

Clinical Remission in Chronic Rhinosinusitis With Nasal Polyps: a Delphi Consensus from the Rhinosinusitis Italian Network (RINET)



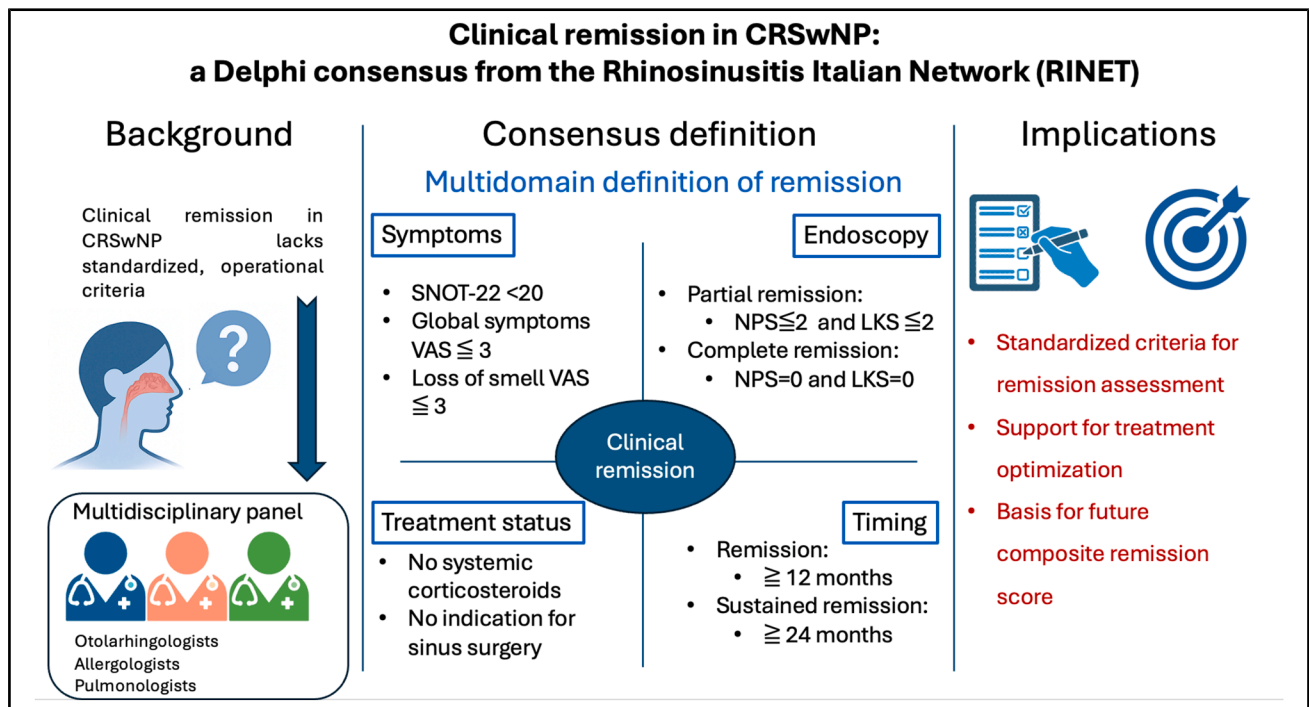
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What is already known about this topic? Clinical remission in chronic rhinosinusitis with nasal polyps (CRSwNP) is an emerging therapeutic goal, but current definitions are broad and heterogeneous, and lack standardized symptom, endoscopic, and management-related criteria, limiting their applicability in research and clinical practice.

What does this article add to our knowledge? This study provides the first operational, consensus-based definition of complete and partial clinical remission in CRSwNP, detailing specific thresholds across symptoms, endoscopy, treatment requirements, and timing, and supports developing a weighted composite remission score.

How does this study impact current management guidelines? The proposed multidomain criteria offer a practical framework to standardize remission assessment, support its implementation as a realistic therapeutic endpoint, and guide treatment optimization, including the distinction between partial and complete remission.

VISUAL SUMMARY



Abbreviations used

ACCESS- Amsterdam Classification of Completeness of Endoscopic Sinus Surgery
CRSwNP- Chronic rhinosinusitis with nasal polyps
ENT- Ear, nose, and throat specialist
LKS- Lund-Kennedy Score
NPS- Nasal Polyp Score
RINET- Rhinosinusitis Italian Network
SD- Standard deviation
SNOT-22- Sino-Nasal Outcome Test-22
TSLP- Thymic stromal lymphopoietin
VAS- Visual analog scale

BACKGROUND: The concept of clinical remission in chronic rhinosinusitis with nasal polyps (CRSwNP) is gaining growing relevance in the era of biologic therapies. However, current definitions remain heterogeneous and lack standardized, operational criteria. This variability limits comparability across studies and hinders the implementation of remission as a therapeutic target in routine practice.

OBJECTIVE: To develop a multidisciplinary, evidence-based, and clinically applicable definition of clinical remission in CRSwNP, integrating symptom-based, endoscopic, therapeutic, and timing-related criteria, and to evaluate expert consensus on the development of a composite remission score.

METHODS: A 3-round Delphi consensus was conducted among experts participating in the Rhinosinusitis Italian Network. Across the 3 rounds, experts rated the statements using a 5-point Likert scale. Positive or negative consensus was defined as $\geq 70\%$ agreement or disagreement, respectively. Descriptive statistics assessed the convergence and stability of responses.

RESULTS: Experts agreed that remission requires meeting concurrent criteria across 4 domains: timing (≥ 12 months), absence of systemic corticosteroid use or surgical indication, symptom thresholds (Sino-Nasal Outcome Test-22 < 20 plus symptoms and hyposmia visual analog scale ≤ 3), and endoscopic thresholds (Nasal Polyp Score and modified Lund-Kennedy score, both 0 for complete remission and both ≤ 2 for partial remission). Consensus emerged on differentiating complete and partial remission, on introducing the concept of sustained remission (≥ 24 months), and on the need for a composite remission score with weighted components and category thresholds.

