CLINICAL UPDATE

Brand Name	Nucala®
Generic Name	mepolizumab
Drug Manufacturer	GlaxoSmithKline LLC

Clinical Update

TYPE OF CLINICAL UPDATE

New Indication and Strength

FDA APPROVAL DATE

January 22, 2022

LAUNCH DATE

June 14, 2022

REVIEW DESIGNATION

N/A

TYPE OF REVIEW

Biologic License Application (BLA): 125526

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Nucala® is an interleukin-5 (IL-5) antagonist monoclonal antibody (IgG1 kappa) indicated for:

- Add-on maintenance treatment of adult and pediatric patients aged 6 years and older with severe asthma and with an eosinophilic phenotype.
- Add-on maintenance treatment of adult patients 18 years and older with chronic rhinosinusitis with nasal polyps (CRSwNP).
- The treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).
- The treatment of adult and pediatric patients aged 12 years and older with hypereosinophilic syndrome (HES) for ≥6 months without an identifiable non-hematologic secondary cause.

Limitations of use: Not for relief of acute bronchospasm or status asthmaticus.

MECHANISMS OF ACTION

Mepolizumab is an IL-5 antagonist (IgG1 kappa). IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Mepolizumab binds to IL-5 with a dissociation constant of 100 pM, inhibiting the bioactivity of IL-5 by blocking its binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface. Inflammation is an important component in the pathogenesis of asthma, CRSwNP, EGPA, and HES. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in inflammation.

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Mepolizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the mechanism of mepolizumab action in asthma, CRSwNP, EGPA, and HES has not been definitively established.

DOSAGE FORM(S) AND STRENGTH(S)

- For injection: 100 mg of lyophilized powder in a single-dose vial for reconstitution.
- Injection: 100 mg/mL, single-dose prefilled autoinjector or single-dose prefilled syringe.
- Injection: 40 mg/0.4 mL, single-dose prefilled syringe.

DOSE & ADMINISTRATION

Nucala® is for subcutaneous use only:

Severe Asthma:

Adults and Adolescents Aged 12 Years and Older: The recommended dosage in adults and adolescents aged 12 years and older is 100 mg administered once every 4 weeks by subcutaneous injection into the upper arm, thigh, or abdomen.

Pediatric Patients Aged 6 to 11 Years: The recommended dosage for injection in pediatric patients aged 6 to 11 years is 40 mg administered once every 4 weeks by subcutaneous injection into the upper arm, thigh, or abdomen.

Chronic Rhinosinusitis with Nasal Polyps:

The recommended dosage is 100 mg administered once every 4 weeks by subcutaneous injection into the upper arm, thigh, or abdomen.

Eosinophilic Granulomatosis with Polyangiitis:

The recommended dosage is 300 mg administered once every 4 weeks by subcutaneous injection as 3 separate 100-mg injections into the upper arm, thigh, or abdomen. Administer individual 100-mg injections at least 5 cm (approximately 2 inches) apart.

Hypereosinophilic Syndrome:

The recommended dosage is 300 mg administered once every 4 weeks by subcutaneous injection as 3 separate 100-mg injections into the upper arm, thigh, or abdomen. Administer individual 100-mg injections at least 5 cm (approximately 2 inches) apart.

EFFICACY

Severe Asthma: The asthma development program for Nucala® in patients aged 12 years and older included 3 double-blind, randomized, placebo-controlled trials: 1 dose-ranging and exacerbation trial (Trial 1, NCT01000506) and 2 confirmatory trials (Trial 2, NCT01691521 and Trial 3, NCT01691508). Mepolizumab was administered every 4 weeks in all 3 trials as add-on to background treatment. All patients continued their background asthma therapy throughout the duration of the trials.

Dose-Ranging and Exacerbation Trial: Trial 1 was a 52-week dose-ranging and exacerbation-reduction trial in patients with severe asthma with a history of 2 or more exacerbations in the previous year despite regular use of high-dose ICS plus additional controller(s) with or without OCS. Patients enrolled in this trial were required to have at least 1 of the following 4 pre-specified criteria in the previous 12 months: blood eosinophil count ≥300 cells/mcL, sputum eosinophil count ≥3%, exhaled nitric oxide concentration ≥50 ppb, or deterioration of asthma control after ≤25% reduction in regular maintenance ICS/OCS. Three IV dosages of mepolizumab (75, 250, and 750 mg) administered once every 4 weeks were evaluated compared with placebo. Results from this trial and the pharmacodynamic study supported the evaluation of mepolizumab 75 mg IV and 100 mg subcutaneous in the subsequent trials. Nucala® is not indicated for IV use and should only be administered by the subcutaneous route.

Confirmatory Trials: A total of 711 patients with severe asthma were studied in the 2 confirmatory trials (Trials 2 and 3). In these 2 trials patients were required to have blood eosinophils of ≥150 cells/mcL at screening (within 6 weeks of dosing) or blood eosinophils of ≥300 cells/mcL within 12 months of enrollment. The screening blood eosinophils of ≥150 cells/mcL criterion was derived from exploratory analyses of data from Trial 1. Trial 2 was a 32-week placebo- and active-controlled trial in patients with severe asthma with a history of 2 or more exacerbations in the previous year despite regular use of high-dose ICS plus additional controller(s) with or without OCS. Patients received mepolizumab 75 mg IV (n = 191), Nucala® 100 mg (n = 194), or placebo (n = 191) once every 4 weeks for 32 weeks. Trial 3 was a 24-week OCS-reduction trial in patients with severe asthma who required daily OCS in addition to regular use of high-dose ICS plus additional controller(s) to maintain asthma control. Patients in Trial 3 were not required to have a history of exacerbations in the previous year. Patients received Nucala® 100 mg (n = 69) or placebo (n = 66) once every 4 weeks for 24 weeks. The baseline mean OCS use was similar in the 2 treatment groups: 13.2 mg in the placebo group and 12.4 mg in the group receiving Nucala® 100 mg.

