

## **SUPPLEMENTARY MATERIAL**

### **RATIONALE**

#### **Sense of smell**

Odor particles enter the nasal cavity through nostrils and dissolve in the mucus to be transported to the receptors located at the cilia of the olfactory cells. This complex neuroepithelium covers the cribriform lamina, the superior zone of the nasal septum, the superior turbinate and some parts of the middle turbinate that contains the cell bodies of mature and immature olfactory sensory neurons (OSN) generated from horizontal and globose basal stem cells. The axons from the olfactory cells converge with the mitral cells, in the olfactory bulbs. The axons from the mitral cells travel in the inferior part of the frontal lobe and split into two: a lateral stria (ending at the primary olfactory cortex at the uncus of temporal lobe) and medial stria (crosses to the olfactory bulb on the opposite side). The primary olfactory cortex sends nerve fibers to many other areas of the brain, notably the piriform cortex, the amygdala, olfactory tubercle and the secondary olfactory cortex. These areas are involved in the memory and appreciation of olfactory sensations [1].

Smell helps humans to protect themselves through detection and avoidance of environmental hazards; influences the drive for appetite and takes place in social behavior since birth as odors from the areola attract infants to breastfeed [2].

## Olfactory terminology

<b>Normosmia</b>	Normal olfactory function
<b>Hyposmia</b> (or 'microsmia')	Quantitatively reduced olfactory function
<b>Anosmia</b>	Absence of all olfactory function
<b>Hyperosmia</b> (or 'superosmia')	Quantitatively increased ability to smell odors to abnormal level (for example, in association with migraine)
<b>Parosmia</b> (or 'dysosmia', 'cacosmia', 'euosmia' or 'troposmia')	Qualitative dysfunction in the presence of an odor(i.e. distorted perception of an odor stimulus)
<b>Phantosmia</b>	Qualitative dysfunction in the absence of an odor (i.e. an odor is perceived without concurrent stimulus, an 'olfactory hallucination')

Adapted from EPOS 2020 [3].

### **Olfactory dysfunction in general population**

Global Allergy and Asthma European Network (GA2LEN) demonstrated self-reported smell loss in 7.6% of 57,128 respondents from across Europe [4]. OLFACAT (OLFAction in CATalonia) is the largest population-based European epidemiological smell self-administered survey (n=9,348), reported an overall prevalence of olfactory dysfunction of 19.4% (0.3% of anosmia and 19.1% of hyposmia) [5]. This data correlates with that found by Brämerson et al., who reported an overall prevalence of olfactory impairment of 19.1% in Swedish population [6].

Smell dysfunction has a significant impact on quality of life (QOL), potentially leading to food poisoning environmental and social anxiety, food and weight disturbances and depression [4].

### **Olfactory dysfunction in chronic rhinosinusitis (CRS)**

CRS is the most frequent cause of gradual olfactory dysfunction, especially if it associates NP. Approximately 67-78% of subjects with chronic rhinosinusitis with nasal polyps (CRSwNP) experience olfactory dysfunction [7].

Smell loss in CRS is caused by a multifactorial combination of mechanical obstruction of odorant transmission in the olfactory cleft due to mucosal type 2 inflammation (edema or nasal polyps), leading to shedding and/or degeneration of the olfactory epithelium and causing the reduction or loss of the sense of smell [8]. CRS inflammation, with or without NP, affects the mucosa of bilateral paranasal sinuses and

nasal cavities, including the olfactory cleft and epithelium. Type 2 inflammation (mainly eosinophilic) of the olfactory cleft mucosa leads to olfactory epithelium shedding and OSN degeneration as potential causes of the loss of smell. Anti-inflammatory therapy (corticosteroids, biologics, and others) potentially reduces olfactory cleft inflammation and induces BSC proliferation and OSN regeneration, causing the partial or total recovery of the sense of smell[9-11].

### Olfactory testing

There are 3 different types of olfactory testing: subjective test, psychophysical test and objective smell tests. See *Table S1*.

**TABLE S1.Olfactory testing. Types of olfactory testing: subjective test, psychophysical test and objective smell tests.** Adapted from Mullol et al, JACI. 2020 [8].

1. Subjective test: patient reported olfactory assessment.				
Test	Range			
Visual or numerical analogue scale (VAS/NAS)	(0-10); 0 = normal smell; 10 = total smell loss			
Loss of smell (LoS)	(0-3) 0 = no symptom; 1 = mild LoS; 2 = moderate LoS; 3 = severe LoS			
2. Psychophysical test: should include 2 or 3 of three components of olfaction				
Test	Country	Components of olfaction (T,D,I)*	Range	Description

University of Pennsylvania Smell Identification Test (UPSIT) [12]	USA	I	(0-40) Anosmia $\leq 18$ Hyposmia 19-34 Normosmia $> 34$	A total of 40 encapsulated self-administered odors ("scratch-and sniff")
Sniffin' sticks test [13]	Germany	TDI	Normosmia if $> 75\%$ forced-choice identification. Updated normative values according to age and sex in Stevens et al, 2019 [14]	Identification: 16 odors in felt-tip pens [15]
Barcelona Smell Test (BAST-24)[16]	Spain	D,I + gustometry	Reference values according to age, sex and smoking habit	A total of 24 odors (semisolid gel) in glass
8-Odorant Barcelona Olfactory Test (BOT-8)[17]	Spain	T,D,I	(0-8) Anosmia $\leq 3$ Hyposmia 3-6 Normosmia 7-8	Semi-solid-state odorants contained in glass jars
T&T olfactometer[18]	Japan	D,T	Anosmia 5.6 -5.8 Hyposmia 1.1 -5.5 Normosmia 2 -1.0	f small vials 7 or 8 log 10 serial dilution concentration steps containing dilutions of five odorants
Connecticut Chemosensory Clinical Research Center (CCCRC)[19]	USA	T	(0-7) Anosmia $< 2$ Hyposmia 2-5 Normosmia 6-7	A total of 10 odors, in jars. Forced choice among 20 descriptors. Separate nostrils
Smell Diskettes[20]	Switzerland	No T	(0-8) Hyposmia $\leq 6$ Normosmia 7-8	A total of 8 diskettes that must be opened to release the odor.
<b>3. Objective smell tests: are expensive and usually limited to experimental and research use in specialized centers.</b>				

