Estimating Clinically Meaningful Change of Efficacy Outcomes in Inadequately Controlled Chronic Rhinosinusitis with Nasal Polyposis

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Objectives/Hypothesis: Clinical trials of biologics to treat chronic rhinosinusitis with nasal polyposis (CRSwNP) have evaluated objective outcomes (e.g., University of Pennsylvania Smell Identification Test [UPSIT], nasal polyps score [NPS], and computed tomography Lund-Mackay score [CT-LMK]) and patient-reported symptoms (e.g., nasal congestion/obstruction [NC], loss of smell [LoS], and total symptom score [TSS]). We estimated anchor-based thresholds for clinically meaningful change in objective and patient-reported outcomes in patients with CRSwNP using data from LIBERTY NP SINUS-24 and SINUS-52 trials (NCT02912468; NCT02898454).

Methods: Target patient-reported outcomes were NC, LoS, and TSS; target objective outcomes were UPSIT, NPS, and CT-LMK. Anchor measures were the 22-item sinonasal outcome test (SNOT-22) rhinologic symptoms domain and total score and rhinosinusitis visual analog scale (VAS). The appropriateness of each anchor measure was evaluated by reviewing correlations between change in anchor measures and target outcomes and descriptive scores on target outcomes by levels of change in the anchor measure. Established thresholds for anchor measures (3.8 points for SNOT-22 rhinologic symptoms, 8.9 points for SNOT-22 total, 1-category improvement for rhinosinusitis VAS) were used to estimate clinically meaningful score changes for each target outcome.

Results: Based on correlations between change in anchor measures and target outcomes, SNOT-22 rhinologic symptoms domain was deemed the most appropriate anchor measure. Using this anchor measure, thresholds for clinically meaningful within-patient change were NC: 1 point; LoS: 1 point; TSS: 3 points; UPSIT: 8 points; NPS: 1 point; and CT-LMK: 5 points.

Conclusion: These thresholds support interpretation of efficacy results for target outcomes in CRSwNP trials.

Key Words: Adult rhinology, quality of life, nose and paranasal sinuses.

Level of Evidence: 2

***Laryngoscope*, 132:265–271, 2022**

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Additional supporting information may be found in the online version of this article.

Editor's Note: This manuscript was accepted for publication on September 21, 2021.

The analyses of data from the LIBERTY NP SINUS-24 and SINUS-52 trials (NCT02912468; NCT02898454) described here were sponsored by Regeneron Pharmaceuticals, Inc. and Sanofi. Funding for medical writing assistance with this manuscript was provided by Regeneron Pharmaceuticals, Inc. and Sanofi.

These analyses were performed under a research contract among RTI Health Solutions, Regeneron Pharmaceuticals, Inc., and Sanofi and were funded by Regeneron Pharmaceuticals, Inc. and Sanofi. J.K.H. is a consultant for Regeneron Pharmaceuticals, Inc. and Sanofi Genzyme. C.B. is a consultant for AstraZeneca, GlaxoSmithKline, Mylan, Novartis Pharmaceuticals, and Sanofi Genzyme. S.E.L. is a consultant for AstraZeneca, Genentech Novartis, GlaxoSmithKline, Regeneron Pharmaceuticals, Inc., and Sanofi Genzyme. C.H. has received fees from AstraZeneca, GlaxoSmithKline, Olympus, and Sanofi for participation in Advisory Boards. E.H. has received research grants from AstraZeneca, Boehringer Ingelheim, Circassia, GlaxoSmithKline, Nestlè Purina, Novartis Pharmaceuticals, Sanofi Genzyme, Teva, and Valeas. P.W.H. is a consultant for AstraZeneca, Mylan/Viatris, Novartis Pharmaceuticals, and Sanofi Genzyme. A.T.P. has been an advisory board member of Regeneron Pharmaceuticals, Inc. and Sanofi; has had research support from and been an advisory board member of AstraZeneca; and has been a consultant for and received research support from Optinose. S.K. and S.S. are employees of Regeneron Pharmaceuticals, Inc. D.W., S.Q., and L.N. are employees of RTI Health Solutions. A.H.K., Y.L., L.P.M., and C-C.C. are employees of Sanofi and may hold shares and/or stock options in the company. I.G. was an employee of Sanofi when these analyses were conducted.

