Prospective, Single-Arm, Longitudinal Study of Biomarkers in Real-World Patients with Severe Asthma

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Original Article

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What is already known about this topic? Serum periostin, blood eosinophil count, serum IgE, and fractional exhaled nitric oxide (FeNO) are biomarkers associated with type 2 inflammation phenotypes of severe asthma that may identify patients at risk of asthma exacerbations.

What does this article add to our knowledge? The primary analysis found no clinically meaningful differences in the exacerbation rates between patients with high versus low periostin levels. *Post hoc* analyses suggested that high blood eosinophils, high FeNO, or both might predict asthma exacerbations.

How does this study impact current management guidelines? The results demonstrated that the clinical utility of periostin as an asthma biomarker is unclear. However, high blood eosinophils or high FeNO may identify patients at risk of an exacerbation. As a secondary objective, the study found that central and local measurements of type 2 biomarker levels were generally in agreement.

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Abbreviations used
CI- Confidence interval
FeNO- Fractional exhaled nitric oxide
FEV_1- Forced expiratory volume in 1 second
GINA- Global Initiative for Asthma
IL-4Rα- Interleukin 4 receptor α
IL-5- Interleukin 5
IL-5R- Interleukin 5 receptor
IQR- Interquartile range
LABA- Long-acting β_2-agonist
LTRA- Leukotriene receptor antagonist
LAMA- Long-acting muscarinic antagonist
MiniAQLQ- Mini Asthma Quality of Life Questionnaire
OCS- Oral corticosteroid

BACKGROUND: ARIETTA was a prospective, single-arm, noninterventional, multicenter study in patients with severe asthma.
OBJECTIVE: To examine the predictive and prognostic abilities of type 2 biomarkers for severe asthma outcomes.
METHODS: Adult patients with severe asthma receiving daily inhaled corticosteroids (fluticasone propionate ≥500 μg or equivalent) and ≥1 second controller medication were enrolled. Biomarker, clinical, and safety data were collected over 52 weeks. The primary endpoint was the asthma exacerbation rate over 52 weeks in serum periostin-high (≥50 ng/mL at baseline) versus periostin-low subgroups (<50 ng/mL). Correlations between biomarker levels (periostin, blood eosinophils, IgE, and fractional exhaled nitric oxide [FeNO]) and between central and local laboratory measurements (blood eosinophils and IgE) were assessed. The study was terminated before planned enrollment was completed.
RESULTS: Of 465 patients, 66.5% were female, 13.3% were receiving oral corticosteroids, 42.4% had ≥1 exacerbation in the previous year, 52.0% were periostin-high, and 87.5% had type 2 inflammation (blood eosinophils ≥150 cells/μL and/or FeNO ≥25 ppb and/or positive skin allergen test). Biomarker levels correlated poorly with each other. Central and local laboratory blood eosinophil and IgE measurements generally agreed. No difference was observed in exacerbation rates over 52 weeks between periostin-high and periostin-low patients (rate ratio, 0.93; 95% confidence interval, 0.67-1.28; $P = .642$). Results suggested higher exacerbation rates in patients with blood eosinophils ≥300 cells/μL and FeNO ≥25 ppb.
CONCLUSIONS: No prognostic value for serum periostin related to exacerbations was detected. Higher blood eosinophils combined with increased FeNO were potentially associated with increased exacerbation rates. **(J Allergy Clin Immunol Pract 2020;8:2630-9)**

Key words: *Periostin; biomarker; blood eosinophil; exacerbation; severe asthma*

Growing recognition of the heterogeneity of asthma and the availability of targeted treatment options make the role of biomarkers in treatment selection, monitoring, and risk prediction increasingly important for patients with severe asthma.[1-5] Biomarkers associated with type 2 inflammation phenotypes (type 2-high) of severe asthma include elevated serum periostin, blood eosinophil count, serum IgE, and fractional exhaled nitric oxide (FeNO).[6-8] The 2019 Global Initiative for Asthma (GINA) recommends considering targeted biologics in patients with type 2-high severe asthma, characterized by ≥1 of the following: blood eosinophils ≥150 cells/μL, FeNO ≥20 ppb, and/or perennial allergy.[9]

Biologics that target IgE, interleukin (IL)-5, IL-5 receptor (IL-5R), and IL-4 receptor α (IL-4Rα) can improve asthma control and reduce oral corticosteroid (OCS) dependence in patients with type 2-high severe asthma when phenotypes are correctly identified.[1,2,10-14] GINA recommends anti-IgE therapy (omalizumab) for patients with severe allergic asthma (positive skin allergen test and/or positive perennial allergen–specific IgE test) and anti-IL-5 (mepolizumab or reslizumab) or anti-IL-5R (benralizumab) therapy for patients with severe eosinophilic asthma (employing thresholds of blood eosinophils that depend on local payer eligibility criteria for the intended treatment regimen).[9] Although type 2 biomarkers are increasingly used to select patients for targeted therapy, the relationships among them and their prognostic value in the real-world clinical setting are not well known.

ARIETTA was a 52-week, prospective, single-arm, longitudinal, international, noninterventional, multicenter study in adult patients with severe asthma.[15] The study was designed to capture data on biomarker phenotypes and treatment patterns in real-world patients with severe asthma and to examine the role of key type 2 biomarkers in routine clinical practice.[15] The primary objective of the study was to compare the asthma exacerbation rate over 52 weeks in patients with high (≥50 ng/mL) versus low (<50 ng/mL) serum levels of periostin at baseline. After inconsistent efficacy results with a pertinent molecule in development, the decision was made by the study sponsor to halt active recruitment for ARIETTA.[16] The findings from ARIETTA based on available data for patients enrolled before the study's early termination are presented here.