The demographics and baseline characteristics of these 3 trials are provided in Table 1.

Table 1. Demographics and Baseline Characteristics of Severe Asthma Trials

Table 1. Demographics and Baseline Characteristics of Severe Asthma Trials			
	Trial 1 (N = 616)	Trial 2 (N = 576)	Trial 3 (N = 135)
Mean age, years	49	49	50
Female, n (%)	387 (63)	328 (57)	74 (55)
White, n (%)	554 (90)	450 (78)	128 (95)
Duration of asthma, years, mean	19	20	19
Never smoked, n (%)	483 (78)	417 (72)	82 (61)
Baseline FEV_1, L	1.88	1.82	1.95
Baseline % predicted FEV1	60	61	59
Baseline % reversibility	25	27	26
Baseline post-SABA FEV_1/FVC	0.67	0.66	0.66
Geometric mean eosinophil count at baseline, cells/mcL	250	290	240
Mean number of exacerbations in previous year	3.6	3.6	3.1

FEV_1 = forced expiratory volume in 1 second, SABA = short-acting beta$_2$-agonist, FVC = forced vital capacity.

Exacerbations:

Efficacy was assessed in Trials 1 and 2 using an endpoint of the frequency of exacerbations defined as worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits. For patients on maintenance OCS, an exacerbation requiring OCS was defined as the use of oral/systemic corticosteroids at least double the existing dose for at least 3 days. Compared with placebo, patients receiving Nucala® 100 mg or mepolizumab 75 mg IV experienced significantly fewer exacerbations. Additionally, compared with placebo, there were fewer exacerbations requiring hospitalization and/or emergency department visits and exacerbations requiring only in-patient hospitalization with Nucala® 100 mg (Table 2).

Table 2: Rate of Exacerbations in Severe Asthma Trials 1 and 2 (Intent-to-Treat Population).

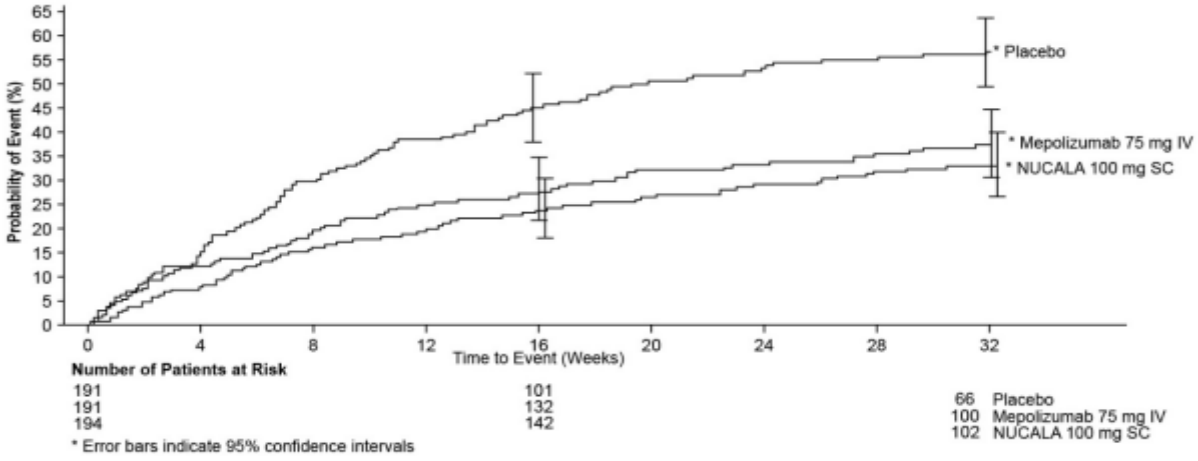
Table 2. Rate of Exacerbations in Severe Asthma Trials 1 and 2 (Intent-to-Treat Population)				
Trial	Treatment	Exacerbations per Year		
		Rate	Difference	Rate Ratio (95% CI)
All exacerbations				
Trial 1	Placebo (n = 155)	2.4		
	Mepolizumab 75 mg IV (n = 153)	1.24	1.16	0.52 (0.39, 0.69)

Trial 2	Placebo (n = 191)	1.74		
	Mepolizumab 75 mg IV (n = 191)	0.93	0.81	0.53 (0.40, 0.72)
	Nucala® 100 mg SC (n = 194)	0.83	0.91	0.47 (0.35, 0.64)
Exacerbations requiring hospitalization/emergency room visit				
Trial 1	Placebo (n = 155)	0.43		
	Mepolizumab 75 mg IV (n = 153)	0.17	0.26	0.40 (0.19, 0.81)
Trial 2	Placebo (n = 191)	0.2		
	Mepolizumab 75 mg IV (n = 191)	0.14	0.06	0.68 (0.33, 1.41)
	Nucala® 100 mg SC (n = 194)	0.08	0.12	0.39 (0.18, 0.83)
Exacerbations requiring hospitalization				
Trial 1	Placebo (n = 155)	0.18		
	Mepolizumab 75 mg IV (n = 153)	0.11	0.07	0.61 (0.28, 1.33)
Trial 2	Placebo (n = 191)	0.1		
	Mepolizumab 75 mg IV (n = 191)	0.06	0.04	0.61 (0.23, 1.66)
	Nucala® 100 mg SC (n = 194)	0.03	0.07	0.31 (0.11, 0.91)

IV = intravenous, SC = subcutaneous, CI°=°Confidence Interval.