CONCLUSION: This Delphi consensus provides the first operational, multidomain definition of complete and partial clinical remission in CRSwNP, developed independently by a large multidisciplinary panel and informed by patient perspectives. The proposed criteria offer a practical framework to standardize remission assessment and support its adoption as a therapeutic goal. © 2026 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>). (J Allergy Clin Immunol Pract 2026;14:937-51)

Key words: Chronic rhinosinusitis with nasal polyps; Biologicals; Clinical remission; Delphi consensus; RINET

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic inflammatory disorder of the nose and paranasal sinuses, typically characterized by a marked mucosal inflammatory infiltrate leading to the development of polypoid formations that occupy the nasal cavities. This results in nasal obstruction (usually severe), loss of smell, and a significant impairment in

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patients' quality of life. The diagnosis of CRSwNP is based not only on the above-mentioned symptoms but also on endoscopic (and, when necessary, radiological) evidence of mucosal inflammation within the sinuses and the presence of polyps protruding into the nasal cavities.¹

From a therapeutic perspective, the standard of care consists of long-term treatment with intranasal topical corticosteroids. Patients who do not respond adequately to medical therapy may require repeated courses of systemic corticosteroids and endoscopic sinus surgery (ESS).¹ However, approximately 40% of patients who undergo ESS experience disease recurrence, necessitating escalation of medical therapy and, in some cases, revision surgery.² This proportion increases significantly in patients with certain comorbidities—such as asthma or intolerance to nonsteroidal anti-inflammatory drugs—or in those exhibiting marked eosinophilic and/or mast cell–driven nasal and sinus inflammation.^{3–5}

The inflammation characterizing the nasal and sinus mucosa of patients with CRSwNP is typically dominated by type 2 inflammation (at least in Europe and North America). This process is marked by aberrant and chronic epithelial activation, leading to the release of thymic stromal lymphopoietin (TSLP) from epithelial cells, activation of both adaptive (particularly T helper 2 lymphocytes) and innate (type 2 innate lymphoid cells, ILC2s) immune subsets, and recruitment and activation of effector cells such as eosinophils and mast cells. These mechanisms are mediated through the release of key cytokines, including IL-4, IL-13, and IL-5.⁶ New biologic therapeutic strategies, based on the use of monoclonal antibodies targeting key mediators of type 2 inflammation, have profoundly transformed the therapeutic landscape and management outlook for patients with CRSwNP. The first biologic agent approved for CRSwNP treatment was dupilumab, which acts by blocking the alpha subunit of the IL-4 receptor, thereby inhibiting both IL-4– and IL-13–mediated inflammatory pathways, as the 2 cytokines share this receptor component.^{7,8} Subsequently, mepolizumab (an anti-IL-5 monoclonal antibody)⁹ and omalizumab (an anti-IgE monoclonal antibody)¹⁰ were also approved for the treatment of CRSwNP. More recently, encouraging phase 3 clinical trial results have been published for tezepelumab (an anti-TSLP monoclonal antibody)¹¹ and depepokimab (a long-acting anti-IL-5 monoclonal antibody).¹² The primary and secondary outcomes evaluated to confirm the efficacy of biologic therapies have thus far included: reduction in the extent of nasal polyp growth (assessed by the Nasal Polyp Score, NPS¹³), improvement in nasal obstruction and in loss of smell (measured through various patient-reported outcomes), improvement in symptom-related quality of life (measured by the Sino-Nasal Outcome Test-22 [SNOT-22]¹⁴), reduction in the use of systemic corticosteroids, and decreased need for revision surgery for nasal polyposis. The efficacy of biologic therapies in CRSwNP is now being confirmed—and in some cases even amplified—by real-life clinical studies.^{15–20}

In the current therapeutic landscape—where innovative biologic treatments are increasingly integrated with standard medical and surgical approaches—it is becoming ever more important to achieve the best possible efficacy outcomes for each individual patient. This goal relies on a thorough phenotypic characterization to guide the choice of biologic therapy, thereby enabling a personalized and precision medicine approach.²¹ A well-reasoned selection of the most appropriate

therapeutic strategy for each patient may also allow the pursuit of broader treatment goals beyond improvement in single outcomes. In this context, similarly to what has occurred in the field of severe asthma,²² the concept of *clinical remission* is gaining ground in rhinology, defined as sustained, concurrent improvement across multiple efficacy endpoints over an extended period of time.²³ To date, the concept of *clinical remission* in CRSwNP is generally defined as a prolonged state of disease control, without bothersome symptoms reported by the patient for at least 12 months, in the absence of both oral corticosteroid use and ESS, and with no endoscopic evidence of active disease.²³ This broad definition—lacking specific criteria regarding which assessment tools and corresponding cutoffs should be used to evaluate the endpoints included—has led to highly variable reports of treatment effectiveness across studies, depending on how individual authors have operationalized the definition of *clinical remission*.^{16,24–27}

In this article, we present the results of a Delphi consensus conducted with the collaboration of a large panel of otorhinolaryngologists, allergists, and pulmonologists participating as investigators in the Italian registry of severe uncontrolled chronic rhinosinusitis (Rhinosinusitis Italian Network, RINET—ClinicalTrials.gov: NCT05935683), an initiative promoted by the Italian Academy of Nasal Cytology and the Italian Academy of Rhinology. The objective of this consensus was to define the concept of *clinical remission* in CRSwNP and to identify the most appropriate endpoints and corresponding cutoffs for its assessment.

METHODS

Study design

A Delphi consensus process was conducted from April to November 2025 to develop a multidisciplinary, evidence-based definition of clinical remission in CRSwNP. The Delphi method was selected for its structured and iterative approach, allowing for systematic collection, refinement, and quantification of expert opinions through multiple questionnaire rounds. Three consecutive rounds were carried out online, each designed to progressively refine the statements and reach agreement among participants.

Scientific board and expert panel

The study was overseen by a scientific board made up of 3 allergologists and 8 ear nose, and throat (ENT) specialists, who were responsible for designing the study, developing and validating the survey content, and analyzing the findings. A multidisciplinary expert panel participated in the Delphi process, including 38 ENT specialists, 33 allergologists, and 5 pulmonologists. All panel members were recognized specialists with established clinical and/or research expertise in managing chronic rhinosinusitis and were designated by each RINET center (2 experts per center). Participation in all Delphi rounds was voluntary and anonymous to promote independent judgment and minimize bias.

Involvement of patient associations

Before launching the Delphi survey, the topics included in the round 1 questionnaire were presented at a meeting with representatives from several patient associations, namely *Respiriamo Insieme*, *Associazione Pazienti della Sindrome di Churg Strauss* (eosinophilic granulomatosis with polyangiitis), *Federasma e Allergie Odv*, and *Apnoici*. The meeting aimed to explain the rationale and overall structure of the project, outline the Delphi methodology

and its objectives, present the structure and content of the round 1 Delphi questionnaire, and gather insights and suggestions to ensure that the definition of clinical remission also reflects the patient's perspective. The scientific board discussed the feedback received during this consultation and used it to refine the questionnaire before distributing it to the expert panel.

Delphi procedure

The Delphi process involved 3 rounds. The first-round questionnaire included 53 statements addressing 6 key thematic areas: the definition of clinical remission in CRSwNP, timing-related evaluation criteria, endoscopic evaluation criteria, treatment- or management-related evaluation criteria, symptom-related evaluation criteria, and the role of inflammatory markers in defining remission. Lastly, it also explored the proposal of a composite remission score for CRSwNP.

After analyzing the responses from round 1, statements were revised to improve clarity, remove redundancy, and incorporate participant feedback. The second-round questionnaire included 44 refined statements that maintained the same thematic focus while introducing new aspects related to partial remission and disease management. The third-round questionnaire featured 32 statements and aimed to finalize or refine consensus on items that remained controversial after earlier rounds.