METHODS

Study design

The ARIETTA study (NCT02537691) was designed to enroll approximately 1200 patients with severe asthma. The study protocol was amended to reflect the halt of active recruitment.

Patients were treated according to their physicians' standard practices and discretion in this real-life, noninterventional study. Data were collected during 3 visits (baseline, week 26, and week 52) and 2 phone interviews (week 13 and week 39) (Figure 1).[15] All medications that patients received during the study were reported. Blood eosinophil count and serum IgE level were measured at both central and local laboratories to assess potential variability. Patients and treating physicians were not made actively aware of centrally or locally measured eosinophil and/or IgE concentrations. Periostin was measured as a batch after conclusion of the study, using the Elecsys Periostin Immunoassay (Roche Diagnostics, Penzberg, Germany).

The study was conducted with informed written consent from participating patients and with the approval of the ethics committee/institutional review board for each participating study site (Online Repository at www.jaci-inpractice.org).

Patients

Adult patients (aged ≥18 years) with severe asthma (GINA steps 4-5) receiving daily inhaled corticosteroids (fluticasone propionate

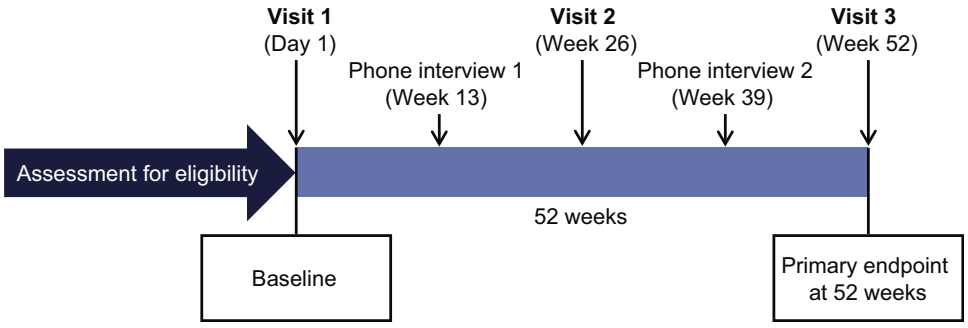

FIGURE 1. Study design of ARIETTA.

TABLE I. Baseline demographics and clinical characteristics

Characteristic	Periostin high* (n = 242)	Periostin low* (n = 223)	Total population (N = 465)
Age (y), median (range)	57 (17-83)	52 (20-79)	54 (17-83)
Female, n (%)	175 (72.3)	134 (60.1)	309 (66.5)
White, n (%)	203 (91.0)	212 (87.6)	415 (89.2)
Body mass index (kg/m^2), mean (SD)	30.0 (11.6)	30.6 (7.5)	30.3 (9.8)
History of smoking, n (%)			
Yes	39 (16.1)	46 (20.6)	85 (18.3)
No	203 (83.9)	177 (79.4)	380 (81.7)
Time since asthma diagnosis (y), median (range)	18.7 (0-76)	19.9 (0-63)	19.4 (0-76)
Exacerbations in previous year, n (%)			
0	136 (56.2)	132 (59.2)	268 (57.6)
1	53 (21.9)	48 (21.5)	101 (21.7)
2	20 (8.3)	27 (12.1)	47 (10.1)
3	16 (6.6)	4 (1.8)	20 (4.3)
≥4	17 (7.0)	12 (5.4)	29 (6.2)
MiniAQLQ overall score, mean (SD)	4.5 (1.2)	4.5 (1.2)	4.5 (1.2)
Prebronchodilator FEV_1, mean (SD)			
Actual, L	1.8 (0.6)	1.9 (0.7)	1.9 (0.6)
Predicted, L	2.8 (0.7)	3.0 (0.8)	2.9 (0.8)
Predicted, %	64.7 (13.2)	63.8 (12.5)	64.3 (12.9)
GINA classification, n (%)			
Step 4	144 (59.5)	140 (62.8)	284 (61.1)
Step 4+	55 (22.7)	54 (24.2)	109 (23.4)
Step 5	31 (12.8)	22 (9.9)	53 (11.4)
Missing or not classifiable	12 (5.0)	7 (3.1)	19 (4.1)
Prior asthma medications, n (%)†			
LABA	238 (98.3)	218 (97.8)	456 (98.1)
LTRA	80 (33.1)	75 (33.6)	155 (33.3)
LAMA	46 (19.0)	44 (19.7)	90 (19.4)
OCS	37 (15.3)	25 (11.2)	62 (13.3)
Theophylline	14 (5.8)	16 (7.2)	30 (6.5)

FEV_1, Forced expiratory volume in 1 second; *GINA*, Global Initiative for Asthma; *LABA*, long-acting β_2-agonist; *LAMA*, long-acting muscarinic antagonist; *LTRA*, leukotriene receptor antagonist; *MiniAQLQ*, Mini Asthma Quality of Life Questionnaire; *OCS*, oral corticosteroid; *SD*, standard deviation.
*Periostin-high and periostin-low subgroups comprised patients with baseline periostin ≥50 and <50 ng/mL, respectively.
†A patient may have had >1 type of prior asthma medication.