- Olfactory event-related potentials: collection of the electrical activity of external electrodes while presenting the patient with odors.
- Olfactory electrogram: recording the electrical activity of the nasal olfactory epithelium by applying intranasal electrodes.
- Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI): identifies the brain cortical areas that are activated in the presence of an olfactory stimulus.

\*Threshold (T), Identification (I), Discrimination (D)

- **Subjective test:** Delanket al. showed that 30-40% of CRS patients with impaired olfactory function rated themselves as unimpaired [21]. Therefore, even subjective tests are useful to evaluate smell and clinical response to therapies, they should not be undertaken in isolation, given its poor accuracy.

- **Psychophysical test** should include 2 or 3 of three components of olfaction:

- **Threshold (T):** is the concentration of an odorant where 50% of the stimuli are detected and 50% remain undetectable to a subject.

- **Identification (I):** the detection of ‘something’, usually in comparison to a blank, odorless stimulus.

- **Discrimination (D):**describes the non-verbal ability to differentiate between different odors. Odor identification involves both recognition of a stimulus and communication of its correct identity (i.e., the ability to name an odor).

Olfactory threshold preferentially tests peripheral causes of olfactory loss (for example due to CRS), whereas the discrimination and identification tests preferentially assess central or cognitive causes of olfactory dysfunction.

Psychophysical tests provide a more reliable assessment of olfactory function than subjective testing. Psychophysical testing requires a cooperative subject who can understand and follow instructions, as well as communicate choices to the clinician/investigator, so they should be reliable and validated for the target population because odor identification tasks are culturally dependent.

Although smell can be assessed by patients themselves, psychophysical assessment is strongly recommended despite the absence of an established minimal clinically important difference (MCID) for any available test [22].

- **Objective smell tests** are expensive and usually limited to **experimental and research** use in specialized centers.

### **Quality of life in CRSwNP**

CRSwNP is associated with poor quality of life and comorbid depressive illnesses. Quality of life of these patients can be assessed by different tests:

- **Rhinosinusitis Disability Index (RSDI)** evaluates with 30 questions impact of CRS on quality of life across 3 dimensions (physical, functional, emotional) [23].
- **Sino-Nasal Outcomes Test (SNOT-22)** assesses the impact on quality of life of 22 items affecting subjects with CRS. Measures ranging from 0 (not a problem) to 5 (severe problem). Includes just one item assessing smell loss subjectively [24].

### **Biologics approved for treatment of CRSwNP**

Biologic treatments present an opportunity to address the severe, unresponsive subgroup of individuals with CRSwNP. At present, EMEA and FDA approved the use of dupilumab, omalizumab, and mepolizumab in chronic rhinosinusitis with nasal polyposis (CRSwNP) as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control. The EUFOREA consensus concluded that biologics are indicated in patients with bilateral nasal polyps who had undergone sinus surgery in the past and meet 3 of the following criteria: evidence of T2 inflammation, need for systemic corticosteroids (2 or more courses in the last year), significantly impairment of quality of life, significant loss of smell, diagnosis of comorbid asthma [25].

**Dupilumab (Dupixent®)** is a fully human monoclonal antibody binding to the IL-4  $\alpha$  receptor, which inhibits signaling of IL-4 and IL-13, therefore blocking the pathways leading to differentiation of B cells into IgE production, eosinophil activation, mucus secretion, and airway remodeling. Dupilumab is approved for the treatment of severe atopic dermatitis and severe asthma in adults and children. It was the first biologic indicated in CRSwNP, approved in 2019. The standard dose is a first dose of 600 mg subcutaneous (sbc) followed by 300 mg sbcevery 2 weeks. Its mechanism of action against IL4/13 lies in the reduction of type 2 inflammation that underlies most NP.

**Omalizumab (Xolair®)** is a recombinant humanized immunoglobulin-G1 $\kappa$  monoclonal antibody that selectively binds to the C $\epsilon$ 3 domain of the Fc region of human IgE in blood and interstitial fluid, blocking its action and preventing it from binding to the high-affinity receptor (Fc $\epsilon$ RI) on the surface of mast cells, basophils, and dendritic cells, thereby interfering with activation. The increased local production of



IgE in patients with CRSwNP indicates that this drug hold potential. Omalizumab is indicated to treat severe asthma and was approved in 2020 for CRSwNP not controlled with INCS. It is administered sbcat doses varying from 75 to 600 mg every 2-4 weeks based on body weight and total peripheral blood IgE.

**Mepolizumab (Nucala®)** is an IgG1 kappa monoclonal antibody that antagonizes interleukin-5, causing a decrease in airway eosinophils. The standard dose is 100 mg, administered sbc every 4 weeks. It is indicated in severe asthma and eosinophilic granulomatosis with polyangiitis (EGPA) and was approved for uncontrolled CRSwNP in 2021.

