Biologicals in severe chronic rhinosinusitis with nasal polyps: translation to clinical practice while waiting for head-to-head studies*

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Dear Editor:

Chronic rhinosinusitis with nasal polyps (CRSwNP) affects 1.0-2.6% of the population [1] and results in relevant direct and indirect costs. Recently, several randomized controlled trials (RCTs) with Type 2-targeting biologicals (anti-IL4Rα, anti-IL5R, anti-IL5 and anti-IgE) opened a new treatment field for patients refractory to first-line treatments [2,3].

While these biologicals provide an innovative treatment option, the published Phase III RCTs displayed relevant differences in participants' eligibility criteria, baseline treatments and measured outcomes, potentially compromising an indirect comparison of the effectiveness of different biologicals [2-5]. In fact, even though recent systematic reviews (SRs) and network meta-analysis providing indirect comparisons between biologicals for CRSwNP [2-4,6,7] consistently favored anti-IL4Rα antibodies (e.g., the only associated with sense of smell improvement and significant improvements over placebo for all outcomes and comparisons) [3,4,6,7], these SR found high heterogeneity, likely resulting from different inclusion criteria and outcomes' definitions.

In 2020, a National Institute of Allergy and Infectious Diseases Workshop stated that "in addition to the dynamics between forces that range from guidelines and payers' policies to patients' and physicians' preferences, new evidence derived from well-designed studies will determine the use and impact of biologics in CRSwNP" [8]. In 2021, the Food and Drug Administration released a draft guidance for the industry on conducting RCTs with biologicals in CRSwNP [9]. Although we disagree with some points addressed in that document, such as the recommendation against the Sino-Nasal Outcome Test (SNOT-22) as a key study outcome (the only outcome in CRSwNP trials with reported minimal clinically important differences [MCID]) [4], such an initiative has been a landmark in promoting standardized research in this field.

Considering these limitations and published recommendations [8,9], we searched the ClinicalTrials.gov platform for unpublished/ongoing trials on biologicals for CRSwNP to assess whether there has been an increased consistency in eligibility criteria and outcomes definition, comparatively to the high heterogeneity observed so far. Thirty-eight RCTs with biologicals in CRSwNP (Suppl Table 1) were identified (seven Phase III and seven Phase IV ongoing studies).

All ongoing Phase III studies compare biologicals (Benralizumab, CM310, Tezepelumab, Depemokimab, and Mepolizumab) with placebo (Table 1). As inclusion criteria, the endoscopic nasal polyp score (NPS) was common to all RCTs; previous treatment with systemic corticosteroids or polyp surgery were used as inclusion criteria in six studies, and SNOT-22 in two. Regarding primary outcomes (Suppl Table 2), all ongoing Phase III RCTs used NPS changes, similarly to previous pivotal studies [2-7].

For secondary outcomes lack of uniformity was still the rule, evidenced by the wide variety of criteria (e.g., loss of smell [LoS], University of Pennsylvania Smell Identification Test [UPSIT], Lund Mackay score, systemic corticosteroids, forced expiratory volume in the first second [FEV_1], Sino-Nasal Outcome Test [SNOT-22], Asthma Control Questionnaire-5 [ACQ-5], time to first nasal polyp surgery) and the variability in the evaluation time (Weeks 24 to 56).

Phase IV studies (Suppl Table 3) involve omalizumab, mepolizumab and dupilumab, including the first dupilumab/omalizumab head-to-head RCT. The latter is recruiting CRSwNP adult

Table 1. Inclusion criteria in seven ongoing interventional Phase III studies using biologics in CRSwNP registered at ClinicalTrials.gov*. Part 1

