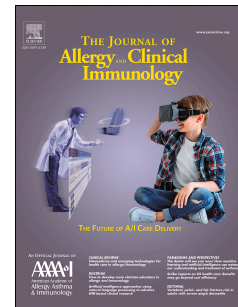


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Long-term efficacy and safety of omalizumab for nasal polyposis in an open-label extension study

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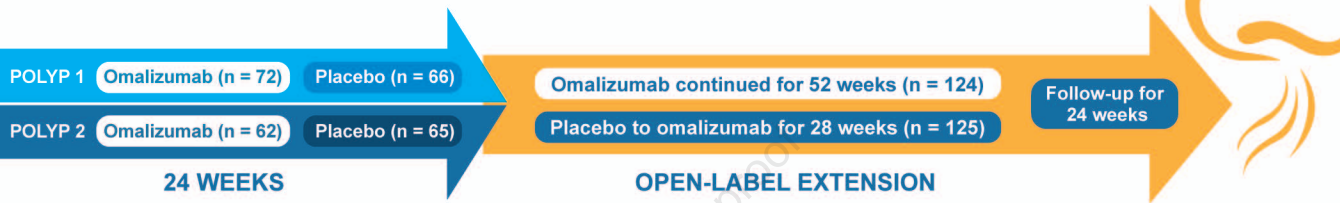
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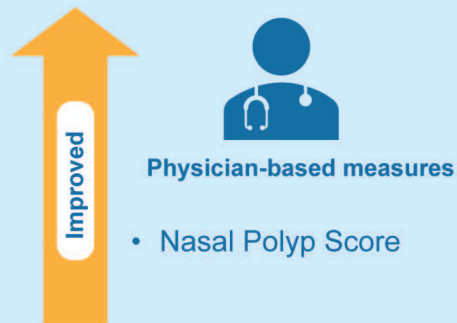
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Omalizumab in patients with nasal polyposis: open-label long-term extension study



Patients who continued omalizumab experienced further improvements in endoscopic, clinical, and patient-reported outcomes through 52 weeks



Long-term efficacy and safety of omalizumab for nasal polyposis in an open-label extension study

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ABSTRACT [250/250 words]

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) frequently remains uncontrolled despite maximal medical therapy and sinonasal surgery, presenting several unmet needs and challenges. Omalizumab previously demonstrated efficacy in CRSwNP in duplicate, phase 3, randomized, placebo-controlled trials (POLYP 1, POLYP 2).

Objective: This open-label extension evaluated continued efficacy, safety, and durability of response of omalizumab in adults with CRSwNP who completed POLYP 1 or 2.

Methods: After 24 weeks of omalizumab or placebo in POLYP 1 and 2, patients (n = 249) received open-label omalizumab plus background nasal mometasone for 28 weeks and were subsequently followed for 24 weeks after omalizumab discontinuation. Efficacy endpoints assessed change from baseline for the coprimary endpoints, Nasal Polyp Score and Nasal Congestion Score, and the secondary endpoints of Sino-Nasal Outcome Test-22, Total Nasal Symptom Score and its components, and University of Pennsylvania Smell Identification Test scores. Safety objectives included incidence of adverse events (AEs) and AEs leading to omalizumab discontinuation.

Results: Patients who continued omalizumab experienced further improvements across coprimary endpoints and secondary endpoints through 52 weeks. Patients who switched from placebo to omalizumab experienced favorable responses across endpoints through week 52 that were similar to POLYP 1 and 2 at week 24. After omalizumab discontinuation, scores gradually worsened over the 24-week follow-up, but remained improved from pretreatment levels for both groups. The safety profile was similar to previous reports.

Conclusion: The efficacy and safety profile from this study supports extended omalizumab treatment up to 1 year for CRSwNP with inadequate response to nasal corticosteroids.

Trial registration: NCT03478930

Clinical implications [31/35 words]

Results from this study reinforce and extend the findings of previous trials showing that omalizumab is a viable longer-term alternative treatment for patients with CRSwNP with inadequate response to nasal corticosteroids.

Capsule summary [35/35 words]

In this open-label extension study of POLYP 1/2, patients with severe CRSwNP with inadequate response to nasal corticosteroids who were treated with omalizumab experienced significant improvements in endoscopic, clinical, and patient-reported outcomes over 52 weeks.

Key words

Nasal polyps, rhinosinusitis, omalizumab, quality of life, nasal obstruction, IgE, asthma, nasal corticosteroids, Nasal Polyp Score, Nasal Congestion Score

98 Abbreviations

99 AE: Adverse event

100 AERD: Aspirin-exacerbated respiratory disease

101 AQLQ: Asthma Quality of Life Questionnaire

102 CRS: Chronic rhinosinusitis

103 CRSwNP: Chronic rhinosinusitis with nasal polyps

104 EPOS: European Position Paper of Rhinosinusitis and Nasal Polyps

105 MCID: Minimal clinically important difference

106 MMRM: Mixed-effect model of repeated measures

107 NCS: Nasal Congestion Score

108 NPS: Nasal Polyp Score

109 OLE: Open-label extension

110 QoL: Quality of life

111 SCS: Systemic corticosteroids

112 SNOT-22: Sino-Nasal Outcome Test-22

113 TNSS: Total Nasal Symptom Score

114 UPSIT: University of Pennsylvania Smell Identification Test

115

INTRODUCTION

Chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) is a common disorder of the sinonasal passages.¹ Estimated prevalence of CRS is up to 15% of the population based on a symptomatic definition, and between 3% and 6.7% of the population based on a combination of symptoms and/or endoscopic findings.²⁻⁴ Nasal polyps are present in approximately 18% of patients with CRS,² equating to an estimated CRSwNP prevalence between 2% and 4%.⁵⁻⁷

CRSwNP, often used synonymously with nasal polyps, remains a disease with unmet need because many patients remain uncontrolled despite standard of care treatment with nasal corticosteroids, systemic corticosteroids (SCS), nasal irrigation, antileukotrienes, antibiotics, aspirin desensitization, nasal antihistamines, and complex sinonasal surgeries.^{1,8,9} Additionally, patients often experience diminished quality of life (QoL)^{10,11} across physical functioning, facial pain, general health, vitality and social functioning, and emotional and mental health domains, and are more likely than the general population to experience anxiety and depression.¹²