The authors have no other funding, financial relationships, or conflicts of interest to disclose.

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DOI: 10.1002/lary.29888

INTRODUCTION

Patients with chronic rhinosinusitis with nasal polyposis (CRSwNP) frequently experience nasal symptoms, including nasal congestion/obstruction (NC), loss of smell (LoS), and rhinorrhea.[1,2] The high level of symptom burden associated with CRSwNP can impair patients' health-related quality of life (HRQoL).[3–5] In addition, CRSwNP often occurs with other inflammatory conditions, with up to 67% of patients with CRSwNP also having asthma.[1,6–9]

Several biologic treatments, including dupilumab, omalizumab, mepolizumab, and benralizumab, are being evaluated or have been evaluated in randomized controlled trials (RCTs) among patients with uncontrolled CRSwNP despite prior use of steroids or sinus surgery.[10–20] RCTs of biologics include objective endpoints such as the University of Pennsylvania Smell Identification Test (UPSIT), the nasal polyps score (NPS), and the computed tomography Lund-Mackay score (CT-LMK), as well as patient-reported endpoints such as NC, LoS, and total symptom score (TSS).[21]

In the context of the populations of patients with CRSwNP that are enrolled in such RCTs, no well-defined thresholds exist to infer clinical meaningfulness of within-patient change in scores for objective and patient-reported treatment outcomes. The threshold of meaningful within-patient change in a clinical outcome measure, often called responder definition, is defined as "a score change in a measure, experienced by an individual patient over a predetermined time period that has been demonstrated in the target population to have a significant treatment benefit." The goal of this analysis was to estimate thresholds for clinically meaningful within-patient change in objective and patient-reported endpoints in patients with CRSwNP, using data from the LIBERTY NP SINUS-24 and SINUS-52 RCTs (NCT02912468 and NCT02898454).[10]

METHODS

Data Source

This study used data from 2 phase 3 trials of dupilumab in CRSwNP, SINUS-24 (n = 276) and SINUS-52 (n = 448), and included patients aged ≥18 years with CRSwNP (defined as NPS ≥5 out of 8, NC score ≥2 out of 3 at screening, and at least 1 other symptom of LoS or rhinorrhea [anterior or posterior]) that was inadequately controlled (defined as prior treatment with systemic corticosteroids any time within the past 2 years and/or a medical contraindication/intolerance to systemic corticosteroids and/or prior surgery for nasal polyps).

The studies were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from all patients prior to enrollment, and the protocol and its amendments were approved by the appropriate institutional review boards and ethics committees.

Outcome Measures

Target Outcomes. The target patient-reported outcomes (i.e., NC, LoS, and TSS from a symptoms e-diary) and objective outcomes (i.e., UPSIT, NPS, and CT-LMK) used in this analysis are described in Table I. The symptoms e-diary is composed of 4 patient-reported items assessing the daily severity of NC, LoS, anterior rhinorrhea, and posterior rhinorrhea. The monthly averages computed from the daily e-diary responses were for individual symptoms of NC and LoS on a scale of 0 to 3, in addition to a 0 to 9 TSS as the sum of the NC, LoS, and rhinorrhea (average of the anterior and posterior items) symptom scores.

Objective outcomes included the UPSIT assessing olfactory function (with scores ranging from 0 to 40 points), the NPS assessing the extent or severity of nasal polyps (with scores ranging from 0 to 8 points), and the CT-LMK score assessing radiographic opacification of the paranasal sinuses (with scores ranging from 0 to 24 points).