Rating scale and definition of consensus

In all rounds, participants used a 5-point Likert scale to indicate their level of agreement, where 1 meant strongly disagree, 2 disagree, 3 neither agree nor disagree, 4 agree, and 5 strongly agree. A positive consensus was predefined as at least 70% of respondents rating a statement with scores of 4 or 5. A negative consensus (disagreement) was defined as at least 70% of respondents rating a statement with scores of 1 or 2, indicating strong or moderate disagreement. Statements that did not reach either positive or negative consensus were reformulated and reevaluated in subsequent rounds, enabling the ongoing refinement of expert opinions.

Statistical analysis

All responses were analyzed using descriptive statistics. For each statement and each round, mean, median, standard deviation (SD), and interquartile range were calculated to describe the distribution of scores and assess the degree of convergence across rounds. The stability of consensus was evaluated by comparing measures of central tendency and dispersion throughout the Delphi process.

RESULTS

A total of 53 statements, initially developed by the board, were then submitted for evaluation in round 1. The Delphi panel consisted of 76 multidisciplinary experts, including 38 ENT specialists, 33 allergologists, and 5 pulmonologists (Figure 1). In round 1, 74 of 76 panelists completed the survey, resulting in a response rate of 97.3%. Consensus was reached on 31 of the 53 statements. One item (statement 48) was intentionally designed as an exploratory, open-ended question, for which panelists were not required to express agreement or disagreement. It was therefore excluded from the consensus assessment. In round 2, the number of statements was reduced to 44 based on the results and qualitative feedback from the earlier round. A total of 69 experts participated (response rate: 90.7%), and consensus was achieved for 42 of the 44 statements (72.7%).

In round 3, 32 statements were re-evaluated. The participation rate stayed steady at 69 of 76 experts (90.7%). Consensus was reached on all 32 statements in this final round (100%).

The list of statements is shown in Table I. The main results of the Delphi are shown in Figures 2 and 3.

Definition of clinical remission in CRSwNP

The panel showed strong agreement that the definition of remission in CRSwNP should include specific thresholds for both symptoms and objective findings, with 98.5% of respondents supporting this principle (mean \pm SD, 4.66 \pm 0.51). Panelists favored a 2-tiered concept of remission: complete clinical remission, defined as the total absence of symptoms and endoscopic signs for at least 12 months (91.3%; mean \pm SD, 4.43 \pm 0.78), and partial clinical remission, characterized by minimal residual symptoms or signs while maintaining overall disease stability (84.1%; mean \pm SD, 4.19 \pm 0.84).

There was broad agreement that clinical remission is a realistic treatment goal in CRSwNP (95.7%; mean \pm SD, 4.49 \pm 0.63), and that differentiating between complete and partial remission has clinical importance (84.1%; mean \pm SD, 4.33 \pm 0.89). Partial clinical remission was also seen as a useful intermediate stage that could lead to full remission and help optimize treatment (85.5%; mean \pm SD, 4.19 \pm 0.83). However, the panel agreed that partial remission should not be regarded as true remission but rather as a state of clinical control (81.2%; mean \pm SD, 4.14 \pm 0.93).

The concept of clinical control was generally understood as the absence of symptoms, exacerbations, and the need for oral corticosteroids or surgery during ongoing treatment, regardless of the time frame (86.8%; mean \pm SD, 4.09 \pm 0.86). Finally, 85.3% of experts (mean \pm SD, 4.18 \pm 0.79) emphasized that the mucosal inflammatory component should also be considered when defining clinical remission.

Timing-related evaluation criteria

The panel strongly agreed that clinical remission in CRSwNP should require meeting remission criteria for at least 12 consecutive months, with 94.2% of experts endorsing this time frame (mean \pm SD, 4.51 \pm 0.61). Similarly, 89.9% agreed that remission should be evaluated retrospectively based on 12 months of sustained indicators of disease stability (mean \pm SD, 4.29 \pm 0.73).

Experts also supported the concept of sustained remission, defined as a long-lasting remission of 24 months or more, reaching a consensus with 85.5% agreement (mean \pm SD, 4.23 \pm 0.73).

Endoscopic evaluation criteria

The panel emphasized the importance of endoscopic evaluation in determining remission. A total of 73.9% of experts supported including the Lund-Kennedy endoscopic score, highlighting its ability to assess not only polyp size but also nasal secretions and mucosal health (mean \pm SD, 4.03 \pm 0.86). Furthermore, 82.6% recommended using both a modified Lund-Kennedy score (LKS) and the NPS when evaluating endoscopic remission (mean \pm SD, 4.13 \pm 0.77).

Panelists also agreed on specific endoscopic thresholds: an NPS of 2 or less combined with a modified LKS of 2 or less was considered consistent with partial remission (79.4%; mean \pm SD, 3.93 \pm 0.72), whereas complete remission was defined by an NPS of 0 and a modified LKS of 0 (89.9%; mean \pm SD,