In CRSwNP, exposure to inhalant allergens,¹³ fungi,¹⁴ and *Staphylococcus aureus*¹⁵ can initiate local, functional, polyclonal IgE production, which perpetuates inflammation and disease progression in tissues by binding to or activating mast cells.¹⁶ The monoclonal antibody omalizumab inhibits targets that cause symptoms¹⁷ and blocks perpetuation of inflammation by selectively binding to IgE.^{18,19}

Omalizumab reduced nasal polyp size and improved symptoms in 2 randomized, placebo-controlled, phase 3 trials (POLYP 1 and 2) in patients with CRSwNP with inadequate response to nasal corticosteroids.²⁰ POLYP 1 and 2 met both coprimary endpoints, with

significant reductions in Nasal Polyp Score (NPS) and average daily Nasal Congestion Score (NCS) from baseline at week 24.²⁰ Furthermore, secondary endpoints, including Sino-Nasal Outcome Test-22 (SNOT-22), average daily sense of smell, postnasal drip, runny nose, and smell test (University of Pennsylvania Smell Identification Test [UPSIT]), were significantly improved. Rescue treatment with SCS or surgery was low. Improvements in NPS, NCS, and SNOT-22 were similar in patients with CRSwNP with or without comorbid asthma.²⁰ Pooled safety data in POLYP 1 and 2 were similar for omalizumab and placebo. Adverse reactions were consistent with those from clinical trials in patients with moderate-to-severe allergic asthma or chronic spontaneous urticaria.

This open-label extension (OLE) study evaluated efficacy, safety, and durability of response of omalizumab in an open-label setting in adults with CRSwNP who completed POLYP 1 or POLYP 2.

METHODS

Study design and patient population

In this OLE, adults who were previously treated with omalizumab or placebo for 24 weeks during the replicate, phase 3, randomized, multicenter, double-blind, placebo-controlled trials, POLYP 1 (NCT03280550) or POLYP 2 (NCT03280537), received open-label omalizumab for an additional 28 weeks (up to week 52). Protocol and results for POLYP 1 and 2 have been published previously.²⁰ Patients aged 18-75 years with CRSwNP with inadequate response to nasal corticosteroids could enroll in POLYP 1 and 2 if they had NPS of 5 or higher (≥ 2 for each nostril), SNOT-22 of 20 or higher, and NCS of 2 or higher. Previous surgery and/or SCS use were not required. Demographic data and medical history were collected during POLYP 1 and 2.

Omalizumab- or placebo-treated patients from POLYP 1 and 2 who completed treatment and assessments through 24 weeks and completed eDiary daily assessments for at least 4 of 7 days in the week before the week 24 study visit were eligible to enroll in the OLE. Patients initially randomized to omalizumab in POLYP 1 and 2 continued on omalizumab for 28 additional weeks (from weeks 24-52), for 52 total weeks of treatment, and are referred to as patients who continued omalizumab (Fig 1). Patients initially randomized to placebo in POLYP 1 and 2 received omalizumab for 28 weeks (from weeks 24-52), and are referred to as patients who switched treatment. Patients and evaluating physicians remained blinded to treatment assignment from POLYP 1 and 2, with no adjustments in dosing made through the OLE. Protocol-specified study drug dosing was 75-600 mg by subcutaneous injection every 2 or 4 weeks, based on serum total IgE level (30-1500 IU/mL) and body weight (30-150 kg) measured before treatment initiation in POLYP 1 and 2, as described previously.²⁰ Omalizumab was

withdrawn after the treatment period and patients were observed for an additional 24 weeks (from weeks 52-76) as part of an off-treatment follow-up period to determine durability of response to omalizumab. All patients remained on background nasal mometasone furoate daily (400 µg, or 200 µg if intolerant to 400 µg) during POLYP 1 and 2 and the OLE.

The protocol was approved by respective institutional review boards and ethics committees. All patients provided written informed consent. The study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice,²¹ Declaration of Helsinki,²² and all applicable laws and regulations.

Assessments

The coprimary endpoint, NPS, was determined by video nasal endoscopy and scored by 2 independent sinus surgeons who were blinded to treatment group and period (randomized, open-label vs follow-up). Scores ranged from no polyps (0) to nasal polyps reaching the floor of the nasal cavity (4). Total NPS was the sum of both nasal cavities (score range, 0-8).²⁰

Patient-recorded efficacy outcomes of nasal congestion, sense of smell, postnasal drip, and runny nose were collected daily using an eDiary (score range, 0 [not at all] to 3 [severe] for each). Scores were analyzed individually and together in the combined Total Nasal Symptom Score (TNSS) (score range, 0-12) as 7-day average scores. The nasal congestion question from the eDiary forms the coprimary endpoint, NCS.²⁰

The validated health-related QoL measure, SNOT-22 (score range, 0-110; lower scores indicate better disease control and QoL), was assessed at various study visits (Fig 1). Minimal clinically important difference (MCID) is at least 8.9-point improvement.²³ UPSIT is a

standardized, 40-item, “scratch-and-sniff” measure of olfactory function (score range, 0-40; higher scores indicate better smell). Scores below 19 indicate complete loss of smell (anosmia).²⁴ Asthma Quality of Life Questionnaire (AQLQ) was administered to patients with comorbid asthma (score range, 1-7; higher scores indicate better QoL).^{25,26}

To estimate a reduction in the need for sinonasal surgery, NPS and SNOT-22 measures were intended to serve as proxy indicators to identify patients who were unlikely to require surgical intervention. Criteria for those unlikely to need sinonasal surgery included NPS ≤ 4 (with unilateral score of ≤ 2 on each side) when accompanied by SNOT-22 improvement of at least 1 MCID (≥ 8.9 point) improvement.

Adverse events (AEs) and concomitant medications (including SCS) were monitored throughout the OLE. If sinonasal surgery was required during the treatment phase, study medication was discontinued, while study assessments continued throughout the treatment phase.

Statistical analyses

No formal sample size calculation was performed because most patients completing the POLYP 1 and 2 studies were eligible for enrollment. Data for all efficacy analyses are pooled from POLYP 1 and 2 and are presented by assigned treatment group in POLYP 1 and 2; patients who switched and continued omalizumab were formerly randomized to placebo and omalizumab, respectively. Baseline was defined as last measurement before randomization in POLYP 1 and 2 to allow for continuous graphical assessment of each endpoint over the 52-week treatment period.