≥500 μg or equivalent) and ≥1 second controller medication (long-acting β_2-agonist [LABA], leukotriene receptor antagonist [LTRA], long-acting muscarinic antagonist [LAMA], theophylline) or OCS therapy were enrolled.[17] Notably, patients with an acute asthma exacerbation ≤6 weeks before baseline or who received biologics ≤6 months before baseline were excluded. (See the Methods section for additional description of inclusion and exclusion criteria in this article's Online Repository at www.jaci-inpractice.org.)

Outcomes and statistical analyses

At the planned enrollment (approximately 1200 patients, estimating 30% dropouts), the study would have had ≥80% power for

TABLE II. Biomarker levels at baseline

Biomarker	Periostin high* (n = 242)	Periostin low* (n = 223)	Total population (N = 465)
Serum periostin level (ng/mL), median (IQR)†	61.7 (55.6-70.5)	43.0 (38.0-46.3)	50.9 (43.3-62.1)
Blood eosinophil count (cells/μL), median (IQR)			
Local laboratory	300 (150-511)	200 (100-300)	230 (130-402)
Central laboratory	280 (170-450)	180 (125-280)	230 (140-360)
Blood eosinophil count subgroups (cells/μL), n (%)†			
<150	51 (21.1)	69 (30.9)	120 (25.8)
≥150	184 (76.0)	147 (65.9)	331 (71.2)
<300	126 (52.1)	166 (74.4)	292 (62.8)
≥300 (high)	109 (45.0)	50 (22.4)	159 (34.2)
Serum IgE level (IU/mL), median (IQR)			
Local laboratory	143.5 (49.0-418.0)	79.0 (29.0-243.0)	110.0 (37.0-310.0)
Central laboratory	140.1 (41.7-438.2)	74.4 (24.7-242.0)	100.7 (33.0-324.2)
Serum IgE level subgroups, n (%)†‡			
IgE low	129 (53.3)	147 (65.9)	276 (59.4)
IgE high	112 (46.3)	75 (33.6)	187 (40.2)
FeNO (ppb), median (IQR)§	24.0 (15.0-46.0)	19.0 (12.0-30.0)	21.0 (13.0-36.0)
FeNO subgroups (ppb), n (%)			
<25 (normal)	122 (50.4)	144 (64.6)	266 (57.2)
≥25	119 (49.2)	78 (35.0)	197 (42.4)
<50	186 (76.9)	204 (91.5)	390 (83.9)
≥50 (high)	55 (22.7)	18 (8.1)	73 (15.7)
Allergen skin test, n (%)			
Positive	127 (52.5)	110 (49.3)	237 (51.0)
Negative	23 (9.5)	26 (11.7)	49 (10.5)
Inconclusive	2 (0.8)	0	2 (0.4)
Unknown result	6 (2.7)	9 (3.7)	15 (3.2)
Test not performed	57 (23.6)	59 (26.5)	116 (24.9)
Unknown	24 (9.9)	22 (9.9)	46 (9.9)

FeNO, Fractional exhaled nitric oxide; *IQR*, interquartile range; *ppb*, parts per billion.
*Periostin-high and periostin-low subgroups comprised patients with baseline periostin ≥50 and <50 ng/mL, respectively.
†Results from a central laboratory. Patients with missing baseline data were not included.
‡IgE low and high were defined as baseline serum IgE levels <150 and ≥150 IU/mL, respectively.
§Results from a local laboratory. Patients with missing baseline data were not included.

detecting a ≥35% increase in asthma exacerbation rates between periostin-high and periostin-low subgroups at 2-sided 5% alpha, assuming a mean exacerbation rate of 0.637 exacerbations/patient/year in the periostin-low subgroup. Because of early termination, the reduced analysis population yielded 56% power to detect the prespecified difference. The analyses were conducted 52 weeks after the last patient was enrolled and included all eligible patients with available baseline biomarker data (whether or not they had completed 52 weeks). All analyses were descriptive.

The primary endpoint was the asthma exacerbation rate over 52 weeks in serum periostin-high (≥50 ng/mL at baseline) versus serum periostin-low subgroups (<50 ng/mL). The unadjusted exacerbation rate was estimated as the total number of exacerbations observed over 52 weeks divided by the total patient-weeks. Exacerbation rates were reported per patient-year. No imputation was performed for early discontinuations. The relative difference in exacerbation rates between periostin subgroups (expressed as the ratio of exponential group regression coefficients) and associated 2-sided 95% confidence interval (CI) was estimated using univariate and multivariable (adjusted for age [years], sex [male/female], smoking history [previous/never], body mass index [kg/m^2], and baseline % predicted forced expiratory volume in 1 second [FEV_1]) scaled Poisson regression models with overdispersion. Poisson regression models with zero inflation were used as sensitivity analyses due to low observed exacerbation rates.