Biologic	Trial Study start date	Treatment period	Inclusion criteria Age (years)	Diagnosis	NPS	Symptoms
Benralizumab (anti-IL-5 receptor)	ORCHID (NCT04157335) 25th Nov, 2019	56 weeks	18-75	Bilateral sinonasal polyposis	≥ 5 at enrolment and randomization (unilateral score of at least 2 for each nostril)	Ongoing symptoms for at least 12 weeks prior to enrolment
	NAPPREB (NCT04185012) 4th Dec, 2019	24 weeks; follow up phase at 32 and 52 weeks	≥18	CRSwNP (allergic and non-allergic)	> 5	Symptoms VAS scores (for nasal obstruction, hyposmia, post-nasal drip, sneezing, rhinorrea; 0-10 for each symptom) > 24
CM310 (anti-IL-4 receptor alpha)	CROWNS-2 (NCT05436275) 30th Aug, 2022	24 weeks for double-blind and 28 weeks for open-label maintenance treatment	18-75	CRSwNP	≥ 5 with a minimum score of 2 in each nasal cavity	-
Tezepelumab (anti-TSLP)	WAYPOINT (NCT04851964) 22nd April, 2022	52 weeks; 12-24 weeks of post-treatment follow-up for participants who complete the 52 weeks treatment period	≥18	Physician-diagnosed CRSwNP	≥ 5 (≥ 2 for each nostril) at screening	Ongoing documented NP symptoms over > 8 weeks prior to screening, such as rhinorrhea and/or reduction/loss of smell
Depemokimab (long-acting IL-5 receptor antagonist)	ANCHOR-1 (NCT05274750) 22nd April, 2022 ANCHOR-2 (NCT05281523) 25th Aug, 2022	52 weeks	≥18	CRSwNP	Endoscopic bilateral NPS of at least 5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity)	Presence of symptoms of CRS as described by at least 2 different symptoms for at least 12 weeks prior to Visit 1, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip), plus facial pain/pressure and/or reduction or loss of smell
Mepolizumab (anti-IL-5)	MERIT (NCT04607005) 08th Feb, 2021	52 weeks	≥18	CRSwNP / Eosinophilic chronic rhinosinusitis	Endoscopic bilateral NPS of at least 5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity)	Presence of symptoms of CRS as described by at least 2 different symptoms for at least 12 weeks prior to Visit 1, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip), plus facial pain/pressure and/or reduction or loss of smell

BEC, blood eosinophil count; CRSwNP, chronic rhinosinusitis with nasal polyposis; IL-4, Interleukin-4; IL-5, Interleukin-5; INCS, intranasal corticosteroids; NBS, nasal blockage score; NCS, nasal congestion score; NP, nasal polyposis; NPS, nasal polyp score; NSAIDs, nonsteroidal anti-inflammatory drugs; SCS, systemic corticosteroids; SNOT-22, Sino-Nasal Outcome Test; TSLP, thymic stromal lymphopoietin; VAS, visual analogue scale
*https://clinicaltrials.gov/ct2/results?cond=Nasal+Polyps&flds=aby&age_v=&gndr=&type=&rslt=&Search=Apply Accessed in November 1st, 2022.

patients with NPS ≥5, nasal congestion and LoS, and physician-diagnosed comorbid asthma for ≥ 12 months. The primary endpoints are changes at 24 weeks in NPS and UPSIT, and key secondary outcomes changes in LoS, Nasal Congestion scores and prebronchodilator FEV_1.

In summary, despite the published recommendations [8,9], ongoing trials on biologics for CRSwNP are still quite heterogeneous in inclusion criteria and secondary outcomes. These observations reinforce the relevance of additional calls for standardization of inclusion criteria and outcomes. In the supplementary material, we provide some additional recommendations to achieve that goal. Meanwhile, while waiting results of more complex head-to-head studies, meta-analytic studies [2-4,6,7] may provide the evidence and guidance to practicing clinicians in this new era of biological treatments in CRSwNP.

Abbreviations

ACQ-5: Asthma Control Questionnaire-5; CRSwNP: Chronic rhinosinusitis with nasal polyps; FEV_1: Forced expiratory volume in the first second; LoS: Loss of smell; MCID: Minimal clinically important differences; NPS: Nasal polyp score; PROMs: Patient-reported outcomes measures; RCTs: Randomized controlled trials; SNOT-22: Sino-Nasal Outcome Test; SRs: Systematic reviews; TNSS: Total nasal symptom score; UPSIT: University of Pennsylvania Smell Identification Test; VAS: Visual Analogue Scales.

