK, and AstraZeneca, Elizabeth Van Staeyen: No conflict of interest to declare. Claire Hopkins: Advisory Board, GSK, Dianosic and Sanofi, Speaker's bureau; Mylan, Olympus. Joaquim Mullol: Member of national and international scientific advisory boards, done consulting, received fees for lectures, and grants for research projects or clinical trials from AstraZeneca, Genentech-Roche, GSK, LETI, Menarini, MSD, Mitsubishi-Tanabe, Viatris/MEDA Pharma, Novartis, OPTINOSE, Proctor & Gamble, Sanofi-Genzyme & Regeneron, UCB Pharma, and NOUCOR/Uriach Group. Anju Peters: Research support: Sanofi Regeneron, Optinose, Merck. Consultant/Advisory board: Sanofi Regeneron, Optinose, AstraZeneca, Merck. Sietze Reitsma: Acted as consultant for and have received research funding from GSK, Sanofi, and Novartis. Brent A Senior: Stryker Consultant, Lyra Consultant. Peter W. Hellings: Consultant and recipient of lecture fees and/or research grants from Sanofi, Regeneron, Novartis, GSK, ALK and Viatris.

Funding

No funding to declare.

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