Anchor Measures. Anchor-based methods are recommended as the primary approach for determining clinically meaningful within-patient changes in scores on clinical outcome assessments.[22,23] Using the anchor-based method, score changes on a target clinical outcome assessment are compared with scores on an external measure (the anchor measure).[24] Establishing clinically meaningful within-patient change thresholds is supported by first selecting appropriate anchor measures and then estimating the change in scores on the target outcome that corresponds to a meaningful improvement in the anchor measures.[22]

Patient global assessments of severity and/or change are commonly used anchor measures. As the SINUS-24/52 trials did not include such global assessments, the 22-item sinonasal outcome test (SNOT-22) rhinologic symptoms domain score, SNOT-22 total score, and the rhinosinusitis visual analog scale (VAS) score were evaluated for their suitability as anchor measures to establish within-patient thresholds for the target outcomes (NC, LoS, TSS, UPSIT, NPS, and CT-LMK). Table I describes the anchor measures used in this analysis.

The SNOT-22 questionnaire assesses a range of concepts related to chronic rhinosinusitis (CRS), including rhinologic and nonrhinologic symptoms, as well as sleep and psychological function.[25] The SNOT-22 rhinologic symptoms domain comprises 6 items relating to nasal symptoms (need to blow nose, nasal blockage, sneezing, runny nose, thick nasal discharge, and decreased sense of smell/taste).[26,27] Rhinologic symptoms domain scores range from 0 to 30, and a clinically meaningful change estimated as 3.8 points or greater based on Chowdhury et al.[28] was selected as the primary, responder-based anchor for this analysis. Because this responder-based anchor can include score improvements far above the threshold for meaningful change (i.e., patients with improvements much greater than 3.8 points), a categorized change-based anchor was also defined to represent small-to-moderate improvement to inform supportive analyses; the lower limit of the categorized change anchor was defined as the published threshold (i.e., change of 3.8 points), and the upper limit was arbitrarily defined as 2 × the published threshold (i.e., change of 2 × 3.8 = 7.6 points).

SNOT-22 total scores range from 0 to 110, and a clinically meaningful change has been defined as 8.9 points or greater using anchor-based methods based on a global rating of change.[25] Thus, a secondary responder-based anchor for the present analysis was defined as an improvement in SNOT-22 total score ≥8.9 points. To address the potential for the responder-based anchor to include large score improvements far above the threshold for meaningful change, a supportive, categorized, and change-based anchor was defined to represent a small-to-moderate improvement by using the published threshold (change of 8.9 points) and 2 × the published threshold (change of 2 × 8.9 = 17.8 points) as the lower and upper limits of the category, respectively.

Several studies have demonstrated the psychometric properties and interpreted classification of the rhinosinusitis VAS in patients with CRS, including patients with CRSwNP.[29,30] The European Position Paper on Rhinosinusitis and Nasal Polyps

TABLE I.
Target Outcomes and Anchor Measures.

Measure	Recall Period and Response Scale	Scoring
Target outcomes		
Symptoms e-diary	Past 24 hr	Items: 0–3
Four items: NC, LoS, anterior rhinorrhea, and posterior rhinorrhea	0 = No symptoms 1 = Mild symptoms 2 = Moderate symptoms 3 = Severe symptoms	TSS: 0–9 (sum of NC, LoS, and average of anterior and posterior rhinorrhea) Higher scores indicate more severe symptoms
UPSIT total	Current	0–40
40 odorants	Patient selects best description of odor out of 40 choices	Higher scores indicate better olfactory function
NPS	Current	0–8 (sum of the right and left scores; average of 2 independent raters)
Video recordings of nasal endoscopy	0 = No polyps 1 = Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate 2 = Polyps reaching below the lower border of the middle turbinate 3 = Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate 4 = Large polyps causing complete obstruction of the inferior nasal cavity	Higher scores indicate more extensive or severe nasal polyps
CT-LMK scores	Current	0–24 (bilateral sum of all sinuses and the ostiomeatal unit)
Based on CT scans of each sinus area (maxillary, anterior ethmoid, posterior ethmoid, sphenoid, frontal sinus on each side)	Extent of mucosal opacification (0 = Normal, 1 = Partial opacification, 2 = Total opacification) Patency of the ostiomeatal complex (0 or 2)	Higher scores indicate worse opacification
Anchor measures		
SNOT-22	Past 2 wk	0–110 (sum of the 22 items)
22 items: symptoms and social/emotional consequences of CRS Rhinologic symptoms domain: 6 items relating to nasal symptoms (need to blow nose, nasal blockage, sneezing, runny nose, thick nasal discharge, and decreased sense of smell/taste)	0 = No problem 1 = Very mild problem 2 = Mild or slight problem 3 = Moderate problem 4 = Severe problem 5 = Problem as bad as it can be	Higher scores indicate greater impacts of CRS on HRQoL
Rhinosinusitis VAS (cm): "How troublesome are your symptoms of rhinosinusitis?"	Current 0 = Not troublesome to 10 = Worst thinkable troublesome (sic)[31]	0–10 Higher scores indicate more severe CRS Severity categories: 0–3 = mild, >3–7 = moderate, >7–10 = severe