The time to first exacerbation was longer for the groups receiving Nucala® 100 mg and mepolizumab 75 mg IV compared with placebo in Trial 2 (Figure 1).

Figure 1. Kaplan-Meier Cumulative Incidence Curve for Time to First Exacerbation (Severe Asthma Trial 2)



IV = intravenous, SC = subcutaneous.

Trial 1 data were explored to determine criteria that could identify patients likely to benefit from treatment with Nucala®. The exploratory analysis suggested that baseline blood eosinophil count of ≥150 cells/mcL was a potential predictor of treatment benefit. Exploratory analysis of Trial 2 data also suggested that baseline blood eosinophil count (obtained within 6 weeks of initiation of dosing) of ≥150 cells/mcL was a potential predictor of efficacy and showed a trend of greater exacerbation benefit with increasing blood eosinophil count. In Trial 2, patients enrolled solely on the basis of the historical blood eosinophil count of ≥300 cells/mcL in the previous 12 months, but who had a baseline blood eosinophil count.

The Asthma Control Questionnaire-5 (ACQ-5) was assessed in Trials 1 and 2, and the St. George's Respiratory Questionnaire (SGRQ) was assessed in Trial 2. In Trial 1, the ACQ-5 responder rate (defined as a decrease in score of 0.5 or more as threshold) for the 75-mg IV mepolizumab arm was 47% compared with 50% for placebo with an

odds ratio (OR) of 1.1 (95% CI: 0.7, 1.7). In Trial 2, the ACQ-5 responder rate for the treatment arm for Nucala® 100 mg was 57% compared with 45% for placebo with an OR of 1.8 (95% CI: 1.2, 2.8). In Trial 2, the SGRQ responder rate (defined as a decrease in score of 4 or more as threshold) for the treatment arm for Nucala® 100 mg was 71% compared with 55% for placebo with an OR of 2.1 (95% CI: 1.3, 3.2).

Oral Corticosteroid Reduction

Trial 3 evaluated the effect of Nucala® 100 mg on reducing the use of maintenance OCS. Efficacy was assessed using an endpoint of the percent reduction of OCS dose during Weeks 20 to 24 compared with baseline dose, while maintaining asthma control. Patients were classified according to their change in OCS use during the trial with the following categories: 90% to 100% decrease, 75% to <90% to decrease, 50% to <75% decrease, >0% to <50% decrease, and no improvement (i.e., no change or any increase or lack of asthma control or withdrawal of treatment). Compared with placebo, patients receiving Nucala® 100 mg achieved greater reductions in daily maintenance OCS dose, while maintaining asthma control. Sixteen (23%) patients in the group receiving Nucala® 100 mg versus 7 (11%) in the placebo group had a 90% to 100% reduction in their OCS dose. Twenty-five (36%) patients in the group receiving Nucala® 100 mg versus 37 (56%) in the placebo group were classified as having no improvement for OCS dose. Additionally, 54% of patients receiving Nucala® 100 mg achieved at least a 50% reduction in the daily prednisone dose compared with 33% of patients receiving placebo (95% CI for difference: 4%, 37%). An exploratory analysis was also performed on the subgroup of 29 patients in Trial 3 who had an average baseline and screening blood eosinophil count.

Lung Function

Change from baseline in mean forced expiratory volume in 1 second (FEV1) was measured in all 3 trials. Compared with placebo, Nucala® 100 mg did not provide consistent improvements in mean change from baseline in FEV1.

Table 2: Change from Baseline in FEV_1 (mL) in Severe Asthma Trials

Table 3. Change from Baseline in FEV1 (mL) in Severe Asthma Trials

Trial	Difference from Placebo in Mean Change from Baseline FEV1 (mL) (95% CI)		
	Week 12	Week 24	Weeks 32/52
1[a]	10 (-87, 108)	5 (-98, 108)	61 (-39, 161)[b]
2[c]	52 (-30, 134)	76 (-6, 159)	98 (11, 184)[d]
3[c]	56 (-91, 203)	114 (-42, 271)	NA

FEV1 = Forced Expiratory Volume in 1 Second, CI = Confidence Interval.

[a]Dose = 75 mg intravenous.

[b]Forced expiratory volume in 1 second (FEV1) at Week 52.

[c]Dose = 100 mg subcutaneous.

[d]FEV1 at Week 32

The effect of mepolizumab on lung function was also studied in a 12-week placebo-controlled trial enrolling patients with asthma on a moderate dose of ICS with evidence of symptoms and lung function impairment. Enrollment was not dependent on a history of exacerbations or a pre-specified eosinophil count. Change from baseline in FEV1 at Week 12 was numerically lower in the mepolizumab treatment groups than the placebo group.