**Benralizumab (Fasenra®)** is an afucosylated monoclonal antibody that directly targets the  $\alpha$  chain of the IL-5 receptor, inducing an apoptotic effect on eosinophils, resulting in rapid eosinophil depletion. It is indicated in severe eosinophilic uncontrolled asthma. It is administered 30mg sbcevery 4 weeks for the first 3 weeks and maintained with a dose of 30mg sbcevery 8 weeks. It has not approval for CRSwNP.

**Reslizumab (Cinqaero®)** is a monoclonal antibody against human IL5. It is indicated insevereeosinophilic asthma but it is not approved for CRSwNP. It is given as an intravenous infusion once every four weeks, adjusted for weight (100-575mg).

**Mepolizumab, benralizumab and reslizumab** are **anti IL5** biological treatment. IL-5 is a key cytokine responsible for the differentiation, maturation, recruitment and activation of human eosinophils. Its potential for action on CRSwNP lies in binding to human IL-5, blocking its biological function. Consequently, survival and activity of eosinophils are reduced.

**Table S2a. Quality assessment of randomised controlled trials selected for inclusion according to the CASP system.**

Study reference	Type of study	Quality level	CASP results		
			Design	Methods	Outcomes
Dupilumab					
Bachert, Mannent et al. 2016	RCT	High	+++	++0++	++
Bachert, Han et al. 2019	RCT	Very high	+++	+++++	++
Mullol, Bachert et al. 2022	Posthoc analysis of SINUS-24 and SINUS-52 phase 3 trials	Very High	+++	+++++	++
Hellings, Peters et al. 2022	Posthoc analysis of SINUS-24 and SINUS-52 phase 3 trials	Very high	+++	+++++	++
Fujieda, Matsune et al. 2022	Posthoc analysis of SINUS-52 phase 3 trial	Very high	+++	+++++	++
Trimarchi, Indelicato et al. 2021	Single case report				
Omalizumab					
Gevaert, Calus et al. 2013	RCT	High	+++	++0++	++
Gevaert, Omachi et al. 2020	RCT	Very high	+++	+++++	++
Damask, Chen et al. 2022	Posthoc analysis of POLYP 1 and POLYP 2 phase 3 trials	Very high	+++	+++++	++
Gevaert, Saenz et al. 2022	OLE from RCT	Medium-High	+++	+++00	++
Mepolizumab					
Gevaert, Van Bruaene et al. 2011	RCT	High	+++	++0++	++
Bachert, Sousa et al. 2017	RCT	Very high	+++	+++++	++

Han, Bachert et al. 2021	RCT	High	+++	++0++	++
<b>Benralizumab</b>					
Tversky, Lane et al. 2021	RCT	High	+++	++0++	++
Takabayashi, Asaka et al. 2021	RCT	High	+++	++0++	++
Bachert, Han et al. 2022	RCT	Very high	+++	+++++	++

Quality assessment was performed using CASP checklists for each type of study (<https://casp-uk.net/casp-tools-checklists/>). Results depicted in the table correspond to questions related to design (questions 1-3), methodology (questions 4-6) and outcomes (questions 7-8) in the corresponding checklists. Each positive (yes) response in the questionnaire is depicted as (+), negative it is indicated as (-), and “can’t tell” is depicted as (0). The increasing number of (+) indicates a greater quality assessment score.  
RCT: randomized clinical trial.

**TABLE S2b. Quality assessment of cohort studies selected for inclusion according to the CASP system.**

Study reference	Type of study	Quality level	CASP results	
			Validity	Outcomes
Dupilumab				
Napolitano, Maffei et al. 2021	Observational retrospective study	Medium-High	+++00+	+
van der Lans, Fokkens et al. 2022	Observational prospective study	Very high	+++++	+
Nettis, Brussino et al. 2022.	Observational prospective study	Medium-High	+++00+	+
Nettis, Patella et al. 2021	Observational prospective study	Medium-High	+++00+	+
Omalizumab				
Ruiz-Hornillos, Rodríguez Jiménez et al. 2020.	Observational prospective study	High	+++0++	+
Tiotiu, Oster et al. 2020	Observational retrospective study	High	+++0++	+
Mepolizumab				
Cavaliere, Incorvaia et al. 2019	Single case report			

Kassem, Cohen-Confino et al. 2021	Observational retrospective study	Medium-low	+++0+	+
Yilmaz, Türk et. 2020	Observational retrospective study	High	+++0++	+
<b>Benralizumab</b>				
Shimizu, Kato et al. 2021	Single case report			
Bagnasco, Brussino et al. 2020	Observational retrospective study	Medium	+++0?+	+
<b>Multiple biologics</b>				
Meier, Schmid-Grendelmeier et al. 2021	Observational retrospective study	Medium	+++0?+	+
Tiotiu, Mendez-Brea et al. 2022	Observational retrospective study	Medium	+++0?+	+
De Corso, Montuori et al. 2022	Observational retrospective study	Medium	+++0?+	+
Barroso, Valverde-Monge et al. 2022	Observational retrospective study	Medium	+++0?+	+

Quality assessment was performed using CASP checklists for each type of study (<https://casp-uk.net/casp-tools-checklists/>). Results depicted in the table correspond to questions related to validity (questions 1-6), and outcomes (questions 7) in the corresponding checklists. Each positive (yes) response in the questionnaire is depicted as (+), negative it is indicated as (-), and “can’t tell” is depicted as (0). The increasing number of (+) indicates a greater quality assessment score.