CRS = chronic rhinosinusitis; CT = computed tomography; CT-LMK = computed tomography Lund-Mackay score; HRQoL = health-related quality of life; LoS = loss of smell; NC = nasal congestion/obstruction; NPS = nasal polyps score; SNOT-22 = 22-item sinonasal outcome test; TSS = total symptom score; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analog scale.

guidelines[31] use this measure to categorize disease severity as mild (VAS 0–3), moderate (>3–7), and severe (>7–10). A 1-category improvement on the rhinosinusitis VAS score categories (i.e., a change from severe to moderate or from moderate to mild) was used to represent small-to-moderate improvement to anchor change in scores for the target outcomes that can be considered clinically meaningful.

Statistical Analyses

In the analyses, all data were observed, and no imputation for missing data was performed. Before applying the anchor-based methodology, correlations between change in the anchor measure and change in each target outcome, as well as patterns of mean and median changes in the target outcome across levels of change in the anchor measure, were reviewed to evaluate the appropriateness of each proposed anchor. Specifically, correlational analyses between change in SNOT-22 rhinologic symptoms domain, SNOT-22 total, and rhinosinusitis VAS scores and change in NC, LoS, TSS, UPSIT, NPS, and CT-LMK were conducted. Appropriateness of an anchor measure was determined by using the criteria for correlation strength between change in the anchor measure and change in a target outcome of ≥0.371[32] and the presence of predicted patterns in the descriptive statistics for the change in NC, LoS, and TSS by levels of the change in the anchors.

For those anchors deemed to be appropriate, mean and median changes in NC, LoS, TSS, UPSIT, NPS, and CT-LMK corresponding to different levels of change in the anchor measures outlined in Table I were used to evaluate clinically meaningful within-patient change thresholds. To provide supportive lower bounds for the responder thresholds, distribution-based estimates using half standard deviations (SDs) of the baseline scores were also computed.

RESULTS

Baseline Characteristics

The pooled SINUS-24 and SINUS-52 analysis sample included a total of 696 patients who had both baseline

TABLE II.
Baseline Descriptive Statistics for the Target Outcomes and Anchor Measures.

Measure	Phase 3 Pooled (SINUS-24 and SINUS-52 Studies)		
	n	Mean Score (SD)	Median Score
Target outcomes			
NC	696	2.40 (0.57)	2.4
LoS	696	2.73 (0.54)	3.0
TSS	696	7.15 (1.42)	7.2
UPSIT	685	14.03 (8.22)	11.0
NPS	693	5.98 (1.25)	6.0
CT-LMK	681	18.33 (4.10)	19.0
Anchor measures			
SNOT-22 rhinologic symptoms	686	19.70 (5.03)	20.0
SNOT-22 total	686	50.57 (20.47)	49.0
Rhinosinusitis VAS	682	7.87 (2.06)	8.3

n: Number of patients with corresponding endpoint data at baseline among those who had both baseline and week 24 monthly scores for at least 1 symptoms e-diary item. For NC, LoS, and TSS, baseline refers to the weekly averaged scores before randomization.