Authorship contribution

JLB and BSP: conception and design of the work; analysis and data interpretation; drafting the work; critical revision of the manuscript. LD and DS: conception of the work; analysis and data interpretation; critical revision for important intellectual content. All: final approval of the version to be published; agreement

Table 1. Inclusion criteria in seven ongoing interventional Phase III studies using biologics in CRSwNP registered at ClinicalTrials.gov*. Part 2

Inclusion criteria							
SCS use	Prior surgery	INCS use	Comorbidities	NBS	SNOT-22	BEC	NCS
History of treatment with SCS (but not within 4 weeks prior to screening) or prior surgery (but not within 3 months prior to enrolment)		> 4 weeks prior to enrolment and throughout screening	Documented physician-diagnosed asthma	≥ 2 at enrolment Bi-weekly mean NBS ≥ 1.5 at randomization	Total score ≥ 20 at enrolment and randomization	> 2% or ≥ 150/μL at enrolment	None
History of requiring at least 1000 mg oral prednisone over the previous 12 months to control symptoms of CRS		-	-	-	-	-	-
None	None	None	None	None	None	None	2 or 3 at screening period, and at least 2 at baseline
Documented treatment of NP exacerbation with SCS for at least 3 consecutive days or one IM depot-injectable dose (or contraindications/intolerance to) within the past 12 months prior to Visit 1 but not within the last 3 months prior to Visit 1 and/or any history of NP surgery (or contraindications/intolerance to), but not within 6 months of screening		Any standard of care for treatment of CRSwNP provided the participant is stable on that treatment for 30 days prior to Visit 1	None	None	Total score ≥ 30 at screening (Visit 1)	None	≥ 2 at Visit 1
At least one of the following at Visit 1: previous nasal surgery for the removal of NP; have used at least three consecutive days of SCS in the previous 2 years for the treatment of NP; medically unsuitable or intolerant to SCS		Daily treatment for at least 8 weeks prior to screening (except for participants in Japan)	None	Nome	Nome	Nome	Score of 2 or 3 and loss of smell or rhinorrhea (runny nose)
At least one of the following at Visit 1: previous nasal surgery for the removal of NP; have used at least three consecutive days of SCS in the previous 2 years for the treatment of NP; medically unsuitable or intolerant to SCS		None	None	Severe NP symptoms defined as a nasal obstruction VAS symptom score of greater than 5	None	> 2% in 12 months prior to Visit 0 or between Visit 0 and Visit 1. BEC over 2% to 5% must also have comorbidities (bronchial asthma, aspirin /NSAIDs intolerance) at Visit 1	None

BEC, blood eosinophil count; CRSwNP, chronic rhinosinusitis with nasal polyposis; IL-4, Interleukin-4; IL-5, Interleukin-5; INCS, intranasal corticosteroids; NBS, nasal blockage score; NCS, nasal congestion score; NP, nasal polyposis; NPS, nasal polyp score; NSAIDs, nonsteroidal anti-inflammatory drugs; SCS, systemic corticosteroids; SNOT-22, Sino-Nasal Outcome Test; TSLP, thymic stromal lymphopoietin; VAS, visual analogue scale
*https://clinicaltrials.gov/ct2/results?cond=Nasal+Polyps&flds=aby&age_v=&gndr=&type=&rslt=&Search=Apply Accessed in November 1st, 2022.

to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interest

JLB: Sanofi – Honoraria for a lecture in a Symposium in a National Congress of Allergy in October 2022; BSP: No conflict of interest exists; LD: Laboratorios Vitoria, SA – Advisory board, honoraria; LETI Pharma – honoraria for lectures; DS: No conflict of interest exists.