Chronic Rhinosinusitis with Nasal Polyps: A total of 407 adult patients with CRSwNP were evaluated in a randomized, double-blind, placebo-controlled, multicenter, 52-week trial (NCT03085797). Patients received Nucala® 100 mg or placebo administered subcutaneously once every 4 weeks while continuing nasal corticosteroid therapy. Patients must have received background nasal corticosteroid for ≥8 weeks pre-screening. Patients had

recurrent and symptomatic CRSwNP and had at least 1 surgery for the removal of nasal polyps within the previous 10 years. Patients were required to have nasal obstruction symptoms with a visual analog scale (VAS) score of >5 out of a maximum score of 10. Patients were also required to have an endoscopic bilateral nasal polyp score (NPS) of ≥5 out of 8 with NPS ≥2 in each nasal cavity. Patients reported nasal obstruction VAS scores daily by placing a single mark on a continuous line labeled from 0 (none) to 100 (as bad as you can imagine). The distance along the line was converted to a 0-to-10-point scale for scoring. For NPS, polyps on each side of the nose were graded on a categorical scale (0 = no polyps, 1 = small polyps in the middle meatus not reaching below the inferior border of the middle concha, 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 concha, 4 = large polyps causing almost complete congestion/obstruction of the inferior meatus) for a total score of 0 to 8. Sinus CT scans were not performed at baseline nor during treatment to evaluate for sinus opacification.

The co-primary endpoints were change from baseline to Week 52 in total endoscopic NPS (0 to 8 scale) as graded by independent blinded assessors and change from baseline in nasal obstruction VAS score (0 to 10 scale) during Weeks 49 to 52. The key secondary endpoint was the time to 25 first nasal surgery (nasal polypectomy) up to Week 52 in this trial. Other secondary endpoints were change from baseline in loss of smell VAS score during Weeks 49 to 52, and proportion of patients requiring systemic steroids for nasal polyps up to Week 52. All VAS scores were collected daily by the patients and reported on a 0 to 10 scale (0 = none, 10 = as bad as you can imagine).

The demographics and baseline characteristics of patients in this trial are provided in Table 4.

Table 4. Demographics and Baseline Characteristics in CRSwNP

	N = 407
Mean age, years	49
Female, n (%)	143 (35)
White, n (%)	379 (93)
Mean CRSwNP duration in years (SD)	11.4 (8.4)
Patients with ≥1 surgery in past 10 years (%)	407 (100)
Patients with ≥3 surgeries in past 10 years (%)	124 (30)
OCS use (≥1 course) in past 12 months, n (%)	197 (48)
Mean bilateral endoscopic NPSa, (SD), range 0-8	5.5 (1.29)
Mean nasal obstruction VAS score, (SD), range 0-10	9.0 (0.83)
Geometric mean blood eosinophil cells/mcL (95% CI)	390 (360, 420)
Asthma, n (%)	289 (71)
AERD, n (%)	108 (27)

CRSwNP = Chronic Rhinosinusitis with Nasal Polyps, SD = standard deviation, OCS = Oral corticosteroid, NPS = nasal polyp score, VAS = visual analog scale, AERD = Aspirinexacerbated respiratory disease.

[a]As graded by independent blinded assessors

Endoscopic Nasal Polyp Score and Nasal Obstruction Visual Analog Scale Scores

Patients who received Nucala® 100 mg had a statistically significant improvement (decrease) in bilateral NPS at Week 52 and nasal obstruction VAS score from Weeks 49 to 52 at the end of the 52 week treatment period (Table 5).

Table 5. Analyses of Endpoints in CRSwNP

Scores[a] (range)	Placebo n = 201		Nucala® 100 mg n = 206		Mean Difference vs. Placebo (95% CI)
	Baseline Mean (SD)	Mean Change[b] (SE)	Baseline Mean (SD)	Mean Change[b] (SE)	

NPS (0-8)	5.6 (1.41)	0.06 (0.14)	5.4 (1.17)	-0.87 (0.14)	-0.93 (-1.31, -0.55)
Nasal obstruction (0-10)	9.02 (0.83)	-2.54 (0.25)	8.92 (0.83)	-4.40 (0.25)	-1.86 (-2.53, -1.19)

CRSwNP = Chronic Rhinosinusitis with Nasal Polyps, SD = standard deviation, SE = standard error, CI = Confidence Interval, NPS = Nasal polyp score at Week 52.