**TABLE S2c. Quality assessment of systematic reviews with meta-analysis selected for inclusion according to the CASP system.**

Study reference	Type of study	Quality level	CASP results		
			Design	Methods	Outcomes
Comparison of Different Biologics					
Cai, Xu et al. 2022	SR and NMA of 7 RCTs	Very high	++	+++	++
Wu, Zhang et al. 2022	SR and NMA of 9 RCTs	Very high	++	+++	++
Peters, Han et al. 2021	SR and indirect treatment comparison of 4 RCTs	High	++	+--	++

Wang, Sun et al. 2022	SR and NMA of 7 RCTs	Very high	++	+++	++
Oykhman, Paramo et al. 2022	SR and NMA of 29 RCTs	High	++	++	++

Quality assessment was performed using CASP checklists for each type of study (<https://casp-uk.net/casp-tools-checklists/>). Results depicted in the table correspond to questions related to design (questions 1-2), methodology (questions 3-5) and outcomes (questions 6-7) in the corresponding checklists. Each positive (yes) response in the questionnaire is depicted as (+), negative it is indicated as (-), and “can’t tell” is depicted as (0). The increasing number of (+) indicates a greater quality assessment score. SR=systematic review; NMA=Network meta-analysis; RCTs=randomized clinical trials

**TABLE S3. PRISMA Checklist.**

Section and Topic	Item #	Checklist item	Location where item is reported
<b>TITLE</b>			
Title	1	Identify the report as a systematic review.	Line 1-2
<b>ABSTRACT</b>			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Line 4-63
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Line 65-241
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Line 243-245
<b>METHODS</b>			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Line 421-487
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Line 249-251
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Line 248-256

Section and Topic	Item #	Checklist item	Location where item is reported
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Line 488-494
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Line 488-494
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Line 492-494
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	.Line 492-494
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Line 155-161
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Line 488-491
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	

Section and Topic	Item #	Checklist item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Line 155-161
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Line 155-161
<b>RESULTS</b>			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Line 497-503
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Line 497-503
Study characteristics	17	Cite each included study and present its characteristics.	Table S3 of Supplementary material
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table S3 of Supplementary material
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of	

Section and Topic	Item #	Checklist item	Location where item is reported
		bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Line
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Line 1197-1217
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
<b>DISCUSSION</b>			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Line 1231-1359
	23b	Discuss any limitations of the evidence included in the review.	Line 1341-1348
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	Line 1221-1229
<b>OTHER INFORMATION</b>			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Line 420
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	.
Support	25	Describe sources of financial or non-financial support for the	Line 1615-1617



Section and Topic	Item #	Checklist item	Location where item is reported
		review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	Line 1605-1613
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NOT PUBLICLY

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.doi: 10.1136/bmj.n71 For more information, visit: <http://www.prisma-statement.org/>

**TABLE S4. DETAIL OF THE STUDIES INCLUDED IN THE SYSTEMATIC REVIEW**

Study reference	Design	Intervention (n=sample size) – follow up time (weeks)	Asthma <sup>†</sup> (%)	N-ERD <sup>†</sup> (%)	≥1 FESS <sup>†</sup> (%)	Blood eosinophil count <sup>†</sup> (mean-SD)	NPS <sup>†</sup> (mean-SD)	Years with CRSwNP <sup>†</sup> (mean-SD)	Basal smell – test <sup>†</sup> (mean-SD)	Smell outcomes- LS mean difference vs placebo (95% CI); p value
<b>Dupilumab – clinical trials</b>										
Bachert, Mannent, et al. 2016 [17]	Randomized, double-blind, placebo-controlled parallel-group	Placebo q2w (n = 30) or dupilumab q2w (n=30) plus mometasone furoate nasal spray– 16w	63.3 vs 53.3	30.0 vs 20.0	63.3 vs 53.3	0.4 (0.6) vs 0.4 (0.2)	5.7 (0.9) vs 5.9 (1.0)	7.6 (6.1) vs 11.5 (8.7)	UPSIT* 12.8 (8.3) vs 15.6 (7.9)	UPSIT* 14.8 (10.9 to 18.7); p<0.001
Bachert, Han, et al. 2019 [18]	Randomised, double-blind, placebo-controlled, parallel-group (SINUS-24)	Placebo q2w (n=133) or dupilumab q2w (n=143)– 24w	59 vs 57	59 vs 63 vs 57	74 vs 69	0.4 (0.3) vs 0.4 (0.3)	5.9 (1.3) vs 5.6 (1.2)	10.7 (8.5) vs 11.4 (9.6)	UPSIT* 14.4 (8.3) vs 14.7 (8.7) LoS** 2.7 (0.5) vs 2.7 (0.6)	UPSIT* 10.6 (8.8 to 12.3); p<0.0001 LoS** –1.1 (–1.3 to –0.9; p<0.0001
	Randomised, double-blind, placebo-controlled, parallel-group (SINUS-52)	Placebo (n=143), dupilumab q2w– q4w (n=145) or dupilumab q2w (n=150)– 52w	29 vs 32	29 vs 28 vs 23	58 vs 59 vs 59	0.4 (0.4) vs 0.4 (0.3) vs 0.4 (0.4)	5.9 (1.2) vs 6.3 (1.2) vs 6.1 (1.2)	10.8 (9.4) vs 10.6 (9.1) vs 11.3 (10.4)	UPSIT* 13.8 (8.3) vs 13.6 (7.6) vs 13.5 (8.2)	UPSIT* 0.5 (8.9 to 12.1); p<0.0001