Secondary outcomes included percentage of patients with treatment failure, percentage of patients with changes in standard-of-care treatments considered clinically meaningful by the investigator, time to first asthma exacerbation, time to treatment failure, change from baseline in prebronchodilator FEV_1, change from baseline in FeNO levels, change from baseline in patient-reported quality-of-life measures, and safety over 52 weeks in periostin-high versus periostin-low subgroups. Treatment failure was defined as the first occurrence of asthma exacerbation or clinically meaningful change in standard-of-care asthma treatment as reported by the investigator. Asthma biomarker levels measured over 52 weeks included serum periostin (central laboratory), blood eosinophil count (central and local), serum IgE (central and local), and FeNO (local). At each visit, correlations between biomarker levels (pairwise) and between central and local measurements (blood eosinophils and IgE only) were

TABLE III. Asthma outcomes at week 52 by periostin level

Outcome	Periostin high* (n = 242)	Periostin low* (n = 223)
Patients with ≥1 asthma exacerbation, n (%)	56 (23.1)	61 (27.4)
No. of asthma exacerbations, n (%)		
0	184 (76.0)	157 (70.4)
1	29 (12.0)	36 (16.1)
2	13 (5.4)	11 (4.9)
3	7 (2.9)	8 (3.6)
4	1 (0.4)	2 (0.9)
5	4 (1.7)	3 (1.3)
6	1 (0.4)	0
7	0	0
8	1 (0.4)	1 (0.4)
No postbaseline data available	2 (0.8)	5 (2.2)
Rate of asthma exacerbations per patient-year†	0.47	0.51
Primary analysis: rate ratio (95% CI)‡	0.926 (0.669-1.282)	
	$P = .642$	
Time to first asthma exacerbation (mo), median (range)	3.2 (0-13)	5.4 (0-13)
Patients with clinically meaningful change in standard-of-care asthma treatment during study (as reported by the investigator), n (%)	24 (9.9)	26 (11.7)
Change from baseline in FEV_1 (% predicted), median (range)		
Week 26	5.0 (−20 to 56)	5.0 (−32 to 71)
Week 52	6.4 (−26 to 52)	5.0 (−32 to 63)
Change from baseline in FeNO (ppb), median (range)		
Week 26	1.0 (−130 to 203)	0.0 (−56 to 54)
Week 52	−0.5 (−106 to 119)	0.0 (−61 to 174)

CI, Confidence interval; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *ppb*, parts per billion.
*Periostin-high and periostin-low subgroups comprised patients with baseline periostin ≥50 and <50 ng/mL, respectively.
†Unadjusted exacerbation rates were estimated as the total number of exacerbations observed over 52 weeks divided by the total patient-weeks. Annualized rates were calculated as 0.0091 events/week × 52 weeks in the periostin-high subgroup and 0.0099 events/week × 52 weeks in the periostin-low subgroup.
‡Rate ratio of periostin-high vs periostin-low was estimated using scaled Poisson regression based on scaled Poisson regression models with overdispersion.

assessed. *Post hoc* exploratory analyses assessed the number of patients with type 2-high (blood eosinophils ≥150 cells/μL and/or FeNO ≥25 ppb and/or positive skin allergen test) and type 2-low asthma (blood eosinophils <150 cells/μL, FeNO <25 ppb, and negative skin allergen test); evaluated associations between exacerbation rates and biomarkers using clinically relevant thresholds of blood eosinophils (≥300 vs <300 cells/μL) and FeNO (≥25 vs <25 ppb); and examined the stability of biomarker levels across study visits. (See the Methods section for additional description of outcomes and statistical analyses in this article's Online Repository at www.jaci-inpractice.org.)

RESULTS

Baseline characteristics

Study enrollment was halted after 483 patients were enrolled (sponsor's decision based on efficacy results with a pertinent molecule in development).[16] Of these, 18 patients were excluded: 11 did not meet eligibility criteria and 7 were missing baseline periostin measurements. Of enrolled patients, 436 (93.8%) completed the 52-week study follow-up.

A total of 465 patients from 84 sites in 13 countries were analyzed (Table I; Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Patients had a median (range) age of 54 (17-83) years; 66.5% were female. The median (range) time since asthma diagnosis was 19.4 (0-76) years. Overall, 42.4% of patients had ≥1 asthma exacerbation in the previous year. LABA was the most frequent second controller (98.1%), followed by LTRA (33.3%) and LAMA (19.4%); 13.3% of patients were receiving OCS daily.

At baseline, 242 patients (52.0%) were periostin-high and 223 patients (48.0%) were periostin-low (Table II). Baseline median serum periostin, blood eosinophil count, serum IgE, and FeNO were 50.9 ng/mL, 230 cells/μL (central), 100.7 IU/mL (central), and 21.0 ppb, respectively (Table II, Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). In the periostin-low and periostin-high subgroups, skin allergen tests were performed in 63.7% and 66.5% of patients, respectively (Table II). A total of 237 patients (51.0%) had positive skin allergen results (periostin-high, 52.5%; periostin-low, 49.3%).

Primary endpoint

Asthma exacerbation rates from baseline to week 52 were similar in periostin-high versus periostin-low patients (0.47 vs 0.51 exacerbations/year, respectively) (Table III). The periostin-high versus periostin-low rate ratio estimate of 0.93 (95% CI, 0.67-1.28) suggested no difference in the asthma exacerbation rate between periostin subgroups ($P = .642$). Because of early termination and reduced sample size (with low exacerbation rates), the study was unable to fully address its primary prespecified objective. Findings from multivariable (scaled and with zero inflation) Poisson regression models, adjusted for demographics and baseline characteristics, were consistent with the primary analysis.