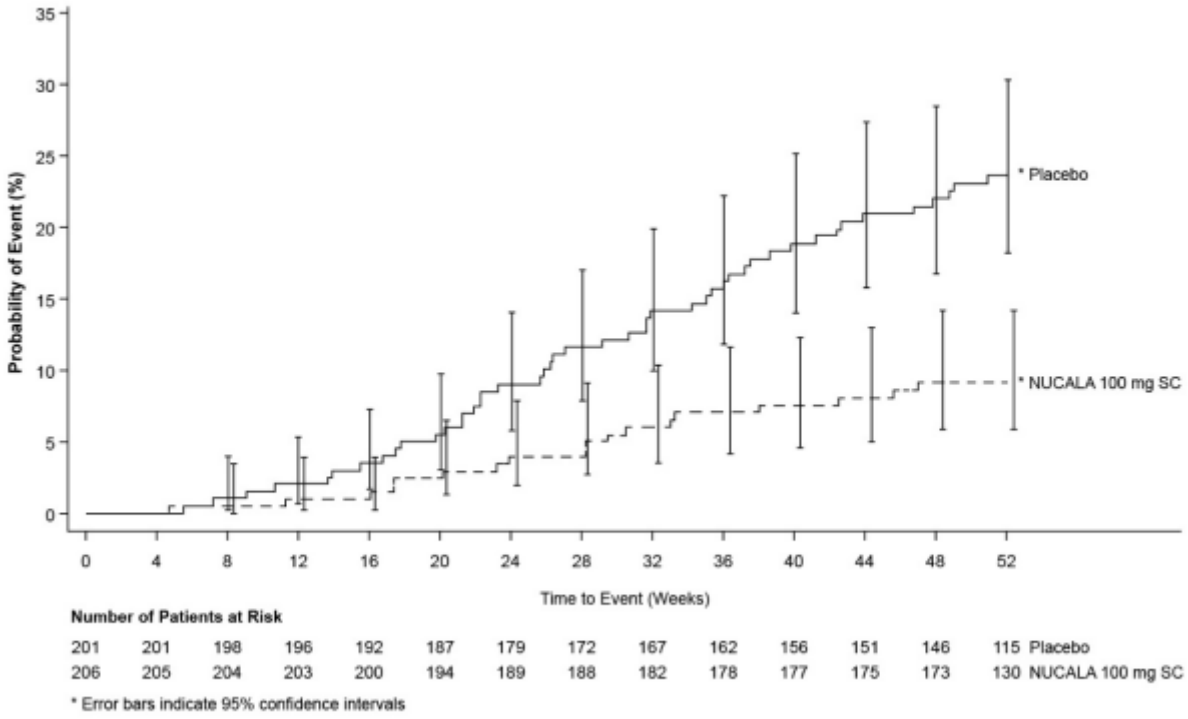
[a] Patients with nasal surgery were assigned worst possible score for the period after nasal surgery. Missing data were imputed based on available off-treatment data across treatment arms. Imputations were made stepwise by visit and conditioned on data from previous visits with the same covariates used in the analysis model.

[b] Least square means from analysis using mixed model repeated measures with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count, visit, interaction terms for visit by baseline and visit by treatment.

Nasal Polypectomy

The key secondary endpoint was the time to first nasal surgery (nasal polypectomy) up to Week 52. The proportion of patients who had surgery was significantly reduced by 57% (hazard ratio: 0.43, 95% CI: 0.25, 0.76) in the group treated with Nucala® 100 mg compared with the placebo group (Figure 2). By Week 52, 18 (9%) patients who received Nucala®100 mg had surgery compared with 46 (23%) patients in the placebo group.

Figure 2. Kaplan-Meier Plot of Time to First Nasal Surgery in CRSwNP



CRSwNP = Chronic Rhinosinusitis with Nasal Polyps, SC = subcutaneous.

Additional CRSwNP Symptoms Scores

For patients who received Nucala® 100 mg, statistically significant improvement was observed in loss of smell compared to placebo and improvements were also observed in the individual VAS symptom scores compared with patients in the placebo group in the 4-weeks prior to the end of the 52-week treatment period (Table 6).

Table 6: Additional Visual Analog Scale Symptom Scores Assessed at Weeks 49-52					
VAS Scores[a] (range)	Placebo n = 201		Nucala® 100 mg n = 206		Mean Difference vs. Placebo (95% CI)
	Baseline Mean (SD)	Mean Change[b] (SE)	Baseline Mean (SD)	Mean Change[b] (SE)	
Loss of smell (0-10)	9.68 (0.60)	-1.46 (0.24)	9.63 (0.83)	-2.92 (0.24)	-1.46 (-2.11, -0.81)
Nasal discharge[c] (0-10)	8.78 (1.25)	-2.49 (0.26)	8.78 (1.07)	-4.38 (0.25)	-1.89 (-2.58, -1.20)
Mucus in the throat[c] (0-10)	8.58 (1.63)	-2.37 (0.26)	8.51 (1.61)	-4.07 (0.26)	-1.70 (-2.41, -0.99)
Facial pain[c] (0-10)	7.77 (2.72)	-2.04 (0.28)	7.76 (2.51)	-3.73 (0.27)	-1.69 (-2.43, -0.95)

VAS = Visual Analog Scale; SD = Standard Deviation; SE = Standard Error; CI = Confidence Interval

[a] Patients with nasal surgery were assigned the worst possible score for the period after nasal surgery. Missing data was imputed based on available off-treatment data across treatment arms. Imputations were made stepwise by visit and conditioned on data from previous visits with the same covariates used in the analysis model.

[b] Least square means from an analysis using mixed model repeated measures with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count visit, interaction terms for visit by baseline and visit by treatment.

[c] This endpoint was not prespecified in the analysis plan to adjust for multiplicity.

Corticosteroid Reduction: Treatment with Nucala® 100 mg significantly reduced the need for systemic steroids for nasal polyps vs. placebo up to Week 52 (odds ratio: 0.58, 95% CI: 0.36, 0.92). In patients who received Nucala® 100 mg, 52 (25%) required ≥1 course of systemic steroids compared with 74 (37%) in the placebo group throughout the 52-week treatment period.