For coprimary (NPS, NCS) and secondary (SNOT-22, postnasal drip, runny nose, sense of smell, TNSS, UPSIT) endpoints, change from baseline was analyzed using a mixed-effect model of repeated measures (MMRM), including the POLYP 1 or 2 studies, baseline score, geographic region, asthma comorbidity, nonsteroidal anti-inflammatory drug-exacerbated respiratory disease status, time point, treatment arm, treatment-time point interaction, and baseline score-time point interaction as covariates. Pre-specified MMRM models were applied to compare patients who were originally randomized to omalizumab versus placebo for all time points, including Week 52, however, without controlling for multiplicity.

Post hoc comparisons between weeks 24 and 52 for patients randomized to omalizumab were performed to evaluate whether extending omalizumab treatment to 52 weeks might further improve outcomes for a restricted set of endpoints: NPS, NCS, SNOT-22, and TNSS. In addition to the primary endpoints, post hoc analyses were performed only on composite symptom scores, and not on individual scores, to limit the chance of spurious results. A further subgroup analysis was performed to assess NPS and NCS change from baseline using a MMRM model in patients with versus without comorbid asthma and aspirin-exacerbated respiratory disease (AERD).

RESULTS

Study disposition, baseline demographics, and clinical characteristics

Of 265 patients enrolled in POLYP 1 and 2, 249 patients enrolled into the OLE. Most enrolled patients completed the OLE treatment (95.6%) and treatment-free follow-up (92.8%) periods. Reasons for discontinuation included AEs (n = 2), lack of efficacy (n = 6), and

withdrawal by patient ($n = 3$) during the OLE treatment period, and lack of efficacy ($n = 1$) and withdrawal by patient ($n = 9$) during the OLE treatment-free follow-up period.

Demographic and clinical characteristics at the start of POLYP 1 and 2 were similar between treatment arms (Table E1), but varied across treatment groups at OLE study initiation (week 24) because a better response profile was observed for omalizumab- versus placebo-treated patients in the POLYP 1 and 2 studies (Table E2). Nasal symptom, NPS, and SNOT-22 scores were lower in omalizumab- versus placebo-treated patients in POLYP 1 and 2. Mean UPSIT scores were higher in omalizumab- versus placebo-treated patients in POLYP 1 and 2.

Changes in primary endpoints: NPS and NCS

At week 24, there was a difference between treatment arms in NPS (treatment difference, -0.82 ; $P < .0001$) and NCS (treatment difference, -0.54 ; $P < .0001$; Fig 2A-B) attributed to omalizumab treatment in POLYP 1 and 2. Week 24 corresponds to the last assessment time point in POLYP 1 and 2 and the start of the OLE. In patients who continued omalizumab, further improvements were observed during the OLE treatment period, with mean changes from baseline of -1.01 at week 24 and -1.31 at week 52 in NPS and -0.85 at week 24 and -1.12 at week 52 in NCS. In patients who switched to omalizumab during the OLE (previously randomized to placebo), large improvements in NPS and NCS were observed after omalizumab initiation. Improvements for NPS and NCS for patients who switched were from -0.19 and -0.31 at week 24 to -0.97 and -0.99 at week 52, respectively.

NPS and NCS gradually worsened during the OLE treatment-free follow-up period from week 52, but remained below omalizumab pretreatment levels for both groups. At week 76,

NPS was -0.54 and -0.48 and NCS was -0.65 and -0.58 in patients who continued and switched to omalizumab, respectively.

Secondary endpoints

Changes in other eDiary-related endpoints. At OLE study initiation at week 24, omalizumab was associated with improvements above placebo in postnasal drip, runny nose, sense of smell, and TNSS (Fig 3A-D). Improvements through the OLE treatment period continued in patients who continued omalizumab, with mean changes from baseline of -2.82 at week 24 and -3.83 at week 52 in TNSS. In patients who switched from placebo to omalizumab during the OLE, large improvements in postnasal drip, runny nose, sense of smell, and TNSS were observed after omalizumab initiation, and reached their peak of -3.01 in TNSS at week 52.

All 4 metrics gradually worsened during the OLE treatment-free follow-up period, but remained improved from baseline. Mean changes from baseline at week 76 in TNSS were -1.63 and -2.18 points in patients who switched and continued omalizumab during the OLE treatment period, respectively.

Changes in UPSIT, SNOT-22, and AQLQ. UPSIT scores improved for omalizumab versus placebo from baseline to week 24 during POLYP 1 and 2 (Fig 4A). Improvements were maintained through week 52 of the OLE treatment period in patients who continued omalizumab, with mean changes from baseline of 4.24 at week 24 and 4.13 at week 52. In patients who switched to omalizumab, improvements in UPSIT scores reached a peak improvement of 3.88 points at week 52. However, this score is still within the range of anosmia.

UPSIT scores gradually worsened during the OLE treatment-free follow-up period, but remained improved by a mean 0.62 and 1.42 points at week 76 in patients who switched and continued omalizumab, respectively.

SNOT-22 scores were improved for omalizumab versus placebo at week 24 of POLYP 1 and 2 (Fig 4B). In patients who continued omalizumab, mean SNOT-22 scores improved from –23.56 points at week 24 to –28.47 points at week 52. In patients who switched to omalizumab, SNOT-22 scores showed a large improvement from baseline after omalizumab initiation to –22.39 points at week 52. SNOT-22 scores gradually worsened during the OLE treatment-free follow-up period to –15.37 and –19.44 points in patients who switched or continued omalizumab, respectively, at week 76.

AQLQ scores in patients with asthma (Fig 4C) also improved rapidly over the OLE treatment period in patients who switched to omalizumab. In patients who continued omalizumab, AQLQ scores were maintained over the OLE treatment period. AQLQ scores declined slowly over the 24-week OLE treatment-free follow-up period, but remained improved versus baseline.

Exploratory endpoints

SCS rescue treatment lasting at least 3 consecutive days from randomization through week 52 (including both the phase 3 randomized studies and the OLE) was required in 10 of 123 patients continuing on omalizumab treatment (8.1%). In comparison, 3 of 129 (2.3%) patients receiving omalizumab and 8 of 129 (6.2%) receiving placebo required rescue SCS treatment in the POLYP 1 and 2 studies (weeks 0-24).²⁰ Sinonasal surgeries from randomization in the phase

3 study portion through week 52 of the OLE was observed for 5 of 123 (4.1%) patients continuing on omalizumab. No sinonasal surgeries were recorded in the POLYP 1 and 2 studies.²⁰ Reduced need for surgery (NPS ≤ 4 and ≥ -8.9 -point SNOT-22 improvement from baseline) by weeks 36 and 52 was estimated in 26 (22.6%) and 32 (27.8%) of 115 patients who received omalizumab in the POLYP 1 and 2 studies and continued on omalizumab in the OLE, respectively.