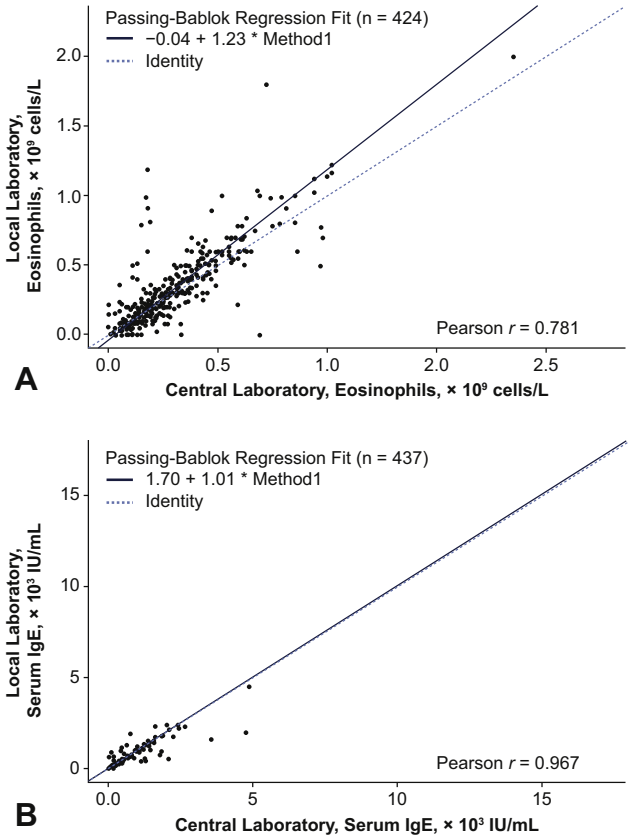

FIGURE 2. Correlation between local and central laboratory measurements at baseline for (**A**) blood eosinophil counts and (**B**) serum IgE levels.

Secondary outcomes

The median time to the first asthma exacerbation was 3.2 and 5.4 months in periostin-high and periostin-low patients, respectively (Table III). In the periostin-high and periostin-low subgroups, ≥1 treatment failure was reported in 60 (24.8%) and 64 patients (28.7%), respectively. The median (interquartile range [IQR]) time to treatment failure was 3.0 (1.5-5.4) and 5.5 (2.2-8.8) months in periostin-high and periostin-low patients, respectively. No clinically meaningful differences were observed between periostin subgroups in the change from baseline to week 52 in prebronchodilator FEV_1 or FeNO levels (Table III).

Quality-of-life measures were generally similar between periostin-high and periostin-low subgroups. The median (IQR) change from baseline in Mini Asthma Quality of Life Questionnaire (MiniAQLQ) scores at 52 weeks was 0.27 (−0.33 to 0.87) and 0.33 (−0.13 to 0.73) in periostin-high and periostin-low patients, respectively. Generalized linear mixed model results suggested no difference in MiniAQLQ scores between periostin-high and periostin-low subgroups over time. Similar trends of no difference between periostin subgroups were observed in Asthma Control Test and Asthma Control Questionnaire 7 scores.

The correlation between central and local laboratory biomarker measurements was generally high for blood eosinophils ($r_s = 0.781$) and serum IgE ($r = 0.967$) at baseline, with local blood eosinophil counts somewhat higher than central laboratory measurements (Figure 2); similar correlations were observed at later visits (Figure E2, available in this article's Online Repository at www.jaci-inpractice.org). Across visits, the correlation between periostin and blood eosinophils, serum IgE, and FeNO was moderate to low ($r_s \leq 0.35$) (Table IV). Levels of serum periostin, blood eosinophils, FeNO, and serum IgE were generally stable across visits (Figure 3; Table E2, available in this article's Online Repository at www.jaci-inpractice.org).

TABLE IV. Correlation between serum periostin level, blood eosinophil count, serum IgE level, and FeNO biomarkers by visit

	Spearman correlation coefficient			
Visit	Serum periostin	Blood eosinophil count	Serum IgE	FeNO
Baseline				
Serum periostin	1.00			
Blood eosinophil count	0.35	1.00		
Serum IgE	0.17	0.23	1.00	
FeNO	0.25	0.47	0.22	1.00
Week 26				
Serum periostin	1.00			
Blood eosinophil count	0.32	1.00		
Serum IgE	0.15	0.25	1.00	
FeNO	0.23	0.38	0.23	1.00
Week 52				
Serum periostin	1.00			
Blood eosinophil count	0.27	1.00		
Serum IgE	−0.11	0.73	1.00	
FeNO	0.21	0.38	0.65	1.00

FeNO, Fractional exhaled nitric oxide.

Post hoc exploratory analyses

In 449 patients with available baseline blood eosinophil and FeNO measurements, 393 patients (87.5%) met the criteria for type 2-high asthma and 12 (2.7%) met the criteria for type 2-low asthma; 44 patients (9.8%) had missing or unknown skin allergen test results (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). Excluding skin allergen tests, 354 (78.8%) and 95 patients (21.2%) met the blood eosinophil count and FeNO criteria defining type 2-high and type 2-low asthma, respectively.

When examined separately, the asthma exacerbation rate ratio estimates suggested a trend of higher exacerbation rates in patients with higher (≥300 cells/μL) versus lower blood eosinophils (<300 cells/μL) and with higher (≥25 ppb) versus lower FeNO (<25 ppb) (Figure 4, *A*; Table E4, available in this article's Online Repository at www.jaci-inpractice.org). When examined in combination, rate ratio estimates suggested increased exacerbation rates in patients with either higher blood eosinophils, higher FeNO, or both compared with patients who had lower blood eosinophils and lower FeNO (Figure 4, *B*; Table E4, available in this article's Online Repository at www.jaci-inpractice.org).