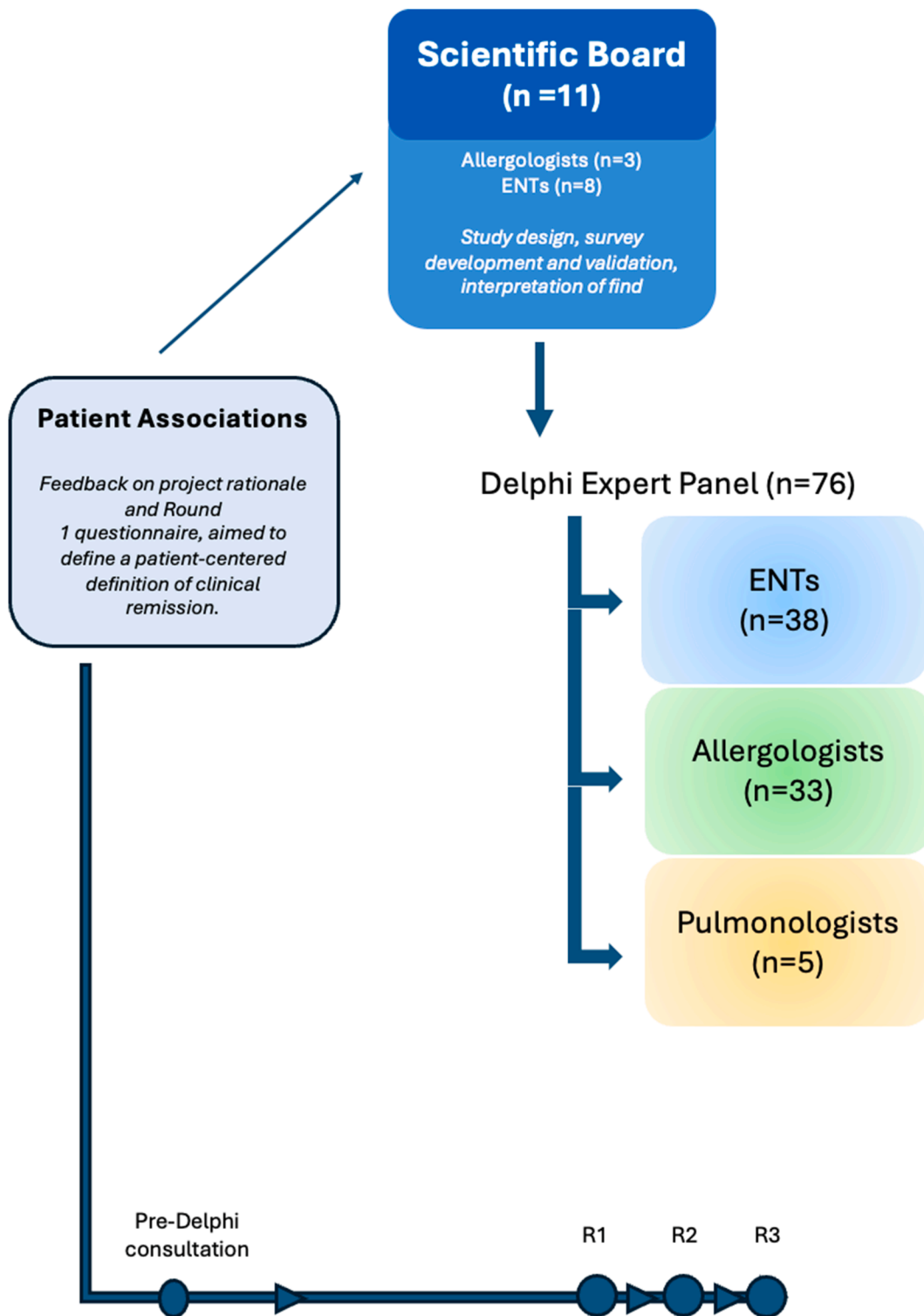


FIGURE 1. Overview of the Delphi study structure and participant flow. The scientific board, consisting of 3 allergologists and 8 ear, nose, and throat specialists (ENTs), oversaw the study design, survey development and validation, and interpretation of findings. Representatives from patient associations were consulted before round 1 to gather feedback on the project rationale and questionnaire, ensuring a patient-centered approach to clinical remission. The Delphi Expert Panel included 38 ENTs, 33 allergologists, and 5 pulmonologists, who participated anonymously in 3 Delphi rounds (R1-R3).

TABLE I. Evolution of statement wording and agreement levels across Delphi rounds

Statements R1	Statements R2	Statements R3	Agreement R1	Agreement in R2	Agreement in R3
1. The definition of remission should include clear thresholds for both symptoms and objective findings.	1. The definition of remission should include clear thresholds for both symptoms and objective findings.	1. The definition of remission should include clear thresholds for both symptoms and objective findings.	95.9%	97.1%	98.5%
Clinical remission in chronic rhinosinusitis with nasal polyps (CRSwNP) should be defined as the following combining parameters, which should be persistent for at least 12 months:	Clinical remission in CRSwNP should be defined as the following combining parameters, which should be persistent for at least 12 months:	Clinical remission in CRSwNP should be defined as the following combining parameters, which should be persistent for at least 12 months:			
2. The complete absence of both symptoms and endoscopic signs of disease.	2. The complete absence of both symptoms and endoscopic signs of disease (complete clinical remission).	2. The complete absence of both symptoms and endoscopic signs of disease (complete clinical remission).	83.8%	85.5%	91.3%
3. The absence of relevant symptoms and signs, allowing for minimal residual findings.	3. The absence of relevant symptoms and signs, allowing for minimal residual findings (partial clinical remission).	3. The absence of relevant symptoms and signs, allowing for minimal residual findings (partial clinical remission).	75.7%	82.4%	84.1%
4. Clinical remission should be understood as a realistic treatment goal.	4. Clinical remission should be understood as a realistic treatment goal.	4. Clinical remission should be understood as a realistic treatment goal.	93.2%	95.7%	95.7%
5. It is useful to distinguish between complete and partial clinical remission in CRSwNP.	5. It is useful to distinguish between complete and partial clinical remission in CRSwNP.	5. It is useful to distinguish between complete and partial clinical remission in CRSwNP.	79.7%	88.4%	84.1%
6. It is useful to define a partial clinical remission as an intermediate state that may precede complete remission and guide therapy optimization.	6. It is useful to define a partial clinical remission as an intermediate state that may precede complete remission and guide therapy optimization.	6. It is useful to define a partial clinical remission as an intermediate state that may precede complete remission and guide therapy optimization.	72.6%	85.5%	85.5%
7. Partial remission should not be considered a true remission, but rather a state of clinical control.	7. Partial remission should not be considered a true remission, but rather a state of clinical control.	7. Partial remission should not be considered a true remission, but rather a state of clinical control.	84.9%	82.4%	81.2%
8. Clinical control can be defined as the absence of symptoms, disease exacerbations, and need for oral corticosteroids or surgery during treatment.	8. Clinical control can be defined as the absence of symptoms, disease exacerbations, and need for oral corticosteroids or surgery during treatment without any time definition.	8. Clinical control can be defined as the absence of symptoms, disease exacerbations, and need for oral corticosteroids or surgery during treatment without any time definition.	88.9%	83.8%	86.8%
9. It should be advisable to consider the mucosal inflammatory component too, when defining clinical remission.	9. It should be advisable to consider the mucosal inflammatory component too, when defining clinical remission.	9. It should be advisable to consider the mucosal inflammatory component too, when defining clinical remission.	74.3%	71.0%	85.3%
10. A more comprehensive definition of "remission plus" in CRSwNP should be based on the absence of disease activity, as evaluated through inflammatory, histological, or cytological markers, and clinical, endoscopic, and radiological parameters.			74.3%	NA	NA
In order to define clinical control before initiating the observation period for remission:	Prospective evaluation of clinical remission should begin:				
11. No minimum time is required.	10. At least after 3 months of any treatment.		8.5%	22.1%	NA
12. A minimum of 6 months is required.	11. At least after 6 months of any treatment.		58.1%	63.8%	NA