									LoS** 2.7 (0.5) vs 2.7 (0.6) vs 2.8 (0.5)	LoS** 0.9 (-1.1 to -0.8); p<0.0001
Mullol, Bachert, et al. 2022 [19]	Posthoc analysis of SINUS-24 and SINUS-52 [18]	See SINUS-24 and SINUS-52 [18]	See SINUS-24 and SINUS-52 [18]	See SINUS-24 and SINUS-52 [18]	See SINUS-24 and SINUS-52 [18]	See SINUS-24 and SINUS-52 [18]	See SINUS-24 and SINUS-52 [18]	See SINUS-24 and SINUS-52 [18]	See SINUS-24 and SINUS-52 [18]	<p>UPSIT* 10.6 (9.0 to 11.7); p&lt;0.0001 at week 2</p> <p>LoS** -0.1 (-0.1 to -0.0); p&lt;0.05 at day 3, and -1.0 (-1.2 to -0.9); p&lt;0.0001 at week 24</p> <p>SNOT-22 item "decreased sense of smell/taste": -1.5 (-1.8 to 1.3); p&lt;0.0001 at week 8</p> <p>Improvements were unaffected by CRSwNP duration, prior sinonasal surgery, or comorbid asthma and/or N-ERD</p> <p>The proportion of patients with anosmia in the dupilumab group declined from 78% at baseline to 45% at week</p>

										<p>2 and 28% at week 24 (both <math>p &lt; 0.0001</math>). In the placebo group, the proportion of patients who were anosmic was unchanged at week 24 relative to baseline</p> <p>Smell outcomes worsened after discontinuation of dupilumab at week 24 in patients in SINUS-24</p>
Hellings, Peters, et al. 2022 [20]	Posthoc analysis of SINUS-24 and SINUS-52 [18]	See SINUS-24 and SINUS-52 [18]	See SINUS-24 and SINUS-52 [18]	See SINUS-24 and SINUS-52 [18]	See SINUS-24 and SINUS-52 [18]	See SINUS-24 and SINUS-52 [18]	See SINUS-24 and SINUS-52 [18]	See SINUS-24 and SINUS-52 [18]	See SINUS-24 and SINUS-52 [18]	<p>UPSIT* 5.5 (4.4 to 6.7); <math>p &lt; 0.0001</math></p> <p>Onset of treatment effect with dupilumab was similar regardless of prior surgery, asthma, N-ERD or allergic rhinitis</p> <p>Improvements with dupilumab continued and were sustained to the end of treatment in both studies</p>
Fujieda, Matsune, et al 2022 [22]	Posthoc analysis of SINUS-52 [18] that	Non-/mild ECRS vs moderate/	See SINUS-52 [18]	See SINUS-52 [18]	See SINUS-52 [18]	See SINUS-52 [18]	See SINUS-52 [18]	See SINUS-52 [18]	See SINUS-52 [18]	<p>UPSIT* 8.4 (5.6 to 11.2) in non-/mild</p>

	uses the JESREC algorithm*** [21] to classify patients into non-ECRS, mild ECRS, moderate ECRS, and severe ECRS subgroups [18]	severe ECRS								ECRS vs 11.7 (9.8 to 13.6) in moderate/severe ECRS; p=0.0692 at week 24; and 8.3 (5.4 to 11.3) in non-/mild ECRS vs 11.6 (9.7 to 13.5) in moderate/severe ECRS; p=0.0733
<b>Dupilumab - real life</b>										
Trimarchi, Indelicato, et al. 2021 [23]	Retrospective, observational, real-life study	A 65-year-old male (n=1) treated with dupilumab – 26w	100	N.M.	7 FESS	N.M.	5 points	10 years	UPSIT 9	UPSIT* of 25 after 26 weeks
Napolitano, Maffei, et al. 2021 [24]	Retrospective, observational, real-life study	19 patients with AD and CRSwNP treated with dupilumab – 24w	47.4	N.M.	N.M.	78.95% with eosinophilia (>500 eosinophils/mm <sup>3</sup> )	N.M.	N.M.	LoS** mean 1.9 (SD ± 0.8) 89.47% anosmia (method N.M.)	LoS** 0.8 ± 0.8 at 16w and 0.5 ± 0.6 at 24w
van der Lans, Fokkens, et al. 2022 [25]	Prospective, observational, real-life study	131 patients treated with dupilumab – 48w	N.M.	N.M.	N.M.	N.M.	N.M.	1.56 (1.74)	Sniffin' Sticks-12 **** 3.6 (2.1) 34.7% anosmic 51.0% hyposmic 14.3% normosmic	Sniffin' Sticks-12 **** 7.3 (2.8) at 24w and 8.3 (3.2) at 48w
Nettis, Brussin, et al. 2022 [26]	Prospective, observational, real-life study	82 patients treated with dupilumab – 16w	62.2	22.4	82.4	5.5 (5.0)	5.0 (2.0)	8.8 (2.0)	LoS** 3.0 (1.0) Smell VAS 9.0 (2.0)	LoS** 1.0 (2.0); p<0.001 Smell VAS 2.0 (4.0); p<0.001