Safety

Similar percentages of patients reported adverse events in the periostin-high and periostin-low subgroups (30.6% vs 31.8%; Table E5, available in this article's Online Repository at www.jaci-inpractice.org). Few patients (3.7%) experienced serious adverse events. One patient in the periostin-high subgroup died

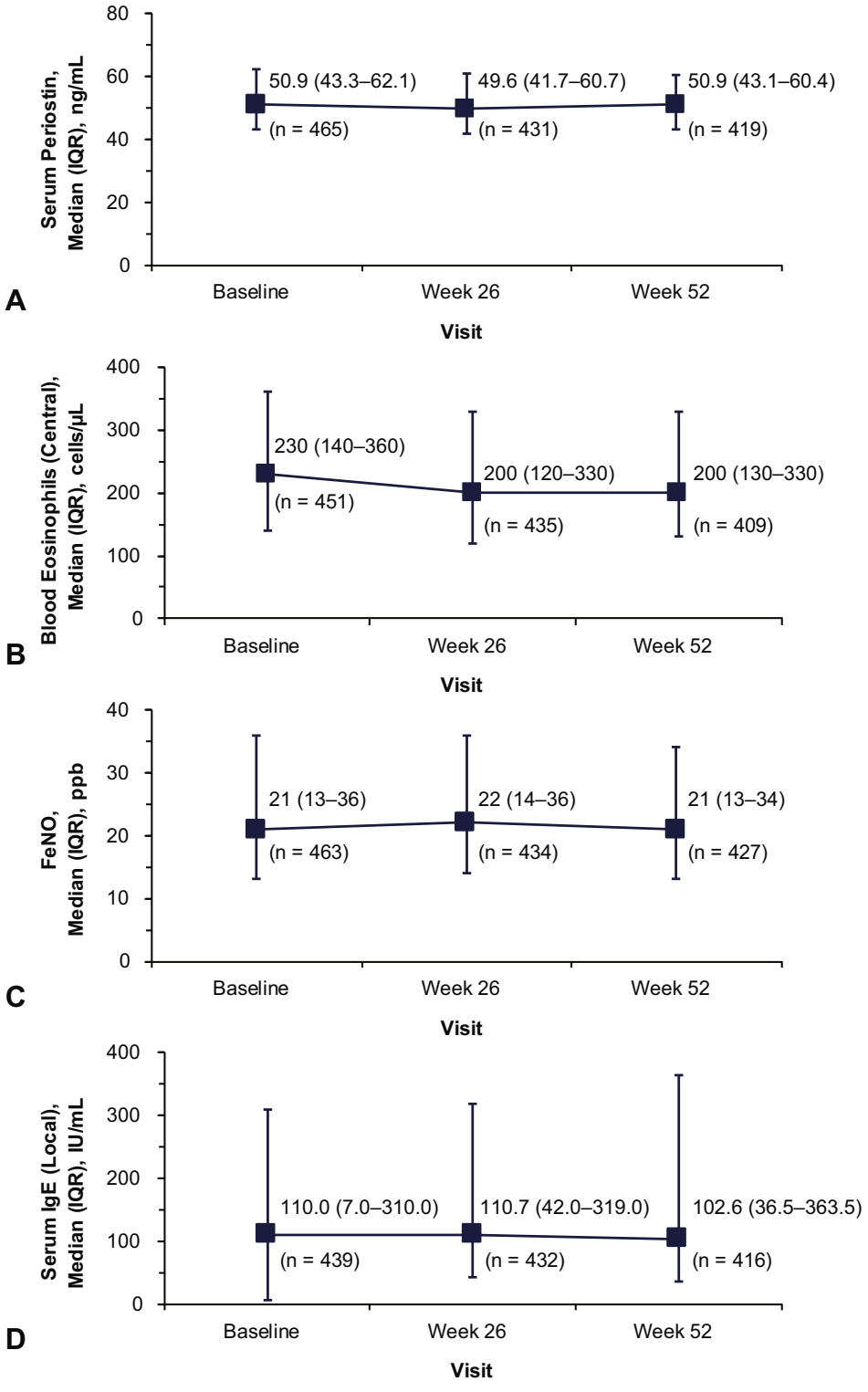

FIGURE 3. Biomarkers over time: (**A**) serum periostin level, (**B**) blood eosinophil count (central laboratory measurements), (**C**) FeNO, and (**D**) serum IgE level (local laboratory measurements) across visits. *FeNO,* Fractional exhaled nitric oxide; *IQR,* interquartile range; *ppb,* parts per billion.