13. Clinical remission should require that remission criteria be met for at least 12 consecutive months.	12. Clinical remission should require that remission criteria be met for at least 12 consecutive months.	10. Clinical remission should require that remission criteria be met for at least 12 consecutive months.	95.9%	95.5%	94.2%
14. Clinical remission should be assessed retrospectively, based on 12 months of sustained remission indicators.	13. Clinical remission should be assessed retrospectively, based on 12 months of sustained remission indicators.	11. Clinical remission should be assessed retrospectively, based on 12 months of sustained remission indicators.	94.6%	87.0%	89.9%
15. Sustained remission should be defined as remission lasting 24 months or longer.	14. Sustained remission should be defined as remission lasting 24 months or longer.	12. Sustained remission should be defined as remission lasting 24 months or longer.	78.1%	82.6%	85.5%
An NPS (Nasal Polyp Score) of 0.					
16. Should be required to define complete remission.			60.3%	NA	NA
17. Is desirable but not mandatory to define remission; minimal residual polyps may be acceptable.			54.1%	NA	NA
18. The Lund-Kennedy endoscopic score should be included in the assessment of clinical remission.	15. The Lund-Kennedy endoscopic score should be included in the assessment of clinical remission.	13. As it provides information not only on polyp size but also on nasal secretions and mucosal status, the Lund-Kennedy endoscopic score should be included in the assessment of clinical remission.	70.3%	69.1%	73.9%
19. A Lund-Kennedy score of ≤ 2 should be considered compatible with remission.		14. A modified Lund-Kennedy score and NPS should both be considered in the assessment of endoscopic remission.	60.8%	NA	82.6%
20. The Lund-Kennedy score and NPS should both be considered in the assessment of endoscopic remission.	16. The Lund-Kennedy score and NPS should both be considered in the assessment of endoscopic remission.		79.5%	77.9%	NA
	17. An NPS of ≤ 2 with a Lund-Kennedy score ≤ 2 should be considered compatible with partial remission.	15. An NPS of ≤ 2 with a modified Lund-Kennedy score ≤ 2 should be considered compatible with partial remission.	NA	82.1%	79.4%
	18. An NPS of 0 with a Lund-Kennedy score of 0 should be considered compatible with complete remission.	16. An NPS of 0 with a modified Lund-Kennedy score of 0 should be considered compatible with complete remission.	NA	85.3%	89.9%
21. Assessment of the extent of sinus surgery using the ACCESS score may help to interpret clinical remission in postsurgical patients.			59.5%	NA	NA
22. Postsurgical anatomical outcomes, including synechiae and sinus ostia patency, should be considered when evaluating remission.			47.3%	NA	NA
23. The use of both NPS and Lund-Kennedy score ensures a comprehensive evaluation of endoscopic remission.	19. The use of both NPS and Lund-Kennedy score ensures a comprehensive evaluation of endoscopic remission.	17. The use of both NPS and Lund-Kennedy score ensures a comprehensive evaluation of endoscopic remission.	83.8%	81.2%	85.3%
24. Remission requires the absence of polyps, edema, and mucopurulent secretions on endoscopy.	20. Remission requires the absence of polyps, edema, and mucopurulent secretions on endoscopy.	18. Complete remission requires the absence of polyps, edema, and mucopurulent secretions on endoscopy.	83.8%	84.1%	92.8%

(continued)

TABLE I. (Continued)

Statements R1	Statements R2	Statements R3	Agreement R1	Agreement in R2	Agreement in R3
Use of systemic corticosteroids for unrelated conditions:					
25. Should be considered a confounding factor but not an exclusion criterion.			61.6%	NA	NA
26. Should be at zero during the remission period.			66.2%	NA	NA
27. Systemic corticosteroid use, regardless of indication, compromises the definition of remission.			67.6%	NA	NA
The following are required to define remission:	The following are required to define remission:	19. Remission should be defined by the absence of systemic corticosteroid use and the absence of indication for nasal surgery.	NA	NA	92.6%
28. No use of systemic corticosteroids.	21. No use of systemic corticosteroids.		90.5%	94.2%	NA
29. No use of systemic corticosteroids and no need for nasal surgery.	22. No use of systemic corticosteroids and no need for nasal surgery.		91.9%	95.7%	NA
30. No need for nasal surgery.	23. No need for nasal surgery.		90.4%	89.9%	NA
31. A clinical remission should be considered achieved in absence of nasal surgery for at least 12 months.	24. A clinical remission should be considered achieved in absence of nasal surgery for at least 12 months.		76.7%	69.6%	NA
32. Clinical remission should be achieved and maintained under biologic therapy or topical corticosteroids.	25. Clinical remission should be achieved and maintained under biologic therapy or topical corticosteroids.		84.9%	80.9%	NA
33. The patient's perception of disease burden should be systematically assessed in remission definitions.	26. The patient's perception of disease burden should be systematically assessed in remission definitions.	20. The patient's perception of disease burden should be systematically assessed in remission definitions.	89.2%	88.4%	91.3%
34. The SNOT-22 score should be used in remission definition.	27. The SNOT-22 score should be used in remission definition.	21. The SNOT-22 score should be used in remission definition.	83.8%	75.4%	84.1%
35. A SNOT-22 score below 20 should be considered indicative of remission.	A remission should be defined as: 28. A combination of SNOT-22 <20 and global VAS ≤ 3 .		39.7%	68.1%	NA
36. A SNOT-22 score below 20 is insufficient to define remission due to confounding non-nasal symptoms.	29. A combination of SNOT-22 <20 and VAS for hyposmia ≤ 3		64.9%	62.3%	NA
37. In order to define remission, the nasal-specific items (1-12) of the SNOT-22 should score zero.	30. A combination of SNOT-22 <20 and VAS for nasal obstruction ≤ 3 .		56.2%	65.2%	NA
38. A combination of SNOT-22 <20 and nasal domain (items 1-12) = 0 should define remission.	31. A combination of SNOT-22 <20 and VAS for rhinorrhea ≤ 3 .		41.9%	56.5%	NA
39. The use of SNOT-11 (nasal-specific version) should be evaluated as an alternative to SNOT-22.			52.7%	NA	NA

40. Visual analog scales (VAS) should be used to assess key nasal symptoms independently.			65.8%	NA	NA
41. A VAS score below 2 for either obstruction, rhinorrhea, facial pressure, and smell loss should indicate remission.			61.6%	NA	NA
42. Normal or near-normal olfactory function, assessed using validated semiobjective methods or VAS scoring with predefined cutoffs, should be considered a criterion for complete remission.			67.6%	NA	NA
43. Normal or near-normal olfactory function should be considered a criterion for complete remission, unless olfactory loss is attributable to irreversible or unrelated causes.	32. Normal or near-normal olfactory function should be considered a criterion for complete remission, unless olfactory loss is attributable to irreversible or unrelated causes.	22. Normal or near-normal olfactory function should be considered a criterion for complete remission, unless olfactory loss is attributable to irreversible or unrelated causes.	71.6%	85.5%	95.7%
		23. Remission should be defined as a combination of SNOT-22 <20 and either a global VAS ≤3 or a VAS for hyposmia <3 (this combination is proposed because, alone, SNOT-22 <20 is not necessarily associated with a significant improvement in the characteristic symptoms of CRSwNP, with particular reference to loss of smell).	NA	NA	82.6%
	33. Assessment of the extent of sinus surgery using the ACCESS score may help to give information on the needs of future surgery to achieve a remission.	24. Assessment of the extent of sinus surgery using the ACCESS score may help to give information on the needs of future surgery to achieve a remission.	NA	71.0%	80.9%
	34. Surgical revision should be considered in cases where postsurgical anatomical or functional alterations contribute to partial remission or persistent symptoms.	25. Surgical revision should be considered in cases where postsurgical anatomical or functional alterations contribute to partial remission or persistent symptoms.	NA	89.9%	92.8%
	35. A more comprehensive definition of “remission plus” in CRSwNP should be based on the absence of disease burden, as evaluated through clinical and endoscopic parameters, and inflammatory (histological or cytological) markers.	26. A more comprehensive definition of “remission plus” in CRSwNP should be based on the absence of disease burden, as evaluated through clinical and endoscopic parameters, and inflammatory (histological or cytological) markers.	NA	73.9%	88.2%
	36. A more comprehensive definition of “remission plus” in CRSwNP should be based on the absence of disease burden, as evaluated through clinical and endoscopic parameters, inflammatory (histological or cytological) markers and radiological parameters.	27. A more comprehensive definition of “remission plus” in CRSwNP should be based on the absence of disease burden, as evaluated through clinical and endoscopic parameters, inflammatory (histological or cytological) markers and radiological parameters.	NA	69.1%	76.8%
44. Persistent hyposmia or anosmia may justify classification as partial remission despite other remission criteria.			52.7%	NA	NA