CT-LMK = computed tomography Lund-Mackay score; LoS = loss of smell; NC = nasal congestion/obstruction; NPS = nasal polyps score; SD = standard deviation; SNOT-22 = 22-item sinonasal outcome test; TSS = total symptom score; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analog scale.

and week 24 monthly scores for at least 1 symptoms e-diary item.

Table II presents baseline descriptive statistics for the target outcomes and anchor measures. The study population reflected a population with moderate-to-severe uncontrolled CRSwNP (Table II). The sample had a mean (SD) age of 51.6 (12.8) years, a mean age at onset of nasal polyposis of 40.6 (13.8) years, and had undergone a mean of 1.2 (1.6) previous surgeries for nasal polyposis.

Appropriateness of the Anchors

NC, LoS, and TSS. Supporting Tables I and II in the online version of this article present change from baseline in the target outcomes corresponding to different levels of change on each anchor measure. Correlations of change in outcome measures are presented in Supporting Table III. Correlations between change from baseline to week 24 in NC, LoS, and TSS scores, and change from baseline to week 24 in SNOT-22 rhinologic symptoms domain, on SNOT-22 total, and on rhinosinusitis VAS scores were equal to or greater than 0.371, the prespecified criterion for correlation strength between change in the anchor measure and change in a target outcome (Table III). In contrast, for UPSIT, NPS, and CT-LMK, only the correlations with change in SNOT-22 rhinologic symptoms domain score were consistently above 0.371 at week 24 (Table III). The descriptive statistics for the changes in the target outcomes by levels of change in the anchor measure followed the anticipated pattern, with the greatest improvements in target outcomes associated with large improvements on the anchor measures, and the least improvement associated with no change or worsening (Supporting Tables I and II). Overall, the larger correlations between changes in the target outcomes and change in the SNOT-22 rhinologic symptoms domain provide support for the SNOT-22 rhinologic symptoms domain as the most appropriate anchor measure.

Clinically Meaningful Within-Patient Change Thresholds

Table IV displays the clinically meaningful within-patient change threshold estimates (characterizing improvement) based on the SNOT-22 rhinologic symptoms, SNOT-22 total, and rhinosinusitis VAS anchors using the pooled phase 3 data for change in target measures from baseline to week 24. The mean change scores on the target measures corresponding to the established threshold for clinically meaningful change in the primary anchor (i.e., an improvement of 3.8 points or more in the SNOT-22 rhinologic symptoms domain) were −1.29 for NC, −1.16 for LoS, −3.54 for TSS, 8.49 for UPSIT, −1.54 for NPS, and −5.06 for CT-LMK (Table IV). Based on these results, the thresholds for clinically meaningful within-patient change are proposed as scores rounded down to the nearest plausible value (i.e., integer): NC,

TABLE III.
Correlation Between the Change in Target Outcome Scores and Change in Anchor Measure Scores.

Target outcome	Correlation of Baseline to Wk 24 Change With Anchor Measures, *r* (n)		
	SNOT-22 Rhinologic Symptoms	SNOT-22 Total	Rhinosinusitis VAS
NC	0.65 (674)	0.55 (674)	0.47 (663)
LoS	0.59 (674)	0.46 (674)	0.46 (663)
TSS	0.73 (670)	0.62 (670)	0.52 (663)
UPSIT	−0.46 (660)	−0.35 (660)	−0.36 (650)
NPS	0.51 (658)	0.40 (658)	0.38 (648)
CT-LMK	0.46 (653)	0.35 (653)	0.35 (641)

For NC, LoS, and TSS, baseline refers to the weekly averaged scores before randomization; week 24 refers to the monthly averaged daily scores from day 142 to day 169.

CT-LMK = computed tomography Lund-Mackay score; LoS = loss of smell; NC = nasal congestion/obstruction; NPS = nasal polyps score; SNOT-22 = 22-item sinonasal outcome test; TSS = total symptom score; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analog scale.

TABLE IV.
Interpretation of Change from Baseline to Week 24 in the NC Score, LoS Score, TSS, UPSIT, NPS, and CT-LMK.