Additional analyses

Improvements were noted for TNSS and SNOT-22 at week 52 when comparing the placebo- versus omalizumab-randomized treatment arms (Table I). This corresponds to 28 or 52 weeks of omalizumab treatment in the placebo versus omalizumab treatment arms, respectively.

In *post hoc* analyses, notable improvements were observed for NPS, NCS, TNSS, and SNOT-22 at week 52 versus week 24 in patients randomized to omalizumab in the POLYP 1 or 2 studies (Table II). This corresponds to 24 or 52 weeks of omalizumab treatment. Patients with comorbid asthma and AERD who continued on omalizumab had similar mean improvements in NPS and NCS at week 52 compared with patients without asthma or AERD (Table E3).

Safety and tolerability

During the OLE treatment period, 278 nonserious AEs and 10 serious AEs were reported. Nasopharyngitis was reported by more than 5% of the POLYP 1 and 2 placebo-treated population. Eleven (4.4%) patients reported 41 investigator-assessed treatment-related events,

all of which were nonserious. One patient withdrew due to itching skin (pruritus). Other common treatment-related AEs were injection site reactions (eg, bruising, pain, inflammation).

During the OLE treatment-free follow-up period, 190 nonserious AEs and 11 serious AEs were reported. Most common AEs were nasal polyps (13 patients; 5.2%), nasopharyngitis (12 patients; 4.8%), and asthma exacerbation (10 patients; 4.0%).

One case of prostate cancer was reported as an AE of special interest during the OLE treatment period and was considered unrelated to omalizumab. There were no cases of drug-induced liver injury as defined by Hy's Law,²⁷ but 1 patient discontinued open-label omalizumab after the first dose due to a nontreatment-emergent AE of nonserious autoimmune hepatitis that developed as the patient was completing the POLYP 1 or 2 studies. The event was considered unrelated to omalizumab. There were no cases of anaphylaxis (Table III).

DISCUSSION

CRSwNP remains a chronic, difficult-to-treat disease, with substantial impact on QoL. The phase 3 placebo-controlled trials, POLYP 1 and 2, previously demonstrated statistically and clinically significant improvements in the coprimary endpoints, NPS and NCS, after 24 weeks of omalizumab with background nasal corticosteroids.²⁰ Improvements in NPS and NCS were accompanied by significant improvements in patient-reported symptoms and disease-related QoL (TNSS, SNOT-22, sense of smell, postnasal drip, runny nose) and smell test (UPSIT).

In this OLE, patients with CRSwNP continuing omalizumab through 52 weeks experienced further improvements in the coprimary endpoints of NPS and NCS and most secondary efficacy endpoints of TNSS, SNOT-22, and AQLQ. Additionally, in patients who received omalizumab for the first time, the findings of this OLE are generally similar to those in POLYP 1 and 2, with large improvements in symptomatic scores and NPS. These data provide further evidence of omalizumab efficacy in the nasal polyp indication, and suggest that efficacy may improve with extended treatment.

Improvements across both coprimary endpoints were noted with extended omalizumab treatment, with further improvements in NPS and NCS versus baseline from weeks 24 through 52. Furthermore, numerical improvements were observed in other eDiary patient-reported symptoms and disease-related QoL measures (postnasal drip, runny nose, sense of smell, TNSS, SNOT-22) with 52 weeks of omalizumab treatment. Smell, as measured with UPSIT, remained similar to previous observations at week 24, but improved numerically when assessed by eDiary. QoL improvements exceeded the commonly accepted SNOT-22 MCID of -8.9 points,²³ with a -28.47-point (>3 MCIDs) change after 52 weeks of omalizumab.

Because of the open-label, nonplacebo-controlled study design, efficacy comparisons were preplanned as descriptive. However, in patients continuing omalizumab from weeks 24 to 52, continuing improvements were observed across coprimary and secondary endpoints, suggesting a benefit of extended omalizumab treatment. Association of reduced nasal polyp burden with omalizumab treatment was strengthened by the observation that NPS was determined by readers blinded to treatment assignment. Because of these findings, despite the limitations, *post hoc* statistical analyses were performed to better understand if extended omalizumab treatment of 52 weeks improved outcomes versus 24 weeks. NPS, NCS, SNOT-22, and TNSS scores were compared between weeks 24 and 52 for those randomized to omalizumab in POLYP 1 and 2, and across treatment arms at week 52.

In the *post hoc* analysis comparing weeks 24 and 52 in those randomized to omalizumab in POLYP 1 and 2, improvements were noted for the coprimary endpoints (NPS, NCS) and both composite symptom scores (SNOT-22, TNSS). Statistical tests excluded the null hypothesis of no effect, although these were not prespecified. Nonetheless, the observed differences, when combined with consistency of improvements across endpoints, make these results noteworthy. Similarly, prespecified outcomes at week 52, comparing patients who had received approximately 6 months of omalizumab versus those who had received 12 months of omalizumab, overall supported the conclusion that further treatment with omalizumab led to improved results. Although *P* values for NPS and NCS were above 0.05, there was again a consistent finding of improvement across endpoints for patients who had received a longer duration of omalizumab.

The selection of which care pathway is suitable for each patient and the choice of when and in which patients to start a biologic is nuanced, and guidance is continually developing. The European Position Paper of Rhinosinusitis and Nasal Polyps (EPOS) criteria state that a patient should have an appropriate medical therapy with or without oral corticosteroids or functional endoscopic sinus surgery with reevaluation after 6 to 12 weeks.²⁸ However, recommendations from the 2021 European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) expert board meeting do not require surgery before biologic use, and note that the decision on choice of biologic should be made in partnership with an informed patient. Moreover, regardless of previous treatment, omalizumab may also be a good therapeutic choice in patients who have comorbid severe asthma and nasal polyps. Although the proportion of patients who fulfilled EPOS criteria was not formally assessed in this study, previous surgery and use of SCS were recorded, which served as a close proxy to EPOS criteria. In this patient population, 59.0% of all patients had received previous surgery upon entering the trial and 22.1% of patients had received SCS in the year leading up to the trial. Altogether, 68.1% of patients had received either SCS in the last year or had a history of surgery.