Nettis, Patella, et al. 2021 [27]	Prospective observational, real-life study	9 patients with AD and CRSwNP treated with dupiluma – 16w	N.M.	N.M.	N.M.	5.7 (3.4)	2.8 (1.2)	N.M.	LoS** 1.6 (1.0)	LoS** 0.2 (0.4); p<0.05
<b>Omalizumab – clinical trials</b>										
Gevaert, Calus, 2013 [28]	A randomized, double-blind, placebo-controlled	Placebo (n=8) or dupilumab (n=16) – 16w	100 vs 100	50 vs 53	N.M.	4.7 (3.6-6.3) vs 3.9 (3.1-6.9)	6 (6-8) vs 6 (4-6)	N.M.	UPSIT* 12 (10-13) vs 12 (10-23)	LoS p=0.004
Gevaert, Omachi, et al. 2020 [29]	Two replicates (identical), phase 3, randomized, multicenter, double-blind, placebo controlled studies (POLYP-1 and POLYP-2)	Placebo or omalizumab and intranasal mometasone-24w POLYP-1: Placebo (n= 66) or omalizumab (n= 72) POLYP-2: Placebo (n=65) or omalizumab (n= 62)	POLYP-1 48.5 vs 58.3 POLYP-2 – 60.0 vs 61.3	POLYP-1 16.7 vs 22.2 POLYP-2 32.3 vs 38.7	POLYP-1 36.4 vs 31.9 POLYP-2 23.1 vs 35.5	POLYP-1 3.5 (3.0) vs 3.3 (2.6) POLYP-2 3.5 (1.96) vs 3.1 (1.7)	POLYP-1 6.2 (1.0) vs 6.3 (0.9) POLYP-2: 6.4 (0.9) vs 6.1 (0.9)	N.M.	UPSIT* POLYP-1: 13.9 (7.4) vs 12.8 (7.9) UPSIT* POLYP-2: 13.1 (7.3) vs 12.8 (7.6) LoS** POLYP-1 2.8 (0.4) vs 2.5 (0.8) LoS* POLYP-2 2.8 (0.6) vs 2.6 (0.8)	UPSIT* POLYP 1 3.81 (1.38 to 6.24); p=0.024 UPSIT* POLYP-2: 3.86 (1.57 to -6.15); p=0.0011 LoS** POLYP-1 - 0.33 (-0.60 to -0.06); p=0.0161 LoS** POLYP-2 - 0.45 (-0.73 to -0.16); p=0.0024
Damask, Chen, et al [30]	Post hoc analysis of POLYP-1 and POLYP-2 [29] – subgroup analysis	Subgroups included blood eosinophil count at baseline (>300 or ≤300 cells/μL), previous FESS (yes/no), asthma status (yes/no), and N-ERD (yes/no)-24w	See POLYP-1 and POLYP-2 [29]	POLYP-1 and POLYP-2 [29]	POLYP-1 and POLYP-2 [29]	POLYP-1 and POLYP-2 [29]	POLYP-1 and POLYP-2 [29]	POLYP-1 and POLYP-2 [29]	POLYP-1 and POLYP-2 [29]	UPSIT improvement regardless of blood eosinophil count, previous FESS, asthma, and N-ERD
Gevaert, Saenz, et al. 2022 [31]	Open-label extension (OLE) of POLYP-1 and POLYP-2 [29]	“Patients who continued omalizumab” = patients initially randomized to omalizumab in POLYP 1 and 2	See POLYP-1 and POLYP-2 [29]	See POLYP-1 and POLYP-2 [29]	See POLYP-1 and POLYP-2 [29]	See POLYP-1 and POLYP-2 [29]	See POLYP-1 and POLYP-2 [29]	See POLYP-1 and POLYP-2 [29]	See POLYP-1 and POLYP-2 [29]	In patients who switched to omalizumab, improvements in UPSIT scores reached a peak improvement

		continued to receive omalizumab for 28 additional weeks (from weeks 24 to 52). "Patients who switched treatment"= patients initially randomized to placebo in POLYP 1 and 2 received omalizumab for 28 weeks (from weeks 24 to 52).								of 3.8 points at 52w  UPSIT gradually worsened during the OLE treatment-free follow-up period but remained improved by a mean 0.6 and 1.4 points at 76w in patients who switched and continued omalizumab, respectively
<b>Omalizumab – clinical trials</b>										
Ruiz-Hornillos, Rodríguez Jiménez, et al. 2020 [32]	Prospective observational, real-life study	16 patients with asthma and CRSwNP – 12 months	100	56.2	N.M.	N.M.	N.M.	N.M.	RSDI*****: 2.5 (2.0-4.0) - quantified through the median scores obtained in RSDI question number 20	No significant differences after 12months of treatment in median score in RSDI question number 20
Tiotiu, Oster, et al. 2020 [33]	Retrospective, observational, real-life study	24 patients with asthma and CRSwNP treated with omalizumab – 6 months	100	37.5	75	0.91 (0.51)	N.M.	N.M.	Smell VAS 8.50 (1.58)	Smell VAS 5.08 (3.42); p<0.001
<b>Mepolizumab – clinical trials</b>										
Gevaert, Van Bruaene, et al. 2011 [34]	Randomized, double-blind, placebo-controlled	Placebo (n=10) vs mepolizumab (n=20) – 8w	33.3 vs 50.5	0 vs 25	N.M.	N.M.	N.M.	8.4 (1.7) vs 7.9 (1.8)	Smell VAS 2.4 (0.8) vs 2.6 (0.6)	Smell VAS this parameter did not reach statistical significance; p=0.079
Bachert, Sousa, et al. 2017 [35]	Randomized, double-blind,	Placebo (n=51) vs mepolizumab (n=54) – 25w	75% vs 81%	N.M.	N.M.	100 vs 100	6.31 (0.88) vs 6.28 (0.88)	N.M.	Smell VAS 9.10 (8.4-9.7)	Smell VAS -1.9 (-2.9 to -0.9); p<0.001