Results in Patients with Co-morbid Asthma: In 289 (71%) patients with co-morbid asthma, pre-specified analyses showed improvements in the co-primary endpoints consistent with those seen in the overall population in the patients who received Nucala® 100 mg compared with placebo. Additionally, based on a post-hoc analysis in these patients, there was a greater response from baseline at Week 52 in asthma control as measured by the Asthma Control Questionnaire (ACQ-5) for Nucala® 100 mg compared with placebo (57% of the Nucala® patients met the responder threshold reduction of ≥0.5, compared to 35% in the placebo group, with an odds ratio of 2.42 (95% CI 1.43, 4.11)).

Eosinophilic Granulomatosis with Polyangiitis: A total of 136 adult patients with EGPA were evaluated in a randomized, placebo-controlled, multicenter, 52-week trial (NCT02020889). Patients received 300 mg of Nucala® or placebo administered subcutaneously once every 4 weeks while continuing their stable OCS therapy. Starting at Week 4, OCS was tapered during the treatment period at the discretion of the investigator. Efficacy was assessed in this trial using co-endpoints of the total accrued duration of remission over the 52-week treatment period, defined as Birmingham Vasculitis Activity Score (BVAS) = 0 (no active vasculitis) plus prednisolone or prednisone dose less than or equal to 4 mg/day, and the proportion of patients in remission at both Week 36 and Week 48 of treatment. The BVAS is a clinician-completed tool to assess clinically active vasculitis that would likely require treatment, after exclusion of other causes.

The demographics and baseline characteristics of patients in this trial are provided in Table 7

Table 7. Demographics and Baseline Characteristics in EGPA	
	N = 136
Mean age, years	48.5

Female, n (%)	80 (59)
White, n (%)	125 (92)
Duration of EGPA, years, mean (SD)	5.5 (4.63)
History of >1 confirmed relapse in past 2 years, n (%)	100 (74)
Refractory disease, n (%)	74 (54)
Recurrence of EGPA symptoms, n (%)	68 (50)
Failed induction treatment, n (%)	6 (4)
Baseline oral corticosteroida daily dose, mg, median (range)	12 (7.5-50)
Receiving immunosuppressive therapy,b n (%)	72 (53)

EGPA = Eosinophilic Granulomatosis with Polyangiitis, SD = standard deviation.

[a] Prednisone or prednisolone equivalent.

[b] e.g., Azathioprine, methotrexate, mycophenolic acid.

Remission

Patients receiving 300 mg of Nucala® achieved a significantly greater accrued time in remission compared with placebo. A significantly higher proportion of patients receiving 300 mg of Nucala® achieved remission at both Week 36 and Week 48 compared with placebo (Table 10). Results of the components of remission are also shown in Table 10. In addition, significantly more patients receiving 300 mg of Nucala® achieved remission within the first 24 weeks and remained in remission for the remainder of the 52-week trial treatment period compared with placebo (19% for 300 mg of Nucala® versus 1% for placebo; OR 19.7; 95% CI: 2.3, 167.9).

Table 8. Remission and Components of Remission in EGPA

Table 8. Remission and Components of Remission in EGPA

	Remission (OCS ≤4 mg/day + BVAS = 0)		OCS ≤4 mg/day		BVAS = 0	
	Placebo n = 68	Nucala® 300 mg n = 68	Placebo n = 68	Nucala® 300 mg n = 68	Placebo n = 68	Nucala® 300 mg n = 68
Accrued duration over 52 weeks, n (%)						
0	55 (81)	32 (47)	46 (68)	27 (40)	6 (9)	3 (4)
>0 to < 12 weeks	8 (12)	8 (12)	12 (18)	5 (7)	15 (22)	13 (19)
12 to < 24 weeks	3 (4)	9 (13)	6 (9)	12 (18)	11 (16)	5 (7)
24 to < 36 weeks	0	10 (15)	2 (3)	10 (15)	17 (25)	2 (3)
≥36 weeks	2 (3)	9 (13)	2 (3)	14 (21)	19 (28)	45 (66)
Odds ratio (Nucala®/placebo) [a] (95% CI)		5.9 (2.7, 13.0)		5.1 (2.5, 10.4)		3.7 (1.8, 7.6)
Proportion of patients at both Weeks 36 and 48						
Patients, n (%)	2 (3)	22 (32)	7 (10)	28 (41)	23 (34)	34 (50)
Odds ratio (Nucala®/placebo) [a] (95% CI)		16.7 (3.6, 77.6)		6.6 (2.6, 17.1)		1.9 (0.9, 4.2)

EGPA = Eosinophilic Granulomatosis with Polyangiitis, OCS = Oral Corticosteroid, BVAS = Birmingham Vasculitis Activity Score, CI = confidence interval.