Extended omalizumab treatment may reduce need for sinonasal surgery over time. In POLYP 1 and 2, 18.8% and 16.9%, respectively, met preestablished NPS and SNOT-22 criteria for reduction in need for surgery.²⁰ In this OLE, 22.6% and 27.8% of patients met criteria for reduction in need for surgery after weeks 36 and 52, respectively.

In POLYP 1 and 2, omalizumab numerically reduced rescue treatment by SCS, but the number of total events was low (2.3% of omalizumab-treated patients and 6.2% of placebo-treated patients), making it difficult to draw conclusions.²⁰ Additionally, there were no surgeries

in POLYP 1 and 2, which one could speculate was due to improved adherence to their intranasal corticosteroid treatment, along with an incentive to complete POLYP 1 and 2 to attain eligibility for open-label omalizumab. In this OLE, again, only a small proportion of patients continuing on omalizumab required rescue treatment (~9%) or surgery (~3%) throughout the OLE treatment period, despite more than 50% of patients having had these interventions previously.

Although all other endpoints were specific to nasal polyps, AQLQ was the only measure that looked at asthma outcomes, which was present in 57.0% of patients in this study. Of note, asthma severity was mostly physician assessed as mild to moderate, and allergic asthma was not assessed for this study. Despite this, AQLQ improvements at week 52 exceeded the MCID (0.5 points)³⁰ in patients who switched (0.52 points) and those who continued omalizumab (0.95 points) during the OLE, suggesting that longer duration of treatment with omalizumab led to better asthma outcomes. This study provides the first evidence that extended omalizumab treatment may continue to improve asthma-related QoL in patients with CRSwNP with comorbid asthma. Similar long-term improvements in AQLQ have been previously described in omalizumab-treated patients with severe asthma, where AQLQ continued to show improvements at 4 and 9 years.³¹

A substantial proportion of patients with CRSwNP and asthma also have AERD.^{20,32} Approximately 27% of the OLE population also had a diagnosis of AERD.²⁰ Although this group remains as one of the hardest to treat,³³ a case series (N = 29) of omalizumab³⁴ suggested biologics may be effective in patients with AERD. Both the pivotal studies²⁰ and this OLE study demonstrate efficacy in this AERD population; however, further study is needed to better understand efficacy in AERD compared with other populations.

This OLE also examined durability of response after omalizumab withdrawal. After discontinuation at week 52, scores gradually worsened across all efficacy endpoints, but remained improved versus pretreatment levels at week 76. Such sustained effects and durable response after discontinuation may be clinically important (eg, in event of a missed dose). Potential explanations for this sustained efficacy include reversion to the mean or improved penetration of nasal corticosteroids after treatment with a biologic. One speculative but intriguing possibility is the potential for a disease-modifying effect of omalizumab on nasal mucosal pathology, because these data also suggest that long-term treatment with omalizumab results in anti-inflammatory effects that persist after stopping therapy. However, these results should be viewed as hypothesis generating, and warrant longer follow-up to confirm. Further studies should be undertaken examining tissue remodeling or regulation of type 2 inflammation with biopsies and/or nasal secretions over time, perhaps with alternative biomarkers, including periostin, tenascin C, or fibronectin.

Omalizumab was well tolerated, with no new or unexpected safety signals identified. AEs were similar with those reported in POLYP 1 and 2²⁰ and to the well-established safety profile for omalizumab in asthma and chronic spontaneous urticaria, based on a cumulative exposure of over 16,000 patient-years in clinical trials and an estimated cumulative patient exposure of over 1,300,000 patient-years in the postmarketing setting (data on file, Novartis).

Patients may be more likely to report symptomatic improvement when they know they are on active drug. Because the OLE was not blinded, this may partially explain why significant improvements are noted in analyses comparing weeks 52 and 24 in the omalizumab arm.³⁵ However, findings for NPS, an objective endpoint assessed by blinded readers, were consistent

with those of more subjective endpoints, suggesting that results were not entirely explained by the open-label nature of this study. Additionally, patients who switched to omalizumab during the OLE treatment period had similar results to those experienced by omalizumab-treated patients during POLYP 1 and 2, making significant open-label bias less likely. The statistical analyses are limited by lack of type I error control and the descriptive nature of the results. Nonetheless, consistency of findings across multiple endpoints lends additional legitimacy to our findings. Lastly, the effect of omalizumab on sinus inflammation cannot be directly determined, only inferred, from symptomatic scores.

In conclusion, this OLE extends POLYP 1 and 2 findings, demonstrating that omalizumab is efficacious and safe up to 52 weeks for treatment of CRSwNP in patients with inadequate response to nasal corticosteroids. Furthermore, continuing efficacy improvements over time support omalizumab for continued treatment in this patient group.

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Data sharing statement

Qualified researchers may request access to individual patient level data through the clinical study data request platform (<https://vivli.org/>). Further details on Roche's criteria for eligible studies are available here (<https://vivli.org/members/ourmembers/>). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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TABLE I. Comparing outcome improvement across treatment arms at the week 52 visit

	Placebo-	Omalizumab-		
Mean change from	randomized	randomized		
baseline of POLYP 1	week 52*	week 52*	Difference	<i>P</i>
or POLYP 2 (0 wk)	(n = 126)	(n = 123)	(95% CI)	value [†]
Total weeks of	28 in OLE only	52	—	—
omalizumab				
NCS	−0.99	−1.12	−0.14	.2340
(score range, 0-3)‡	(−1.14, −0.83)	(−1.28, −0.96)	(−0.36, 0.09)	
NPS	−0.97	−1.31	−0.34	.0954
(score range, 0-8)‡	(−1.25, −0.69)	(−1.60, −1.03)	(−0.74, 0.06)	
TNSS	−3.01	−3.83	−0.82	.0195
(score range, 0-12)‡	(−3.49, −2.53)	(−4.31, −3.34)	(−1.50, −0.13)	
SNOT-22	−22.39	−28.47	−6.07	.0056
(score range, 0-110)‡	(−25.39, −19.40)	(−31.52, −25.42)	(−10.34, −0.92)	

Data are mixed-effect model of repeated measures change from baseline in average daily

NCS averaged over the previous week or NPS for patients enrolled in the OLE.

P value and 95% CI for the differences in adjusted means.

*Patients also received background nasal mometasone.

†Statistical tests were prespecified but not controlled for multiplicity.