Anchor	Estimate of Meaningful Change: Mean (SD), n					
	NC	LoS	TSS	UPSIT	NPS	CT-LMK
SNOT-22 rhinologic symptoms domain score						
Responder: score improvement ≥3.8	−1.29 (0.9), 511	−1.16 (1.0), 511	−3.54 (2.2), 509	8.49 (10.1), 500	−1.54 (1.8), 498	−5.06 (4.9), 495
SNOT-22 total score						
Responder: score improvement ≥8.9	−1.28 (0.9), 501	−1.13 (1.0), 501	−3.52 (2.2), 498	8.44 (10.0), 490	−1.51 (1.8), 488	−4.95 (4.9), 485
Rhinosinusitis VAS severity category (mild, moderate, and severe)						
Improvement by 1 category	−0.99 (0.8), 260	−0.91 (1.0), 260	−2.75 (2.1), 260	6.40 (9.8), 253	−1.11 (1.7), 254	−4.37 (4.8), 249

CT-LMK = computed tomography Lund-Mackay score; LoS = loss of smell; NC = nasal congestion/obstruction; NPS = nasal polyps score; SNOT-22 = 22-item sinonasal outcome test; TSS = total symptom score; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analog scale.

1 point; LoS, 1 point; TSS, 3 points; UPSIT, 8 points; NPS, 1 point; and CT-LMK, 5 points.

To support these estimates of meaningful within-patient change, thresholds also were estimated using the established thresholds for SNOT-22 total score (i.e., an improvement of 8.9 points or more) and rhinosinusitis VAS (i.e., 1-category improvement) anchors. Based on the SNOT-22 total score anchor, mean change scores on the target outcomes were −1.28 for NC, −1.13 for LoS, −3.52 for TSS, 8.44 for UPSIT, −1.51 for NPS, and −4.95 for CT-LMK. Based on the rhinosinusitis VAS anchor, mean change scores on the target outcomes were −0.99 for NC, −0.91 for LoS, −2.75 for TSS, 6.40 for UPSIT, −1.11 for NPS, and −4.37 for CT-LMK.

The thresholds presented above support a clinically meaningful within-patient change. Additional estimates based on the SNOT-22 rhinologic symptoms domain and SNOT-22 total score categorized change anchors are presented in Supporting Tables I and II. These thresholds are consistently lower than the other anchor-based threshold estimates and are useful to inform meaningful within-group change.

DISCUSSION

Assessments of patients' subjective experiences of symptoms and the associated impact on HRQoL provide important information on the benefits of treatment.[33,34] Evidence has shown that the symptom burden and HRQoL impacts associated with CRSwNP are profound.[3–5,35] RCTs of biologic treatments for CRSwNP, including the SINUS-24 and SINUS-52 studies of dupilumab, have included endpoints related to the key symptoms of CRSwNP, in addition to objective clinical measures. To ensure that treatment outcomes from these trials and in practice can be interpreted, it is important to define thresholds for meaningful change in these measures.

Per best practices in the field of clinical outcome assessments, the appropriateness of an anchor measure is determined by the conceptual similarity and degree of correlation between the anchor measure and target outcomes. Using these criteria, the SNOT-22 rhinologic symptoms domain was determined as the most appropriate anchor measure given that this domain assesses specific symptoms of CRSwNP, it has an acceptable level of correlation with the target outcomes, and a threshold for clinically meaningful change has been established.[28] The thresholds for clinically meaningful within-patient change in this analysis (NC: 1 point; LoS: 1 point; TSS: 3 points; UPSIT: 8 points; NPS: 1 point; and CT-LMK: 5 points) were determined using SNOT-22 rhinologic symptoms domain as the most appropriate anchor measure. In addition, the overall SNOT-22 and rhinosinusitis VAS assess the broader impacts of CRSwNP.