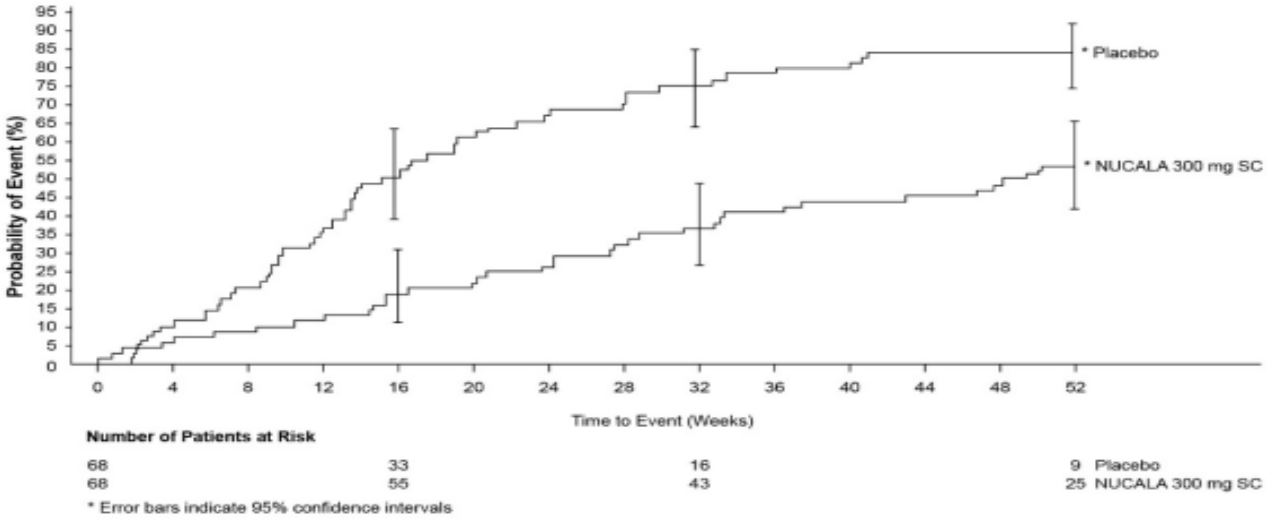
[a]An odds ratio >1 favors Nucala®

Additionally, a statistically significant benefit for these endpoints was demonstrated using remission defined as BVAS = 0 plus prednisolone/prednisone ≤7.5 mg/day.

Relapse

The time to first relapse (defined as worsening related to vasculitis, asthma, or sino-nasal symptoms requiring an increase in dose of corticosteroids or immunosuppressive therapy or hospitalization) was significantly longer for patients receiving 300 mg of Nucala® compared with placebo with a hazard ratio of 0.32 (95% CI: 0.21, 0.5) (Figure 3). Additionally, patients receiving 300 mg of Nucala® had a reduction in rate of relapse compared with patients receiving placebo (rate ratio 0.50; 95% CI: 0.36, 0.70 for 300 mg of Nucala® compared with placebo). The incidence and number of relapse types (vasculitis, asthma, sino-nasal) were numerically lower with Nucala® compared with placebo.

Figure 3. Kaplan-Meier Plot of Time to First Relapse in EGPA



EGPA = Eosinophilic Granulomatosis with Polyangiitis, SC = subcutaneous.

Corticosteroid Reduction

Patients receiving 300 mg of Nucala® had a significantly greater reduction in average daily OCS dose compared with patients receiving placebo during Weeks 48 to 52 (Table 9).

Table 9. Average Daily Oral Corticosteroid Dose during Weeks 48 to 52 in EGPA

	Number (%) of patients	
	Placebo n = 68	Nucala® 300 mg n = 68
0	2 (3)	12 (18)
>0 to ≤4.0 mg	3 (4)	18 (26)
>4.0 to ≤7.5 mg	18 (26)	10 (15)
>7.5 mg	45 (66)	28 (41)
Comparison: Nucala® /placebo[a]		
Odds ratio[b]		0.2
95% CI		0.09, 0.41

EGPA = Eosinophilic Granulomatosis with Polyangiitis, CI = confidence interval.

[a]Analyzed using a proportional odds model with covariates of treatment group, baseline oral corticosteroid daily dose, baseline Birmingham Vasculitis Activity Score, and region.

[b]An odds ratio <1 favors Nucala®.

Asthma Control Questionnaire-6 (ACQ-6)

The ACQ-6, a 6-item questionnaire completed by the patient, was developed to measure the adequacy of asthma control and change in asthma control. The on-treatment ACQ-6 responder rate during Weeks 48 to 52 (defined as a decrease in score of 0.5 or more compared with baseline) was 22% for 300 mg of Nucala® and 16% for placebo (OR 1.56; 95% CI: 0.63, 3.88 for 300 mg of Nucala® compared with placebo).

Hypereosinophilic Syndrome: A total of 108 adult and adolescent patients aged 12 years and older with HES for at least 6 months were evaluated in a randomized, double-blind, placebo-controlled, multicenter, 32-week trial (NCT02836496). Patients with non-hematologic secondary HES (e.g., drug hypersensitivity, parasitic helminth infection, HIV infection, non-hematologic malignancy) or FIP1L1-PDGFRα kinase-positive HES were excluded from the trial. Patients received 300 mg of Nucala® or placebo subcutaneously once every 4 weeks while continuing their stable HES therapy. Patients entering the trial had experienced at least 2 HES flares within the past 12 months and a blood eosinophil count of 1,000 cells/mcL or higher during screening. Historical HES flares for the trial entry criteria were defined as HES-related worsening of clinical symptoms or blood eosinophil counts requiring an escalation in therapy. Patients must have been on stable HES therapy for the 4 weeks prior to randomization. HES therapy could include chronic or episodic oral corticosteroids (OCS), immunosuppressive, or cytotoxic therapy. The efficacy of Nucala® in HES was established based upon the proportion of patients who experienced a HES flare during the 32-week treatment period. A HES flare was defined as worsening of clinical signs and symptoms of HES or increasing eosinophils (on at least 2 occasions), resulting in the need to increase OCS or increase/add cytotoxic or immunosuppressive HES therapy. The demographics and baseline characteristics of patients in this trial are provided in Table 10.