‡Negative scores indicate improvement.

TABLE II. Comparing the outcome improvement at week 24 versus week 52 time points within the omalizumab arm

Mean change from				
baseline of POLYP 1 or POLYP 2 (0 wk)	Omalizumab week 24*	Omalizumab week 52*	Difference (95% CI)	P value†
Weeks of omalizumab	24	52	—	—
NCS	-0.85	-1.12	-0.27	.0001
(score range, 0-3)‡	(-1.00, -0.70)	(-1.28, -0.96)	(-0.41, -0.14)	
NPS	-1.01	-1.31	-0.30	.0236
(score range, 0-8)‡	(-1.24, -0.78)	(-1.60, -1.03)	(-0.57, -0.04)	
TNSS	-2.82	-3.83	-1.01	<.0001
(score range, 0-12)‡	(-3.27, -2.36)	(-4.31, -3.34)	(-1.40, -0.63)	
SNOT-22	-23.56	-28.47	-4.91	.0009
(score range, 0-110)‡	(-26.55, -20.57)	(-31.52, -25.42)	(-7.79, -2.03)	

Data are MMRM change from baseline in average daily NCS averaged over the previous week or NPS for patients enrolled in the OLE.

P value and 95% CI for the differences in adjusted means.

*n = 123 for omalizumab. Patients also received background nasal mometasone.

†Statistical tests were conducted *post hoc* and not controlled for multiplicity.

‡Negative scores indicate improvement.

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588 **TABLE III.** AEs during the OLE treatment and treatment-free follow-up periods

	OLE treatment period			OLE treatment-free
	POLYP 1 and 2 study treatment*			follow-up period
	Placebo (n = 125)	Omalizumab (n = 124)	All patients (n = 249)	All patients (n = 249)
Total no. of AEs/SAEs	128/6	150/4	278/10	190/11
Patients with:				
≥ 1 AE, no. (%)	62 (49.6)	54 (43.5)	116 (46.6)	87 (34.9)
≥ 1 SAE, no. (%)	6 (4.8)	3 (2.4)	9 (3.6)	11 (4.4)
Treatment-related AE, no. (%)	6 (4.8)	5 (4.0)	11 (4.4)	0
≥ 1 AE leading to discontinuation of study drug, no. (%)	1 (0.8)	0	1 (0.4)	—
AEs occurring in $\geq 5\%$ of patients, no. (%)				
Nasopharyngitis	7 (5.6)	5 (4.0)	12 (4.8)	—
Nasal polyps	—	—	—	13 (5.2)
AEs identified as risks associated with omalizumab, no. (%) [†]				

	Malignant neoplasms	0	1 (0.8)	1 (0.4)	0
589	<i>SAE</i> , serious adverse event.				
590	Investigator text for AEs coded using Medical Dictionary for Regulatory Activities version 22.1.				
591	*Patients also received background nasal mometasone.				
592	†AEs identified as risks associated with omalizumab that were not observed in the study population included serum sickness syndrome/serum				
593	sickness–like disease, anti-omalizumab antibodies, eosinophilic granulomatosis with polyangiitis/Churg-Strauss syndrome/hypereosinophilic				
594	syndrome, thrombocytopenia, arterial thrombotic events, and parasitic infections.				

FIG 1. Study design schema for POLYP 1 and 2 and the OLE. *Timing of the visit is defined relative to baseline of POLYP 1 or POLYP 2. Thus, the OLE treatment period of this study is 28 weeks and runs from the week 24 visit (~24 weeks after initiation of study drug in POLYP 1 or POLYP 2) to the week 52 visit (~52 weeks after initiation of study drug in POLYP 1 or POLYP 2). The eDiary was completed daily throughout the study. Q2W, every 2 weeks; Q4W, every 4 weeks.

FIG 2. Mean change from baseline in (A) NPS and (B) NCS in the omalizumab OLE. Lower scores for all indicate improvement from baseline. Dotted blue lines represent omalizumab off-treatment periods; solid red lines reflect omalizumab on-treatment periods.

FIG 3. Mean change from baseline over 76 weeks of POLYP 1 and 2 and the OLE for (A) postnasal drip, (B) runny nose, (C) sense of smell, and (D) TNSS. Lower scores for all indicate improvement from baseline. Dotted blue lines represent omalizumab off-treatment periods; solid red lines reflect omalizumab on-treatment periods.

FIG 4. Mean change from baseline over 76 weeks of POLYP 1 and 2 and the OLE for (A) UPSIT, (B) SNOT-22, and (C) AQLQ. Higher scores for UPSIT and AQLQ indicate improvement from baseline; lower scores for SNOT-22 indicate improvement from baseline. Dotted blue lines represent omalizumab off-treatment periods; solid red lines reflect omalizumab on-treatment periods.

ONLINE REPOSITORY**TABLE E1.** Demographic and clinical characteristics at baseline of POLYP 1 and 2, safety analysis set

	POLYP 1 and 2 study treatment		
	Placebo	Omalizumab	All patients
	(n = 125)	(n = 124)	(n = 249)
Age (y), mean (SD)	51.5 (11.8)	50.0 (13.1)	50.8 (12.5)
Male, no. (%)	81 (64.8)	79 (63.7)	160 (64.3)
Geographic region of study site, no. (%)			
North America*	30 (24.0)	30 (24.2)	60 (24.1)
Ex-North America	95 (76.0)	94 (75.8)	189 (75.9)
Mometasone† daily dose, no. (%)			
400 µg	117 (93.6)	118 (95.2)	235 (94.4)
200 µg	8 (6.4)	6 (4.8)	14 (5.6)
Eosinophils (cells/µL), mean (SD)	353.9 (260.0)	326.7 (228.3)	340.4 (244.7)
Total IgE (IU/mL), mean (SD)	178.1 (175.3)	170.3 (170.7)	174.3 (172.7)
Patients with asthma, no. (%)	68 (54.4)	74 (59.7)	142 (57.0)
Physician-assessed asthma severity, no. (%)			
Mild	28 (41.2)	23 (31.1)	51 (35.9)

Moderate	38 (55.9)	43 (58.1)	81 (57.0)
Severe	2 (2.9)	8 (10.8)	10 (7.0)
AQLQ score, mean (SD)	5.0 (1.3)	4.7 (1.3)	4.9 (1.3)
Patients with physician- assessed AERD, no. (%)	31 (24.6)	36 (29.3)	67 (26.9)
Previous sinonasal surgery, no. (%)	77 (61.6)	70 (56.5)	147 (59.0)
No. of previous sinonasal surgeries, no. (%)			
0	48 (38.4)	54 (43.5)	102 (41.0)
1	37 (29.6)	41 (33.1)	78 (31.3)
≥2	40 (32.0)	29 (23.4)	69 (27.7)
Time since last sinonasal surgery, no. (%)			
>1-5 y	25 (32.5)	15 (22.1)	40 (27.6)
>5 y	52 (67.5)	53 (77.9)	105 (72.4)
SCS use in past year, no. (%)	23 (18.4)	32 (25.8)	55 (22.1)
Previous sinonasal surgery or SCS use in past year, no. (%)	87 (69.6)	82 (66.7)	169 (68.1)
Planned dosing every 4 weeks, no. (%)	108 (86.4)	111 (89.5)	219 (88.0)

*United States, Canada, and Mexico.