	placebo-controlled trial								vs 9.0 (8.4-9.7)	
Han, Bachert, et al. 2021 [36]	<b>Randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial (SYNAPSE)</b>	Placebo (n= 206) vs mepolizumab (n=201)- 52w	74 vs 68	31 vs 22	100 vs 100	5.6 (1.4) vs 5.4 (1.2)	4.0 (0.9) vs 3.90 (0.8)	N.M.	Smell VAS 10.0 (9.6-10.1) vs 10.0 (9.6-10.0)	Smell VAS – 0.3 (–0.6 to –0.1); p=0.020)
<b>Mepolizumab – real life</b>										
Cavaliere, Incorvaia. 2019 [37]	Prospective observational, real-life study	62-year-old female with asthma and CRSwNP– 4 months	100	0	N.M.	N.M.	≥ 300 cells/μl	N.M.	N.M.	Recovered her sense of smell (patient assessment) after 4 months
Kassem, Cohen-Confino, et al. 2021 [38]	Prospective observational, real-life study	11 patients with asthma and CRSwNP treated with mepolizumab-7.4 (±5.5) months	100	45.4	72.7	N.M.	N.M.	N.M.	10 with anosmia (method N.M.)	6/10 with anosmia
Yilmaz, Türk, et al. 2020 [39]	Prospective observational, real-life study	16 subjects with asthma and CRSwNP treated with mepolizumab-24w	100	63	N.M.	N.M.	5.6 (5.9)	N.M.	Smell NAS 4.0 (5.1)	Smell NAS 2.4 (4.2); p>0.05
<b>Benralizumab - clinical trials</b>										
Tversky, Lane, et al. 2021 [40]	Randomized double-blind, placebo-controlled study	Placebo (n=12) vs benralizumab (n=12)– 20w	100 vs 83	67 vs 25	100	8.4 (5.9) vs 6.9 (4.1)	6.2 (0.9) vs 5.7 (0.8)	11.1 (14.4) vs 10.0 (5.1)	UPSIT* 10.7 (4.9) vs 12.2 (4.9)	The benralizumab induced change in UPSIT score compared with placebo was not significant 2.2 (2.2); p=0.530
Takabayashi, Asaka, et al. 2021 [41]	Rndomized, double-blind, placebo-controlled study	Placebo (n=11), a single administration of benralizumab (n=22), or	90.9 vs 81.8 vs 82.6	45.5 vs 27.3 vs 26.1	72.7 vs 59.1 vs 65.2	5.6 (3.2) vs 7.7 (6.2) vs 6.2 (4.3)	5.0 (1.6) vs 5.3 (1.4) vs 5.4 (0.9)	N.M.	Smell VAS 8.9 (2.7) vs 8.9 (2.2) vs 7.3 (3.6)	There was no change in smell assessed by VAS at week 24

		benralizumab q4w (n=23)– 12w								
Bachert, Han, et al. 2022 [42]	Randomized, double-blind, placebo-controlled study (OSTRO)	Placebo (n=206) vs benralizumab (n=207) – 40w	67.0 vs 68.6	29.1 vs 30.0	73.4 vs 72.9	4.4 (2.4) vs 4.4 (3.6)	6.1 (1.1) vs 6.1 (1.1)	N.M.	84.4 vs 82.6 anosmia (UPSIT score of <18)	LoS showed significant improvement against placebo (p=0.003)  Changes in sense of smell measured by UPSIT were not appreciably different between treatment groups
<b>Benralizumab – real life</b>										
Shimizu, Kato, et al. 2021 [43]	Prospective observational, real- life study	52-year-old woman with asthma, eosinophilic otitis media and CRSwNP	100	0	N.M.	N.M.	N.M.	N.M.	N.M.	Experienced partial improvement in sense of smell following therapy with benralizumab – method is not mentioned
Bagnasco, Brussino, et al. 2020 [44]	Prospective observational, real- life study	34 patients with asthma and CRSwNP – 24w	N.M.	N.M.	N.M.	6.3 (3.9)	N.M.	N.M.	Subjective patient's perception of anosmia (yes/ no). 76% perceived anosmia	Anosmia disappeared in 31% patients (p=0.0034)
<b>Reslizumab - clinical trials</b>										
Not found										
<b>Reslizumab – real life</b>										
Not found										
<b>Network meta-analysis</b>										
<b>Study reference</b>	<b>RCTs included (number)</b>	<b>Drugs compared with placebo</b>	<b>Conclusion on smell</b>							