Table 10. Demographics and Baseline Characteristics in HES

	N = 108
Mean age, years	46.0 (15.78)
Female, n (%)	57 (53)
White, n (%)	100 (93)
Mean duration of HES, years	5.55

HES = Hypereosinophilic Syndrome, SD = standard deviation.

Flares

The trial compared the proportion of patients who experienced a HES flare or withdrew from the trial in the Nucala® and placebo treatment groups (Table 11). Over the 32-week treatment 33 period, the incidence of HES flare over the treatment period was 56% for the placebo group and 28% for the group treated with Nucala® (50% reduction).

Table 11. Overview of HES Flares

	Number (%) of patients	
	Placebo n = 54	Nucala® 300 mg n = 54
Patients with ≥1 HES flare or who withdrew from trial	30 (56)	15 (28)
Patients with ≥1 HES flare	28 (52)	14 (26)
Patients with no HES flare who withdrew from trial	2 (4)	1 (2)
Comparison: Nucala®/placebo		

CMH P value		0.002
Odds ratiob		0.28
95% CI		(0.12, 0.64)

HES = Hypereosinophilic Syndrome, CMH = Cochran-Mantel-Haenszel, CI = confidence interval.

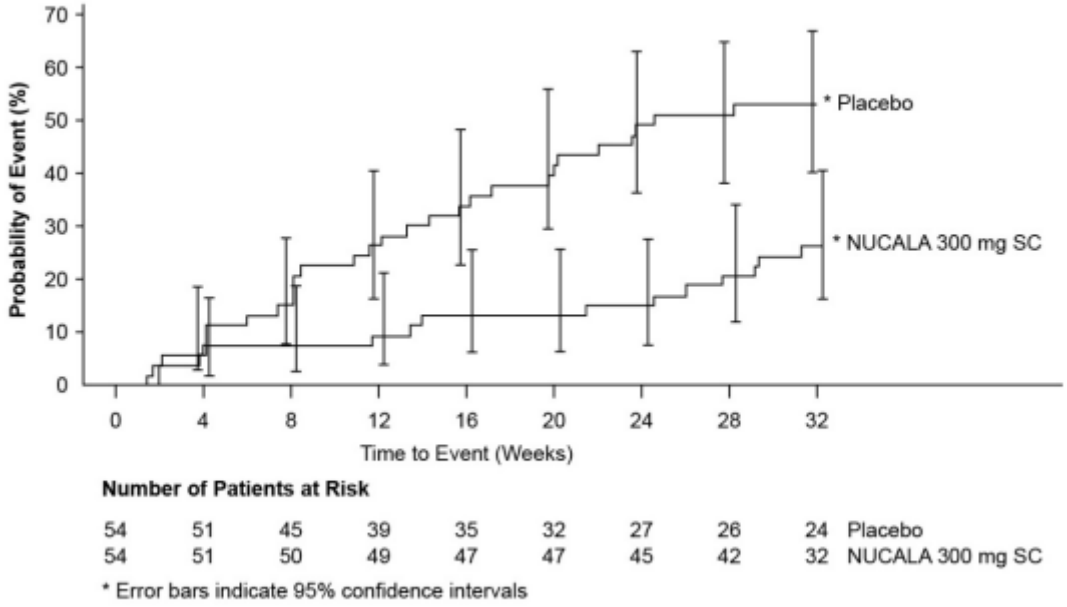
[a]Analysis compared the number of patients who experienced ≥1 HES flare and/or withdrew from the trial prematurely.

[b]An odds ratio <1 favors Nucala®.

Time to First Flare

Difference was observed between Nucala® and placebo arms in the time to first HES flare (Figure 4). The risk of first HES flare over the treatment period was 66 % lower for patients treated with Nucala® compared with placebo (Hazard Ratio: 0.34; 95 % CI 0.18, 0.67, P = 0.002).

Figure 4. Kaplan-Meier Curve for Time to First HES Flare



HES = Hypereosinophilic Syndrome, SC = subcutaneous.

Rate of Flares

Patients who received Nucala® experienced significantly fewer HES flares during the 32-week treatment period compared with the placebo group (Table 12). Treatment with Nucala® resulted in a statistically significant 66% reduction in the annualized rate of HES flares compared with placebo.

Table 12. Frequency of Flares

	Number (%) of patients	
	Placebo n = 54	Nucala® 300 mg n = 54
0	26 (48)	40 (74)
1	15 (28)	11 (20

2	7 (13)	3 (6)
3	5 (9)	0
4	1 (2)	0
≥5	0	0
Comparison: Nucala® /placebo	1.46	
Wilcoxon P value (unadjusted/adjusted) [a]		0.002/0.02
Rate/year		0.5
Rate ratio[b]		0.34
95% CI		(0.19, 0.63)

CI = confidence interval.

[a]Adjusted P values based on pre-specified hierarchy of endpoints.

[b]A rate ratio <1 favors Nucala®.

Brief Fatigue Inventory

Brief Fatigue Inventory (BFI) Item 3 asks patients to record their worst level of weariness/tiredness severity during the past 24 hours (scale: 0 = no fatigue to 10 = as bad as you can imagine). At baseline, median BFI Item 3 scores were similar between treatment groups (4.46 for Nucala® 300 mg and 4.69 for placebo). At Week 32, BFI Item 3 scores improved with Nucala® compared with placebo (P = 0.036). The median change from baseline score for BFI Item 3 at Week 32 was -0.66 in the group treated with Nucala® and 0.32 in the placebo group.