†Patients received nasal mometasone as background treatment.

TABLE E2. Clinical characteristics at the week 24 study visit, safety analysis set

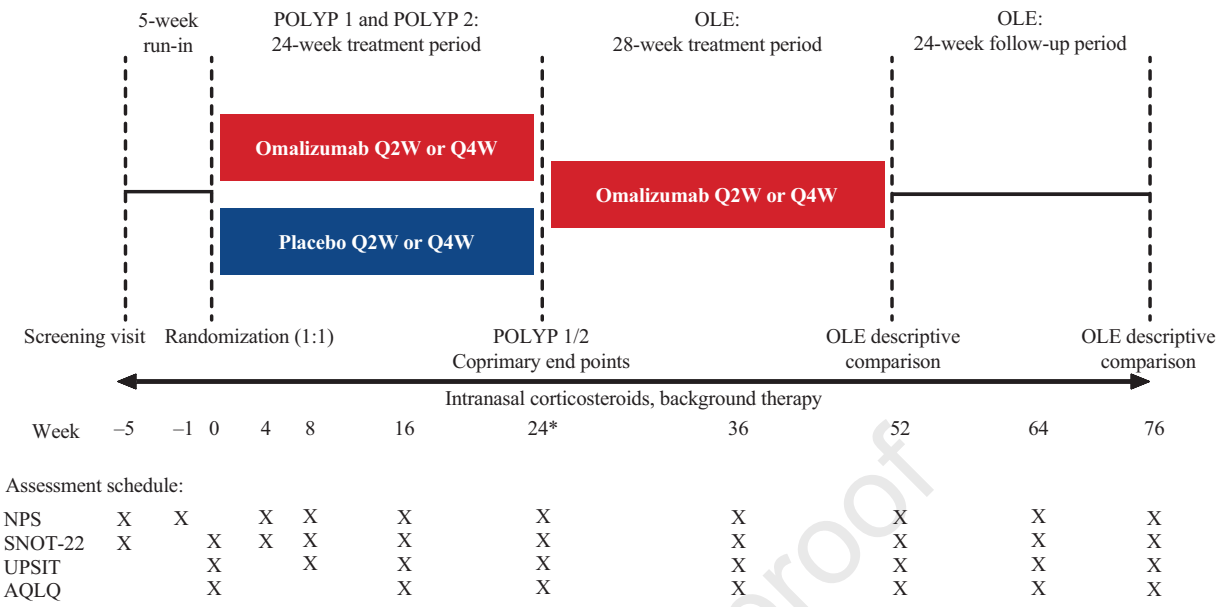
	Parent study treatment		
	Placebo (n = 125)	Omalizumab (n = 124)	All patients (n = 249)
NPS	6.1 (1.4)	5.3 (1.5)	5.7 (1.5)
(score range, 0-8), mean (SD)*			
NCS	2.1 (0.9)	1.5 (1.0)	1.8 (1.0)
(score range, 0-3), mean (SD)*			
Sense of smell	2.6 (0.8)	2.0 (1.0)	2.3 (0.9)
(score range, 0-3), mean (SD)*			
Postnasal drip	1.7 (1.0)	1.1 (0.9)	1.4 (1.0)
(score range, 0-3), mean (SD)*			
Runny nose	1.8 (1.0)	1.2 (0.9)	1.5 (1.0)
(score range, 0-3), mean (SD)*			
TNSS	8.1 (3.0)	5.8 (3.0)	7.0 (3.2)
(score range, 0-12), mean (SD)*			
UPSIT	13.8 (7.7)	17.1 (8.9)	15.5 (8.5)
(score range, 0-40), mean (SD)†			
SNOT-22	52.1 (20.1)	36.4 (23.5)	44.3 (23.2)
(score range, 0-22), mean (SD)*			
Treatment duration (wk), mean (SD)	23.8 (3.7)	23.8 (3.6)	23.8 (3.7)

*Higher scores indicate worse health status.

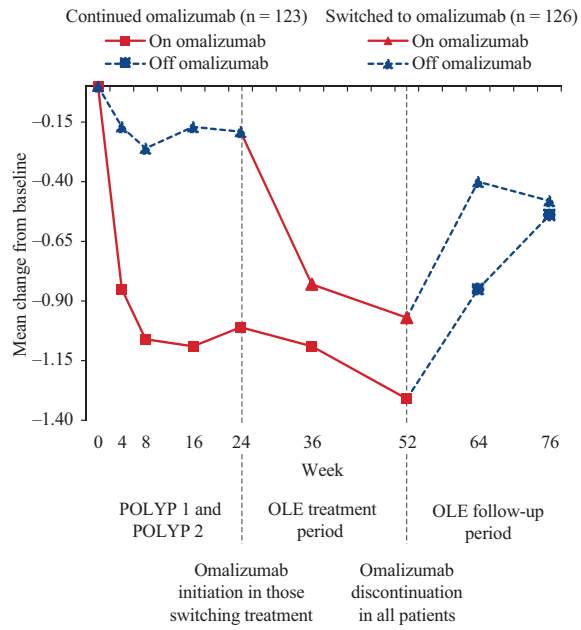
†Higher scores indicate better sense of smell; UPSIT score of 0 to 18 indicates total loss of smell/anosmia.