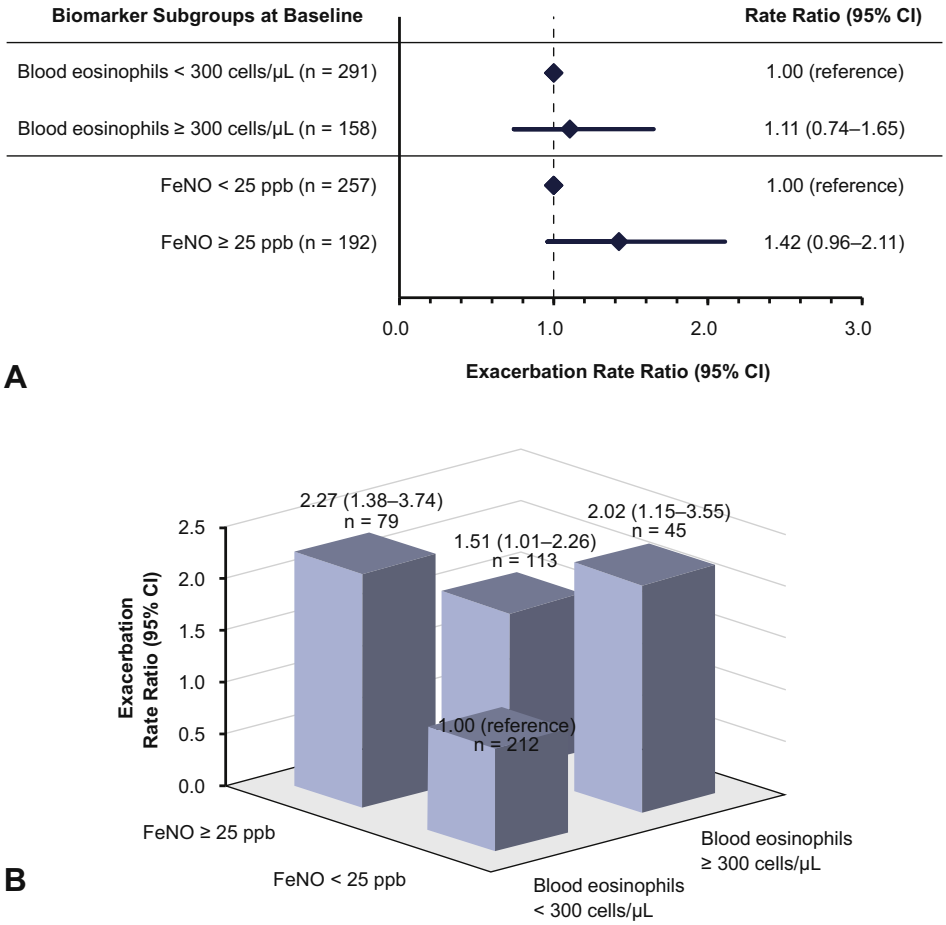

FIGURE 4. The relative difference in asthma exacerbation rates (rate ratios) between blood eosinophil count and FeNO subgroups as assessed (**A**) separately or (**B**) in combination. Rate ratios were based on the multivariable Poisson regression model with zero inflation, adjusted for age (years), smoking history (previous/never), sex (male/female), BMI (kg/m^2), and baseline % predicted FEV_1. *BMI*, Body mass index; *CI*, confidence interval; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *ppb*, parts per billion.

during the study (male, aged 59 years, due to pulmonary embolism).

DISCUSSION

The ARIETTA study aimed to evaluate the predictive and prognostic ability of the type 2 biomarkers for clinical outcomes of severe asthma. Our primary endpoint was to evaluate the ability of periostin to identify exacerbation risk in adult patients with severe asthma observed in routine clinical practice over 52 weeks. Based on the available data, no meaningful differences were found in the asthma exacerbation rate in patients with high (≥50 ng/mL) versus low (<50 ng/mL) serum concentrations of periostin at baseline; however, the observed exacerbation rates were low (0.47 vs 0.51 events/year). Similarly, no meaningful differences were found in change from baseline in FEV_1 or FeNO over 52 weeks between the periostin-high and periostin-low subgroups. Correlations between periostin concentrations and other type 2 biomarkers were generally moderate to low.

At the time of the study design, the research objective was to evaluate the prognostic value of periostin.[15] Together with evidence from randomized controlled trials, our findings demonstrate that the clinical utility of periostin as an asthma biomarker is unclear. In phase II and IIb trials, evidence suggested that high serum periostin levels were predictive of a treatment benefit for a pipeline anti-IL-13 antibody.[18,19] Although phase III trial results demonstrated that periostin levels did not consistently identify patients who would benefit from this molecule, high periostin levels were associated with elevated risk of exacerbations in the placebo group.[16] However, data from ARIETTA did not support a prognostic role for serum periostin with respect to asthma exacerbations. Because the observed number of exacerbations during the study was numerically lower than what was reported in the study population during the preceding year, the ability to detect differences between periostin subgroups was limited.

Our study sheds light on several aspects of the utility of biomarkers in future studies in the real-world setting. First, correlations between central and local laboratory measurements of blood eosinophils and serum IgE and changes in biomarker levels over time demonstrated a high level of agreement observed between central and local laboratory measurements of blood eosinophils and IgE,

supporting the use of biomarker measurements from local hospitals as well as specialty centers. Second, type 2 biomarker levels were generally stable across visits, suggesting that multiple type 2 biomarker assessments over time may not be necessary. In addition, enrolling patients prone to exacerbations may improve the ability to measure differences between groups.

Of patients enrolled in ARIETTA, 87.5% met this study's and the GINA definition for type 2-high asthma, although this may be an underestimate because skin allergen test results were unavailable for many patients.[9] Many of these patients would also qualify for available biologics under the current GINA strategy.[9] For patients sensitized to a perennial allergen with serum IgE 30-1500 IU/mL, anti-IgE therapy could be considered.[2,9] Patients with exacerbations within $\leq$1 year (42.4% of patients in ARIETTA) who have clinically relevant higher blood eosinophil counts ($\geq$300 cells/μL; 34.2% in ARIETTA) qualify for anti-IL-5 or anti-IL-5R therapies, and for those with higher blood eosinophil counts ($\geq$300 cells/μL; 34.2% in ARIETTA) or FeNO $\geq$25 ppb (42.4% in ARIETTA), anti-IL-4Rα therapy could also be considered.[10-13]