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SUPPLEMENTARY MATERIAL

Herein, we provide recommendations for standardization of the inclusion criteria and outcomes assessment of randomized controlled trials (RCTs) in patients with chronic rhinosinusitis with nasal polyposis (CRSwNP). Such standardization would be particularly relevant to ensure comparability between primary studies. As recommendations, the inclusion criteria for RCTs in CRSwNP should consider clinician-rated measures (the Nasal Polyp Score – NPS – being almost a consensus) and patient-reported outcomes measures (PROMs) evaluating ongoing symptoms and severity of nasal congestion, loss of smell, and postnasal drip [1]. As for PROMs, the Sino-Nasal Outcome Test (SNOT-22) is disease-specific, validated, and has an established minimal clinically important difference [2]. Using Visual Analogue Scales (VAS) or Likert scales is also a possibility, but such scales have not been validated, and no studies demonstrated the best approach to symptoms assessment in CRS (e.g.,10-point VAS, 100-point VAS, Likert categorical scale), nor the correlation between different VAS in CRSwNP, still an open field for future studies. Nevertheless, Doulaptsi et al. [3] demonstrated that VAS scores on a 0-10 scale for total nasal symptom score (TNSS) correlated significantly with SNOT-22 and may help in a simple assessment of disease severity. To standardize inclusion criteria, restrictions based on baseline severity or endotype (e.g., use of systemic steroids, previous surgeries, presence of comorbidities, T2-biomarkers) may be replaced by stratified randomization approaches. This allows researchers to evaluate all participants (maintaining the generalizability of the study results), as well as strata with specific characteristics (in a more adequate way than with subgroup analyses).

Finally, due to treatment costs, outcomes of RCTs with biologicals in CRSwNP should include ways to compare interventions not only on their effectiveness, but also on their costs and quality-of-life. In this regard, using tools such as EQ-5D (whose scores can be converted into utilities) may lay the basis for cost-utility studies [4].

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Suppl Table 1. Biologicals for the treatment of CRSwNP in ClinicalTrials.gov*.

		Phase I		Phase II		Phase III		Phase IV	
Biologic	**Mec. of action**	**Concluded**	**Ongoing**	**Concluded**	**Ongoing**	**Concluded**	**Ongoing**	**Concluded**	**Ongoing**
Dupilumab	Anti-IL-4Rα	-	-	1	1	2	-	-	4
Omalizumab	Anti-IgE	-	1	2	-	3	-	-	1
Dupilumab vs Omalizumab	Anti-IL-4Rα and Anti-IgE	-	-	-	-	-	-	-	1**
Mepolizumab	Anti-IL-5	-	-	1	-	1	1	-	1
Benralizumab	Anti-IL-5R	-	-	1	-	1	2	-	-
Tezepelumab	Anti-TSLP	-	-	-	-	-	1	-	-
Depemokimab	Long-acting anti-IL-5	-	-	-	-	-	2	-	-
CM-310	Anti-IL-4Rα	-	-	1	1	-	1	-	-
CM-326	Anti-TSLP	-	-	-	1	-	-	-	-
CBP-201	Anti-IL-4Rα	-	-	1	-	-	-	-	-
AMG-282	Anti-IL-33	1	-	-	-	-	-	-	-
Etokimab	Anti-IL-33	-	-	1	-	-	-	-	-
PF-06817024	Anti-IL-33	1	-	-	-	-	-	-	-
AK-001	Anti-Siglec-8	-	-	1	-	-	-	-	-
TOTAL		2	1	9	3	7	7	0	7

* We performed our search on November 1st, 2022 applying the following query (https://clinicaltrials.gov/ct2/results?cond=Nasal+Polyps&fld s=aby&age_v=&gndr=&type=&rslt=&Search=Apply):

- condition or disease: nasal polyps [nose/nasal polyposis/polypus];
- study type: all
- study results: all studies [with and without results].