TABLE E3. Improvements in NPS and NCS at week 52 by asthma subtype

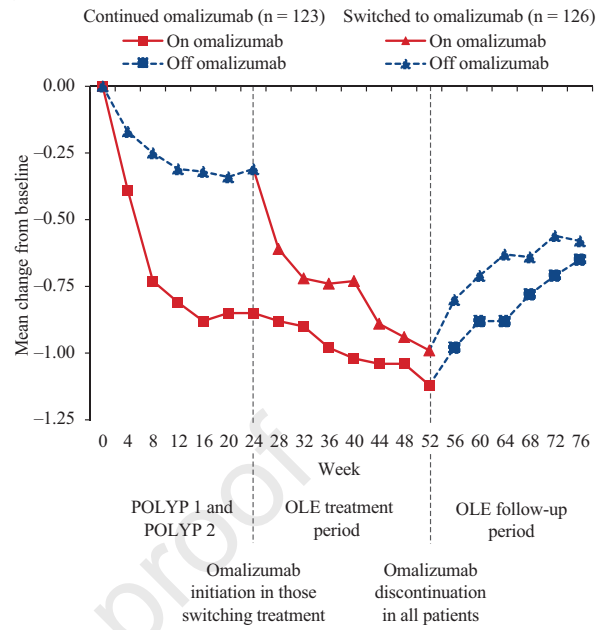
	Patient subgroup		
	Asthmatic and		No asthma
	aspirin sensitive (AERD)	Asthmatic not aspirin sensitive	
NPS (n)	31	42	50
Baseline	6.29	6.14	6.42
Point estimate	-1.00	-1.35	-1.44
(95% CI)	(-1.58, -0.42)	(-1.87, -0.84)	(-1.88, -1.01)
NCS (n)	31	42	50
Baseline	2.36	2.40	2.25
Point estimate	-0.92	-1.26	-1.13
(95% CI)	(-1.24, -0.61)	(-1.54, -0.99)	(-1.39, -0.87)

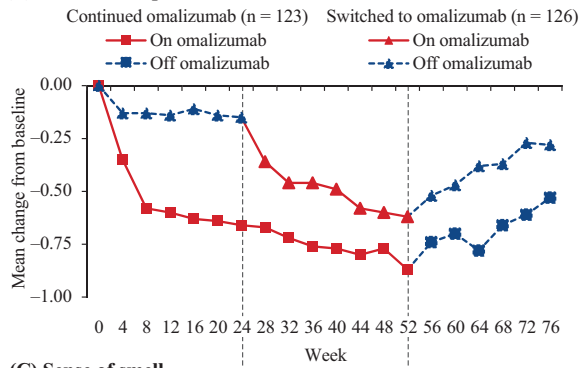
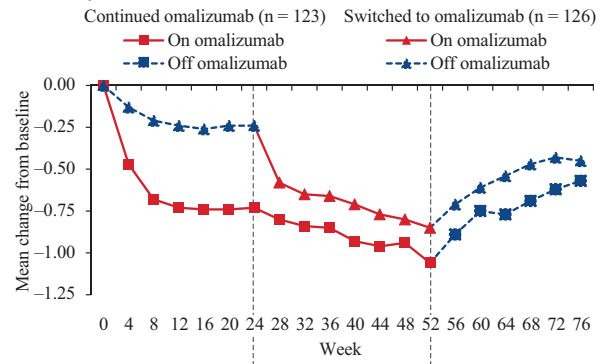
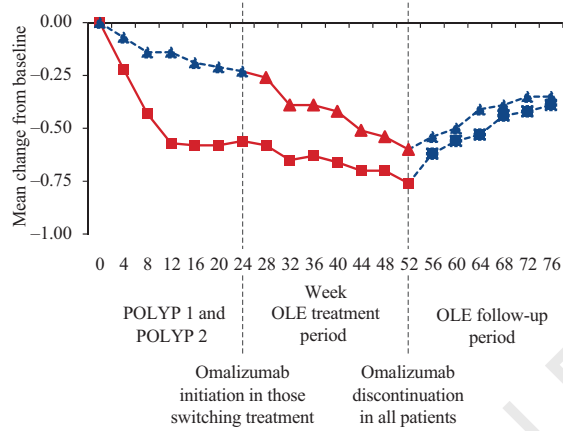
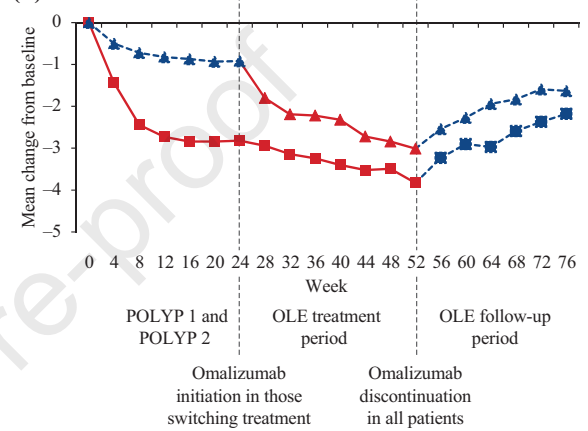


(A) NPS

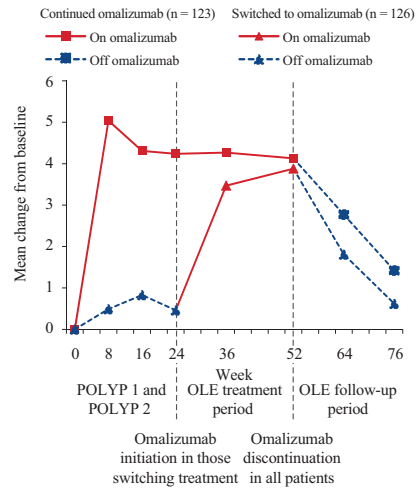


(B) NCS

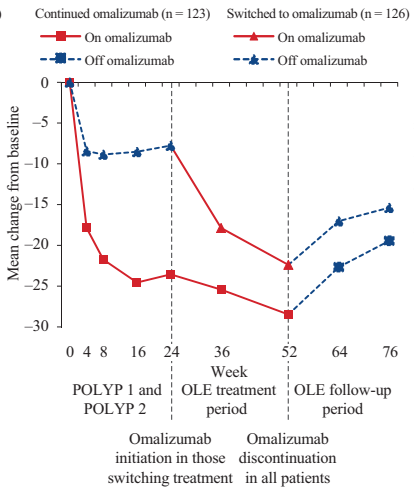


(A) Postnasal drip**(B) Runny nose****(C) Sense of smell****(D) TNSS**

(A) UPSIT



(B) SNOT-22



(C) AQLQ