Peters, Han, et al. 2021 [45]	3	Dupilumab and omalizumab		In the intent to treat population, dupilumab had significantly greater improvements from baseline to week 24 vs omalizumab across least squares mean difference [95% confidence interval], LoS score (0.66 [0.90 to 0.42]) and UPSIT (6.70 [4.67 to 8.73]). Improvement in the 22-item sinonasal outcome test was greater in dupilumab versus omalizumab but was not statistically significant						
Wang, Sun, et al. 2022 [46]	7	Benralizumab, mepolizumab, and reslizumab		Benralizumab improved the UPSIT score (2.30; 95% CI: [0.42, 4.18]; p=0.02) but not mepolizumab (1.30; 95% CI: [-2.38, 4.98]; p=0.49).						
Wu, Zhang, et al. 2022 [47]	9	Dupilumab, omalizumab and mepolizumab		Dupilumab had the best efficacy in terms of UPSIT for surface under the cumulative ranking curve (SUCRA value of 1.000), followed by omalizumab (SUCRA 0.500)						
Oykhman, Paramo, et al. 2022 [48]	14	Dupilumab, omalizumab, mepolizumab, benralizumab and aspirin desensitization (ASA-D)		Compared to placebo, as measured by UPSIT, there was moderate to high certainty evidence that dupilumab (10.96 [95% CI 9.75 to 12.17]), omalizumab (3.75 [95% CI 2.14 to 5.35]), mepolizumab (6.13 [95% CI 4.07 to 8.19]), benralizumab (2.95 [95% CI 1.02 to 4.88]), and ASA-D (2.72 [95% CI 21.17 to 6.61]) improve smell. Among biologics and ASA-D, dupilumab likely improves smell compared to omalizumab (7.21 [95% CI 5.20 to 9.23]), mepolizumab (4.83 [95% CI 2.43 to 7.22]), benralizumab (8.01 [95% CI 5.73 to 10.29]), and ASA-D (8.24 [95% CI 4.16 to 12.32]; all moderate certainty).						
Cai, Xu, et al.2022 [49]	7	Dupilumab, omalizumab, mepolizumab and benralizumab		The results indicate that dupilumab is the most effective and safe treatment route for CRSwNP, when compared with omalizumab, mepolizumab, and benralizumab at 24 weeks of the treatment and end of follow-up						
Comparisons between biologics - real life conditions										
Study reference	Design	Intervention (n=sample size) – follow up time (weeks)	Asthma <sup>+</sup> (%)	N-ERD <sup>+</sup> (%)	≥1 FESS <sup>+</sup> (%)	Blood eosinophil count <sup>+</sup> (mean-SD)	NPS <sup>+</sup> (mean-SD)	Years with CRSwNP <sup>+</sup> (mean-SD)	Basal smell – test <sup>+</sup> (mean-SD)	Smell outcomes- LS mean difference vs placebo (95% CI); p value
Meier, Schmid-Grendelmeier, et al. 2021 [50]	Retrospective, observational, real-life study	29 patients - omalizumab, mepolizumab, or benralizumab	96.4	60.7	36.0	N.M.	N.M.	N.M.	Smell was evaluated based on medical history and the most recent consultation and was classified into 5 categories: -2 (strong worsening), -1 (slight worsening), 0 (no change), +1 (slight improvement).	Sense of smell improved in 58.8% with mepolizumab, 34% benralizumab, and 26% with omalizumab

									and +2 (strong improvement).	
Tiotiu, Mendez-Brea, et al. 2023 [51]	Retrospective, observational, real-life study	72 patients-omalizumab, benralizumab, or mepolizumab	38 vs 50 vs 11	14 vs 13 vs 29	62 vs 56 vs 69	0.9 (0.4) vs 0.7 (0.4) vs 0.8 (0.5)	4.8 (1.4) vs 5.5 (1.0) vs 3.8 (1.6)	N.M.	Loss of smell 18 (86) vs 16 (100) vs 33 (94) -method N.M.	The study showed a statistically significant decrease in the subjects with loss of smell before and after all treatments: mepolizumab (18 to 12, p=0.008), benralizumab (16 to 11, p=0.001), and omalizumab (33 to 21, p<0.001)
De Corso, Montuori, et al. 2022 [52]	Retrospective, observational, real-life study	8 patients - dupilumab, omalizumab, mepolizumab and benralizumab	100	12.5	100	N.M.	5.3 (1.4)	N.M.	Sniffin' Sticks identification test 5.7 (4.6)	A statistically significant difference with the Sniffin' Sticks identification test-16 (SSIT-16; 0–5 anosmia, 6–11 hyposmia, and 12–16 normosmia) was found (from 5.75 ± 4.62 to 11.13 ± 3.04 after 6 months of treatment)
Barroso, Valverde-Monge, et al. 2022 [53]	Retrospective, observational, real-life study	206 patients-omalizumab, mepolizumab, reslizumab, and benralizumab	100	44.7	1 (2-0)	5.4 (3.7)	2 (0-4)	N.M.	14.1% normosmia 33.3% hyposmia	A total or partial improvement in loss of smell was found after

									51.9% anosmia	treatment with all monoclonal antibodies: omalizumab (35.8%), mepolizumab (35.4%), reslizumab (35.7%), and benralizumab (39.1%), with no differences between groups. Partial smell improvement (anosmia to hyposmia) was observed in subjects administered omalizumab (16%), mepolizumab (22%), reslizumab (22%), and benralizumab (17%), with no differences between groups. Total smell improvement was reached in therapy with omalizumab (20%), mepolizumab (14%), reslizumab (14%), and benralizumab
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										(22%), also with no inter-group differences. A comparison of total improvement, partial improvement, and no improvement between subjects with high vs low blood eosinophil count (500/ $\mu$ L) showed no statistical differences. The proportion of patients with improved olfaction was similar between the N-ERD (37%) and non-N-ERD (35.7%) groups
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†Placebo vs drug

ASA-D=aspirin desensitization; CI=confidence interval; CRSwNP=chronic rhinosinusitis with nasal polyps; ECRS= eosinophilic chronic rhinosinusitis; FESS=functional endoscopy sinus surgery; LoS=loss of smell score; LS=least square; NAS=numerical analogue score (0-10); N-ERD= nonsteroidal antiinflammatory drug (NSAID)-exacerbated respiratory disease (NERD); N.M.=not mentioned; NPS=nasal polyp score; RCTs=randomized clinical trials; SD=standard deviation; VAS=visual analogue score (0-10); w=weeks;

\*UPSIT (the University of Pennsylvania Smell Identification Test): scale 0-40; <19=anosmia

\*LoS (loss of smell) symptom score recorded daily using an eDiary with a scale of 0 to 3, where 0=no symptom, 1=mild LoS, 2=moderate LoS, and 3=severe LoS

\*\*\*JESREC (Japanese Epidemiological Survey of Refractory Eosinophilic Rhinosinusitis) algorithm: non-ECRS (<11 points); ECRS ( $\geq$ 11 points)

\*\*\*\*Sniffin' Sticks-12: 0–6=anosmia, 7–10=hyposmia, 11–12=normosmia

\*\*\*\*\* RSDI (Rhinosinusitis Disability Index) - question number 20 is about smell

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