SNOT-22 rhinosinusitis symptom domain showed correlation with all measures, whereas SNOT-22 total scores and rhinosinusitis VAS showed weak correlation with NC and CT-LMK. The strongest correlations in change in outcomes measures were observed for both NC and LoS with change in the SNOT-22 rhinologic symptoms domain, with weaker correlations for SNOT-22 total scores and rhinosinusitis VAS. The strongest correlations in change in individual outcomes measures were observed for both NC and LoS with change in TSS at week 24, in addition to SNOT-22 total scores with change in the SNOT-22 rhinologic symptoms domain. The weakest individual correlations observed were for NC with change in UPSIT, UPSIT with change in SNOT-22 total score, and CT-LMK with changes in SNOT-22 total scores and rhinosinusitis VAS.

Importantly, the responder-based anchors defined using both the SNOT-22 total and rhinologic symptoms domain scores include score improvements of all responders, yielding potentially overestimated thresholds for meaningful change, compared with the lower estimates identified using supportive categorized change-based anchors. However, because the SNOT-22 published thresholds were selected by experts and supported by strong responsiveness correlation, the more conservative estimates from these analyses are recommended to interpret clinically meaningful within-patient change. The lower threshold estimates based on categorized change-based anchors may be more useful to inform meaningful within-group change.

To our knowledge, this is the first analysis to estimate thresholds that can be used to infer clinically meaningful within-patient change in these target outcomes. The within-patient change thresholds estimated in this analysis can help physicians contextualize the observed improvements in clinical and patient-reported endpoints

in terms of patient-relevant clinical meaningfulness. Currently, no baseline biomarker parameters have been identified to select appropriate biologic treatments for individual patients with CRSwNP. In the absence of such biomarkers, treatment effect size and responder analysis results may guide the choice of treatment with the greatest improvements in both objective and subjective measures.

Some limitations of these analyses must be considered. Estimates of meaningful change on a given outcome can be influenced by the characteristics of the sample used to derive the thresholds. The patients in the SINUS-24 and SINUS-52 studies had severe disease, which may not be reflected in broader patient populations. As such, the thresholds estimated in the current analysis might not be applicable to populations with markedly different baseline characteristics. Future studies should determine if these results are consistent with patient populations across various levels of severity of CRSwNP, for example, to assess if a decrease of >1 in NPS is clinically meaningful if the patient's pre-treatment NPSs were higher or lower than scores used in this analysis. However, in the context of interpreting the thresholds for clinically meaningful change, it has been demonstrated that such thresholds may have a low positive association with baseline severity.[36] Further, the SNOT-22 anchor values (3.8-point improvement on the rhinologic symptoms domain and the 8.9-point improvement on the total) were derived in a mixed CRS population undergoing surgery and may differ in a CRSwNP population being treated medically.[28,37] Finally, the meaningful-change thresholds estimated in this analysis are based on quantitative approaches and pooled data from 2 trials, and validation using additional data will need to be conducted. In addition, future studies could consider using qualitative methods (e.g., qualitative interviews with patients) to further inform the meaningfulness of the presented thresholds.

CONCLUSION

In conclusion, our study examined the relationship between scores of the symptoms e-diary for CRSwNP (evaluating NC, LoS, anterior rhinorrhea, and posterior rhinorrhea), UPSIT, NPS, and CT-LMK and those from 2 widely used and validated outcome measures, the SNOT-22 and rhinosinusitis VAS, and the results were used to estimate thresholds for clinically meaningful within-patient improvement on the target outcomes. The estimated thresholds add to the psychometric literature for these measures and provide reference evidence for future CRSwNP trials to support interpretation of efficacy results obtained using these target outcomes.

Author Contributions

J.K.H., C.B., S.E.L., C.H., E.H., P.W.H., A.T.P., S.S., Y.L., L.P.M., and I.G.: provided interpretation of data and critical feedback, and final approval for submission. S.K., A.H.K., and C-C.C.: contributed to the conception and design of the study, provided interpretation of data and critical feedback, and final approval for submission. D.W., S.Q., and L.N.: contributed to the conception and design of the study, acquired data, provided interpretation of data and critical feedback, and final approval for submission. Authors affiliated with Regeneron Pharmaceuticals, Inc. and Sanofi participated in the analysis and interpretation of data, writing of the report, and the decision to submit the manuscript for publication.

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