Out of 191 obtained results, we identified thirty-eight RCTs with biologics in CRSwNP in ClinicalTrials.gov.
Phase was not applicable in 2 studies (NCT05094570 with Dupilumab and NCT04823585 with Mepolizumab, not showed in the Table), totalizing 38 RCTs with biologicals in CRSwNP identified in ClinicalTrials.gov

**refers to a single (head-to-head) study with Dupilumab and Omalizumab

Suppl Table 2. Primary and secondary outcomes in seven ongoing interventional Phase III studies using biologics in CRSwNP registered at ClinicalTrials.gov*

Biologic	Trial Study start date	Treatment period	Outcomes (Changes from baseline, except when indicated)			
			Primary		Secondary	
			Nasal Polyp Score (NPS)	Patient-reported nasal blockage/congestion	Loss of Smell (LoS)	CT Scan (sinus opacification)
Benralizumab (anti-IL-5 receptor)	ORCHID (NCT04157335) 25th Nov, 2019	56 weeks	NPS at Week 56	Mean nasal blockage score (NBS, 0-3 scale) at Week 56,	Difficulty with sense of smell score (DSS) at Week 56	Lund Mackay score at Week 56
	NAPPREB (NCT04185012) 4th Dec, 2019	24 weeks; follow up phase at 32 and 52 weeks	Significant NPS reduction (≥ 1.5) at Week 24	-	Improvement >50% of smell visual analogue scale (VAS, 0-10 scale) at Week 24	Reduction >50% in Lund-Mackay Score at Week 24
CM310 (anti-IL-4 receptor alpha)	CROWNS-2 (NCT05436275) 30th Aug, 2022	24 weeks for double-blind and 28 weeks for open-label maintenance treatment	NPS at Week 24	Nasal Congestion Score (NCS, 0-3 scale) at Week 24	-	-
Tezepelumab (anti-TSLP)	WAYPOINT (NCT04851964) 22nd April, 2022	52 weeks; 12-24 weeks of post-treatment follow-up for participants who complete the 52 weeks treatment period	NPS at Week 52	Mean NCS (evaluated bi-weekly as part of the Nasal Polyposis Symptom Diary) at Week 52. NCS captured rating (0 to 3 scale).the severity of worst nasal congestion over the past 24 hours	Mean LoS (evaluated bi-weekly as part of the Nasal Polyposis Symptom Diary) at Week 52. LoS captured rating (0 to 3 scale) the severity of worst difficulty with sense of smell over the past 24 hours	Lund-Mackay score at Week 52
Depemokimab (long-acting IL-5 receptor antagonist)	ANCHOR-1 (NCT05274750) 22nd April, 2022	52 weeks	NPS at Week 52	Mean nasal obstruction score (4-point verbal response scale - VRS) from Weeks 49 to 52	Mean symptom score for LoS (4-point VRS) at their worst over the last 24 hours, from Week 49 to 52	Lund-Mackay score at Week 52
	ANCHOR-2 (NCT05281523) 25th Aug, 2022		Idem	Idem	Idem	Idem
Mepolizumab (anti-IL-5)	MERIT (NCT04607005) 08th Feb, 2021	52 weeks	NPS at Week 52	Mean nasal obstruction score (VAS, 0-100 scale) up to Week 52	Mean individual VAS symptom score (0-100 scale) for loss of smell up to Week 52	Lund-Mackay score at Week 52