(continued)

TABLE I. (Continued)

Statements R1	Statements R2	Statements R3	Agreement R1	Agreement in R2	Agreement in R3
In the absence of eosinophils, the assessment of inflammation through the evaluation of nasal cytology, should include:					
45. At baseline and after 3 months.			27.0%	NA	NA
46. At baseline and after 6 months.			39.2%	NA	NA
47. At baseline and after 12 months.			63.9%	NA	NA
48. Where should the sample be collected? (open answer)	The cytology sample should be collected from:				
	37. The inferior turbinate		NA	53.6%	NA
	38. The middle turbinate or ethmoid area		NA	56.5%	NA
	39. Directly from the nasal polyp		NA	52.9%	NA
49. A composite score should be developed to assess the level of remission in CRSwNP.	40. A composite score should be developed to assess the level of remission in CRSwNP.	28. A composite score should be developed to assess the level of remission in CRSwNP.	94.6%	98.5%	97.1%
50. Each component of the composite remission score should be weighted according to its clinical relevance.	41. Each component of the composite remission score should be weighted according to its clinical relevance.	29. Each component of the composite remission score should be weighted according to its clinical relevance.	93.2%	97.1%	97.1%
51. A score threshold should categorize patients into no remission, partial remission, or complete remission.	42. A score threshold should categorize patients into no remission, partial remission, or complete remission.	30. A score threshold should categorize patients into no remission, partial remission, or complete remission.	85.1%	88.4%	89.9%
52. A scoring tool should inform therapeutic decisions, including treatment escalation or de-escalation.	43. A scoring tool should inform therapeutic decisions, including treatment escalation or de-escalation.	31. A scoring tool should inform therapeutic decisions, including treatment escalation or de-escalation.	89.2%	91.3%	95.7%
53. The proposed remission score should be validated in independent clinical cohorts.	44. The proposed remission score should be validated in independent clinical cohorts.	32. The proposed remission score should be validated in independent clinical cohorts.	83.8%	85.5%	95.6%

ACCESS, Amsterdam Classification of Completeness of Endoscopic Sinus Surgery; NA, not applicable; SNOT-22, Sino-Nasal Outcome Test-22.

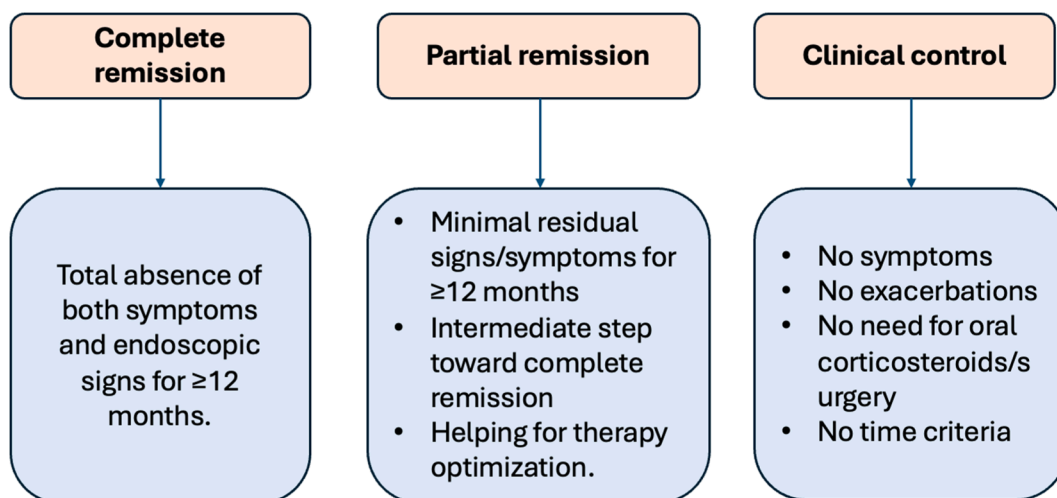


FIGURE 2. Concept of “complete remission,” “partial remission,” and “clinical control” in CRSwNP according to the Delphi results. *CRSwNP*, Chronic rhinosinusitis with nasal polyps.

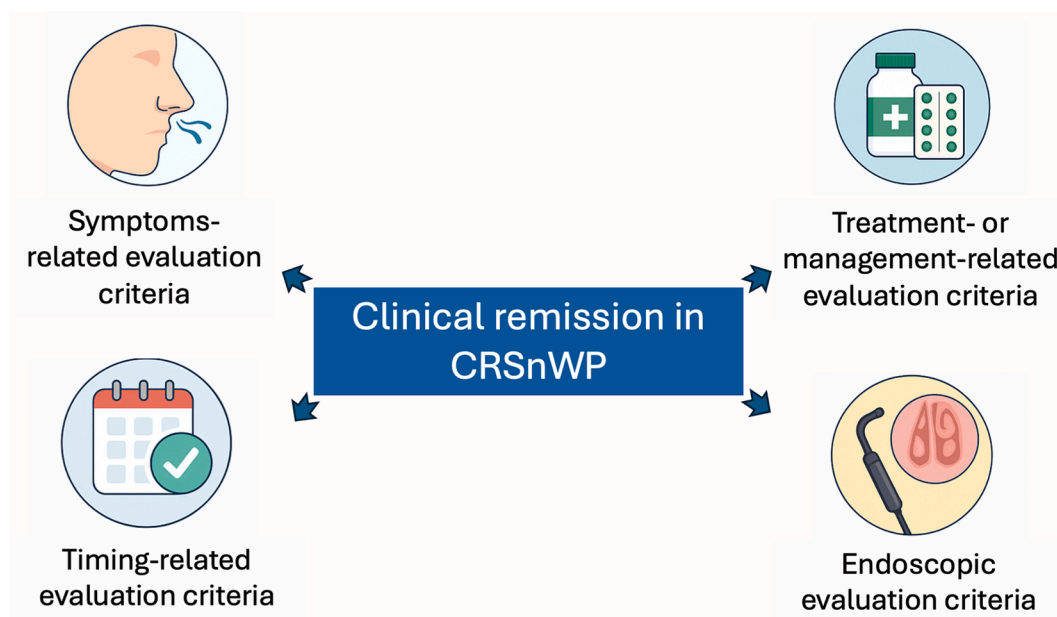


FIGURE 3. Multidimensional criteria contributing to the definition of clinical remission in CRSwNP. Clinical remission in CRSwNP results from combining 4 domains: symptoms-related criteria, timing-related criteria, treatment- or management-related criteria, and endoscopic criteria. Each domain offers complementary information necessary for a thorough and clinically relevant assessment of remission. *CRSwNP*, Chronic rhinosinusitis with nasal polyps.

4.29 ± 0.81). In addition, 85.3% of experts agreed that using both NPS and LKS together provides a comprehensive assessment of endoscopic remission (mean ± SD, 4.18 ± 0.75). There was consensus (92.8%; mean ± SD, 4.45 ± 0.72) that complete remission requires the absence of polyps, edema, and thick secretions on endoscopy, consistent with the choice to use LKS = 0 as a cutoff.

Treatment- or management-related evaluation criteria

There was strong agreement that treatment-related factors should be included in defining remission. Specifically, 92.6% of

panelists agreed that remission requires both the absence of systemic corticosteroid use and no indication for nasal surgery (mean ± SD, 4.53 ± 0.63) for the treatment of CRSwNP.

Symptoms-related evaluation criteria

Patient-reported outcomes were also regarded as essential components of remission. A total of 91.3% of experts agreed that the patient’s perception of disease burden should be systematically incorporated into remission definition (mean ± SD, 4.30 ± 0.71). In line with this, 84.1% supported using the

TABLE II. Conceptual distinctions among complete remission and partial remission

	Complete clinical remission	Partial clinical remission
Time criteria	≥12 months (≥24 months: sustained remission)	≥12 months (≥24 months: sustained remission)
Treatment criteria	No SCS + no surgery	No SCS + no surgery
Symptoms criteria	SNOT-22 <20 Global and hyposmia VAS ≤3	SNOT-22 <20 Global and hyposmia VAS ≤3
Endoscopic criteria	NPS = 0 LKS = 0	NPS ≤2 LKS ≤2

LKS, Lund-Kennedy Score; NPS, Nasal Polyp Score; SCS, systemic corticosteroids; SNOT-22, Sino-Nasal Outcome Test-22.

SNOT-22 score as part of the remission criteria (mean ± SD, 4.17 ± 0.84).

Olfactory function has become a key clinical parameter: 95.7% of panelists agreed that normal or near-normal smell should be required for complete remission, except when olfactory impairment results from irreversible or unrelated causes (eg, neurodegenerative diseases, post-traumatic neurological damage, or congenital pathologies characterized by anosmia) (mean ± SD, 4.35 ± 0.61). The panel also supported a combined definition of remission based on symptom scores, with 82.6% agreeing that remission could be defined as a SNOT-22 <20 along with either a global visual analog scale (VAS) score ≤3 and a VAS for loss of smell ≤3, because SNOT-22 alone may not fully reflect improvement in typical CRSwNP symptoms—particularly olfactory loss (mean ± SD, 4.10 ± 0.81).

Management strategies in case of partial remission in CRSwNP

The importance of previous surgical interventions was also recognized in defining and interpreting remission. A total of 80.9% of experts agreed that evaluating the extent of sinus surgery with the ACCESS (Amsterdam Classification of Completeness of Endoscopic Sinus Surgery) score could help predict the need for additional surgery to achieve remission (mean ± SD, 4.15 ± 0.72). Furthermore, there was consensus (92.8%; mean ± SD, 4.33 ± 0.66) that surgical revision should be considered when postoperative anatomical or functional changes contribute to partial remission or persistent symptoms.

Role of histological inflammation markers in defining “remission plus” in CRSwNP

The panel also discussed the concept of remission plus, which seeks to define a more comprehensive state of disease resolution. A total of 88.2% of experts agreed that this expanded definition should rely on the absence of disease burden, evaluated through clinical and endoscopic parameters along with inflammatory markers, whether histological or cytological (mean ± SD, 4.15 ± 0.78). When radiological parameters were incorporated into this framework, agreement remained strong, with 76.8% supporting their inclusion as part of a broader “remission plus” assessment strategy (mean ± SD, 4.00 ± 0.97).

Proposal of a composite remission score for CRSwNP

The panel strongly endorsed creating a composite tool to measure remission in CRSwNP. A total of 97.1% of experts agreed that a composite score should be developed to assess remission levels (mean ± SD, 4.51 ± 0.56), and an equally high percentage (97.1%; mean ± SD, 4.47 ± 0.61) supported weighting each component of the score according to its clinical importance.

There was also consensus (89.9%; mean ± SD, 4.35 ± 0.70) that the scoring system should categorize patients into no remission, partial remission, or complete remission based on specific thresholds. In addition, 95.7% of respondents supported using such a tool to inform therapeutic decisions, including treatment escalation or de-escalation (mean ± SD, 4.43 ± 0.63). Lastly, the panel emphasized the importance of external validation: 95.6% agreed that the proposed remission score should be confirmed in independent clinical cohorts before it is used in routine practice (mean ± SD, 4.51 ± 0.59).

DISCUSSION

Precisely defining the criteria to assess whether any treatment for CRSwNP can achieve clinical remission is essential; otherwise, there is a risk of relying on a theoretical, high-level definition that is scarcely applicable in real-world clinical practice. The results of our Delphi process provide a robust response to this unmet need, establishing clear and operational criteria for clinical remission in CRSwNP through consensus obtained from a large panel of experts experienced in the management of complex CRSwNP cases and representing a multidisciplinary perspective (with an almost equal number of otorhinolaryngologists and allergists/pulmonologists).

Moreover, during the Delphi process, the main Italian patient associations for respiratory diseases were involved in a consultative role, and their input and suggestions were duly considered by the expert panel when formulating the statements submitted for voting. Another important strength of this work is that the consensus was achieved in a completely independent manner, without any interference from external stakeholders, including pharmaceutical companies.

Clinical remission was considered by the expert panel to be a realistic therapeutic goal for patients with CRSwNP. The panel also agreed on the need to distinguish between partial clinical remission and complete clinical remission. The introduction of the concept of partial clinical remission was deemed necessary to identify those patients for whom additional therapeutic strategies could be implemented with the aim of ultimately achieving complete clinical remission. Specifically, the expert panel recommends that, in patients who have achieved partial clinical remission, the quality and extension of any previous surgical interventions should be evaluated using the ACCESS²⁸ score, and that revision surgery should be considered in cases of postsurgical anatomical or functional alterations that might hinder the achievement of complete clinical remission.

The definition of clinical remission that emerged from the Delphi process is characterized by the multidimensional nature of the domains to be considered. To achieve clinical remission, 4 criteria must be met simultaneously: temporal, therapeutic, symptomatic, and nasal endoscopic criteria (Figure 2).