Outcomes (Changes from baseline, except when indicated)				
		Secondary		
Disease specific health-related quality of life	Nasal polyp surgery	Systemic corticosteroid (SCS) use	Symptoms associated with CRSwNP	Others
SNOT-22 score at Week 56	Time to first nasal polyp surgery, up to Week 56	Time to first SCS course for nasal polyps, up to Week 56	Nasal symptom score at Week 56	Safety and tolerability assessment at Week 56 (adverse events, vital signs, clinical, laboratory, ECG)
Improvement >40% of SNOT-22 at Week 24	-	-	-	-
None of these. Instead, safety parameters (incidence of treatment-emergence adverse events up to Week 60); pharmacokinetics (concentration of CM310 in serum up to Week 60); pharmacodynamics (change from baseline in serum biomarker level of Thymus-and activation-regulated chemokine up to Week 60) and incidence of anti-drug antibodies (up to Week 60)				
SNOT-22 scores at Week 52	Time to nasal polyposis surgery decision, up to Week 52	Time to SCS for nasal polyps, up to Week 52	Mean Nasal Polyposis Symptom Diary Total Symptom Score at Week 52 (an 11-item symptoms diary rated over the past 24 hours, bi-weekly, using a 4-point verbal rating scale of 0 to 3)	Resolution/ near complete resolution of nasal polyps (maximum NPS of 1) at Week 52 and Nasal Polyposis Symptom Diary Total Symptom score response at Week 52. Change in pre-bronchodilator FEV1 at Week 52 and change in Asthma Control Questionnaire-6 (ACQ-6) at Week 52 for patients with asthma and AERD. Change in loss of smell evaluated by UPSIT at Week 52; change in Nasal Peak Inspiratory Flow through Week 52; incidence of anti-drugs antibodies over 52 weeks; serum trough concentrations at each visit.
SNOT-22 score at Week 52	-	-	Mean symptom score for rhinorrhea (4-point VRS) at their worst over the last 24 hours, up to Week 49 to 52; Mean nasal obstruction score (4-point VRS) from Weeks 21 to 24	Asthma Control Questionnaire-5 (ACQ-5) score at Week 52; NPS at Week 26; mean nasal obstruction score (4-point VRS) from Weeks 21 to 24
Idem	-	-	Idem	Idem
SNOT-22 total score at Week 52	Time to first nasal surgery, up to Week 52	Time to first course of SCS, up to Week 52. Record of the number of courses and reason for treatment.	Mean overall VAS score of 5 symptoms (nasal obstruction; nasal discharge; mucus in the throat; loss of smell; facial pain) up to Week 52; Mean composite VAS score (combining VAS scores of individual symptoms) up to Week 52	-

ACQ-5, Asthma Control Questionnaire-5; ACQ-6, Asthma Control Questionnaire-6; AERD, Aspirin-exacerbated Respiratory Disease ; CRSwNP, chronic rhinosinusitis with nasal polyposis; ECG, electrocardiogram ; FEV1, forced expiratory volume in 1 second; LoS, loss of smell; NBS, nasal blockage score; NCS, nasal congestion score; NPS, nasal polyp score; SCS, systemic corticosteroids; SNOT-22, Sino-Nasal Outcome Test; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analogue scale; VRS, verbal response scale.

*https://clinicaltrials.gov/ct2/results?cond=Nasal+Polyps&fld s=aby&age_v=&gndr=&type=&rslt=&Search=Apply Accessed in November 1st, 2022.

Suppl Table 3. Phase IV trials in CRSwNP at ClinicalTrials.gov.

Biologic	Trial identification	Main objective / Treatment duration	Primary outcome	Recruiting / Start date	Real world	Head-to-head
Omalizumab	NCT05405478	Efficacy in refractory NP / 24 weeks	SNOT-22 score	No / -	No	No
Mepolizumab	NCT05598814	Evaluate the effect of combined treatment with biologic and surgery versus biologic treatment only / 24 weeks	SNOT-22 score	No / -	No	No
Dupilumab	NCT05049122	Efficacy and safety in Japanese patients / 52 weeks	NPS	No / -	No	No
	NCT04869436	Olfatory outcomes / 24 weeks	TDI score / Sniffin Sticks Test	Yes / 19th July, 2021	Yes	No
	NCT04596189	Prevention of recurrence after ESS / 12 weeks (4 weeks prior to surgery until 8 weeks post-surgery)	Recurrence of sinus cavity oedema assessed endoscopically	Yes / 25th May, 2021	Yes	No
	NCT04442256	Effect on aspirin intolerance / 24 weeks	Maximally tolerated aspirin dose level	Yes / 1st June, 2020	No	No
Dupilumab versus Omalizumab*	NCT04998604	Evaluate treatment responses of Dupilumab versus Omalizumab in CRSwNP and asthma / 24 weeks	NPS / UPSIT	Yes / 27th Sep, 2021	No	Yes

CRSwNP, chronic rhinosinusitis with nasal polyposis; ESS, endoscopic sinus surgery; NP, nasal polyposis; NPS, nasal polyp score; SNOT-22, Sino-Nasal Outcome Test; TDI, Threshold, Discrimination, Identification; UPSIT, University of Pennsylvania Smell Identification Test.

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