With regard to the temporal criterion, the outcome of the Delphi consensus is consistent with previously proposed definitions for both CRSwNP²³ and severe asthma^{22,29}: clinical remission can only be established if all other criteria are maintained for at least 12 months. No consensus has been reached on how long should elapse between the start of any given therapy and the start of the clinical remission assessment (Table I, items 11 and 12 for the first round, and 10 and 11 for the second round). This is likely because different therapeutic approaches, as well as the different biologics currently available, have different rapidity of action. Even the definitions of clinical remission for severe asthma do not precisely define how long should elapse between the start of treatment and the beginning of the assessment of the 12-month time criterion for clinical remission. More innovative, however, is the introduction in the present definition of sustained clinical remission, which is achieved when remission persists for at least 24 months. This latter aspect is particularly relevant, as treatments for severe and uncontrolled CRSwNP—including biologic therapies—are designed for long-term use and may differ in their onset of action across various clinical outcomes.

The second key pillar of the definition of clinical remission emerging from this study is the absence of any need for systemic corticosteroid treatment or surgical intervention for CRSwNP. This therapeutic criterion is crucial, given the well-known and clinically significant adverse effects associated with systemic corticosteroid use, as well as the need to prevent disease progression, which is typically marked by recurrent episodes leading to surgical indication.

With regard to the endoscopic criterion for clinical remission, the expert panel agreed to include both the NPS and the LKS.³⁰ The inclusion of the latter was motivated by the need to consider not only the absence of nasal polyps but also the absence of endoscopic signs of edema and thick secretions—findings indicative of persistent chronic inflammation that is considered incompatible with the achievement of complete clinical remission. Unlike the NPS, the LKS has not typically been included among the primary endpoints of clinical trials investigating the efficacy of biologic therapies for CRSwNP. However, we believe that when assessed alongside the NPS, it may provide a more comprehensive evaluation of the overall therapeutic effectiveness of different treatment approaches for CRSwNP than the NPS alone. According to the Delphi consensus definition, achieving complete clinical remission requires both the NPS and the LKS to reach zero—indicating the absence of any endoscopic signs of disease, as suggested by the theoretical definition proposed by international recommendations.²³ In contrast, partial clinical remission can be defined when both the NPS and LKS are ≤ 2 . Both definitions have already been at least partially explored as possible scenarios for achieving clinical remission in the recent Italian real-life study on dupilumab use in CRSwNP (“Dupireal” study, 2-year treatment), which unsurprisingly showed markedly different results in terms of the rate of therapeutic goal attainment.¹⁶ It is important to emphasize that the endoscopic criterion must be maintained continuously for a full 12-month period to define a patient as being in clinical remission. Obviously, because nasal endoscopic evaluation is not a continuous process (as symptom monitoring can be), if an interval endoscopy performed before the 12-month time point demonstrates objective endoscopic signs of disease worsening, this finding should be interpreted as a

temporary loss of disease control, and the 12-month criterion for remission should be recalculated starting from the subsequent endoscopic documentation of disease control.

With regard to the symptomatic criterion, the consensus agreed that the patient’s subjective perception of symptoms must be taken into account in the definition of clinical remission, and that this perception should be measured using validated instruments. Moreover, there was strong agreement that achieving a normal or near-normal olfactory function is essential, unless smell loss can be attributed to other causes or to irreversible damage. Specifically, concerning the validated tools for assessing the symptomatic component, the expert panel recommended the combined use of the SNOT-22 and the global VAS both for global CRSwNP symptoms³¹ and selectively for loss of smell.³² This approach aims to avoid the potential paradox of a significant improvement in SNOT-22 scores not being accompanied by normalization of purely rhinologic and olfactory-related symptoms. The inclusion of SNOT-22 in the definition of clinical remission was deemed necessary, given its more holistic assessment of the disease’s impact on patients’ quality of life.³³ To achieve clinical remission, the panel agreed that a SNOT-22 score below 20 (based on previously published evidence identifying this threshold as indicative of a normal value^{34,35}) must be obtained, provided that VAS scores are also consistent with the absence of symptoms (values below 3).^{31,32} A potential limitation of this symptomatic criterion is that even events not strictly related to CRSwNP (eg, upper respiratory tract infections or exacerbations of possibly concomitant allergic rhinitis) can induce a temporary increase in SNOT-22 as well as VAS, thus negatively impacting the achievement of clinical remission defined according to the proposed criteria. This is an aspect that, to date, has not yet been adequately addressed, even in the theoretical definitions of clinical remission proposed by international expert bodies such as EPOS2020/EUFOREA.²³

Table II summarizes the definition of clinical remission that emerged from the Delphi consensus, distinguishing between its 2 forms: complete and partial.

In addition to defining the precise criteria for complete and partial clinical remission as described above, the expert panel also agreed on the need to begin considering potential future evolutions of the concept—such as the inclusion of inflammatory biomarker assessment or radiologic scoring systems (the so-called clinical remission plus). However, consensus could not be reached on which inflammatory biomarkers or radiologic scores should be used, nor on the appropriate cutoff values to apply. The lack of consensus may be explained by the still heterogeneous and inconclusive data regarding the use of local or systemic inflammatory biomarkers in everyday clinical practice.³⁶ Some evidence is available in the literature on the evaluation of cellular infiltrates (eosinophils, neutrophils, mast cells, etc) at the nasal histological^{37,38} or cytological level,^{39,40} the measurement of nasal nitric oxide,⁴¹ and systemic biomarkers such as peripheral eosinophilia⁴² or serum IgE levels.⁴³ Nonetheless, their applicability for phenoendotyping, their prognostic value, and especially their variations during biologic therapy remain insufficiently defined, and further evidence is needed before they can be incorporated into a consensus definition of clinical remission.

Another important potential future perspective that emerged from the expert panel was the proposal to develop, from the outset, a numerical clinical remission score based on the

consensus achieved in this study. It was not the aim of this study to create such a score; therefore, we limited ourselves to evaluating the consensus of the expert panel on the future opportunity to create this tool. This score will, of course, need to be validated in independent clinical patient cohorts, such as those included in the RINET registry, which also promoted this consensus initiative. A similar approach has been proposed in the context of defining clinical remission in severe asthma by the Severe Asthma Network Italy.⁴⁴ That network also applied the clinical remission definition to data from its severe asthma registry.⁴⁵ Likewise, the RINET registry investigators plan to apply the definition of clinical remission that emerged from this Delphi consensus to the prospective data currently being collected in patients with severe, uncontrolled CRSwNP.

In conclusion, this study presents the results of an independent Delphi consensus on the definition of clinical remission in CRSwNP, developed through the involvement of a large panel of experts to ensure the multidisciplinary perspective required for the management of these complex patients. To the best of our knowledge, this represents the first clear and precise definition of the cutoff values for the individual domains necessary to define clinical remission in CRSwNP.

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