This study is important in several ways. The ARIETTA study population comprises a cohort of well-characterized patients with severe asthma who received standard-of-care treatment with accompanying measurement of type 2 biomarker levels. The study population represents one of the last large observational cohorts of patients with severe asthma before the adoption of biologics to treat severe asthma. These data represent the most complete characterization of key type 2 biomarkers to date in patients with severe asthma, including a comparison of local versus central laboratory measurements for blood eosinophils and serum IgE and an assessment of type 2 biomarker stability over time. Importantly, these findings highlight the potential predictive and prognostic ability of blood eosinophil count and FeNO, particularly when used in combination, and provide estimates of the percentage of patients with severe asthma who would qualify for biologic therapies. Notably, *post hoc* analyses of the placebo arms of phase III randomized controlled trials of biologics in patients with type 2 asthma have also found associations between increased risk of exacerbation and higher blood eosinophil counts or higher FeNO levels.[12-14,16,20]

Our study has several limitations including its early termination that prohibited full evaluation of the prespecified primary and secondary study objectives, and its observational single-arm design has the potential for selection bias. Furthermore, all analyses should be regarded as descriptive, and conclusions should be viewed as hypothesis generating. The high heterogeneity in the study population at baseline and low overall asthma exacerbation rates during the study may make it difficult to draw meaningful conclusions in the overall population. Associations between asthma exacerbation rates and blood eosinophils and FeNO biomarkers were exploratory and *post hoc*.

In conclusion, there were no clinically meaningful differences in the exacerbation rates between periostin-high and periostin-low subpopulations of patients with severe asthma in this study. Key type 2 biomarkers, including periostin, blood eosinophils, serum IgE, and FeNO, were not highly correlated with each other. Finally, *post hoc* exploratory analyses suggested a potential clinically relevant predictive and prognostic ability for asthma exacerbation of blood eosinophils and FeNO when used in combination.

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Baseline demographics and clinical characteristics of the ARIETTA study population were presented at the European Respiratory Society International Congress in September 2017. The design of the ARIETTA study was previously published (Buhl R, et al. Respir Med 2016; 115:7-12).

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx. 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: 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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ONLINE REPOSITORY

METHODS

Inclusion and exclusion criteria

Key inclusion criteria were:

- Aged ≥18 years
- Diagnosis of severe asthma (Global Initiative for Asthma steps 4-5)[17]
- Prebronchodilator forced expiratory volume in 1 second (FEV_1) of 30% to 85%
- Documented bronchodilator response (≥12% improvement in FEV_1 after bronchodilator use) or provocative concentration of methacholine needed to produce a 20% fall in FEV_1 (PC_{20}) <8 mg
- Receiving daily inhaled corticosteroid (fluticasone propionate ≥500 μg or equivalent)
- Receiving ≥1 second controller medication (long-acting β_2-agonist, leukotriene receptor antagonist, long-acting muscarinic antagonist, theophylline) or oral corticosteroid therapy for ≥3 months before baseline.

Key exclusion criteria were:

- Acute asthma exacerbation ≤6 weeks before baseline
- Current or former smoking (≥10 pack-years)
- Treatment with a biologic therapy ≤6 months before baseline
- Prior bronchial thermoplasty.

Additional outcomes and analysis

Patient-reported quality-of-life measures assessed at week 52 in periostin-high versus periostin-low subgroups included change from baseline in quality of life as measured by Mini Asthma Quality of Life Questionnaire scores, change from baseline in quality of life as measured by Asthma Control Test scores, and change from baseline in quality of life as measured by Asthma Control Questionnaire 7 scores. A generalized linear mixed-effects model (adjusted for age, sex, smoking history, body mass index [BMI], and baseline % predicted FEV_1) explored differences over time between periostin subgroups in patient-reported outcomes.

To assess correlations between each pair of biomarkers measured at the same visit (eg, periostin vs blood eosinophils at baseline, periostin vs blood eosinophils at week 26), Spearman and Pearson correlation coefficients were computed. To compare central and local laboratory measurements of blood eosinophil count and IgE level, Passing-Bablok regression was conducted.

In *post hoc* exploratory analyses, unadjusted exacerbation rates in biomarker subgroups, defined by clinically relevant thresholds for blood eosinophil count (≥300 vs <300 cells/μL) and fractional exhaled nitric oxide (FeNO) (≥25 vs <25 ppb), were estimated as the total number of exacerbations observed over 52 weeks divided by the total patient-weeks. Exacerbation rates were reported per patient-years. Relative differences in exacerbation rates between biomarker subgroups, defined by blood eosinophil count (≥300 vs <300 cells/μL) and FeNO (≥25 vs <25 ppb), either separately or combined, were estimated (as rate ratios and 2-sided 95% confidence interval) using multivariable Poisson regression models with zero inflation, adjusted for age, sex, smoking history, BMI, and baseline % predicted FEV_1. The stability of serum periostin, blood eosinophil count, serum IgE, and FeNO was examined across study visits using descriptive statistics.

List of Investigators and Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC) Approvals.

The protocol for the ARIETTA study was reviewed and approved by the appropriate IRB for each study site. The names of the investigators, the IRBs or IECs that reviewed and approved the protocol, and the approval dates are listed here, organized by country.

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Tilles SA—Sterling Institutional Review Board, 6300 Powers Ferry Road, Atlanta, GA 30039 (November 30, 2015)

Wexler P—Sterling Institutional Review Board, 6300 Powers Ferry Road, Atlanta, GA 30039 (September 25, 2015)

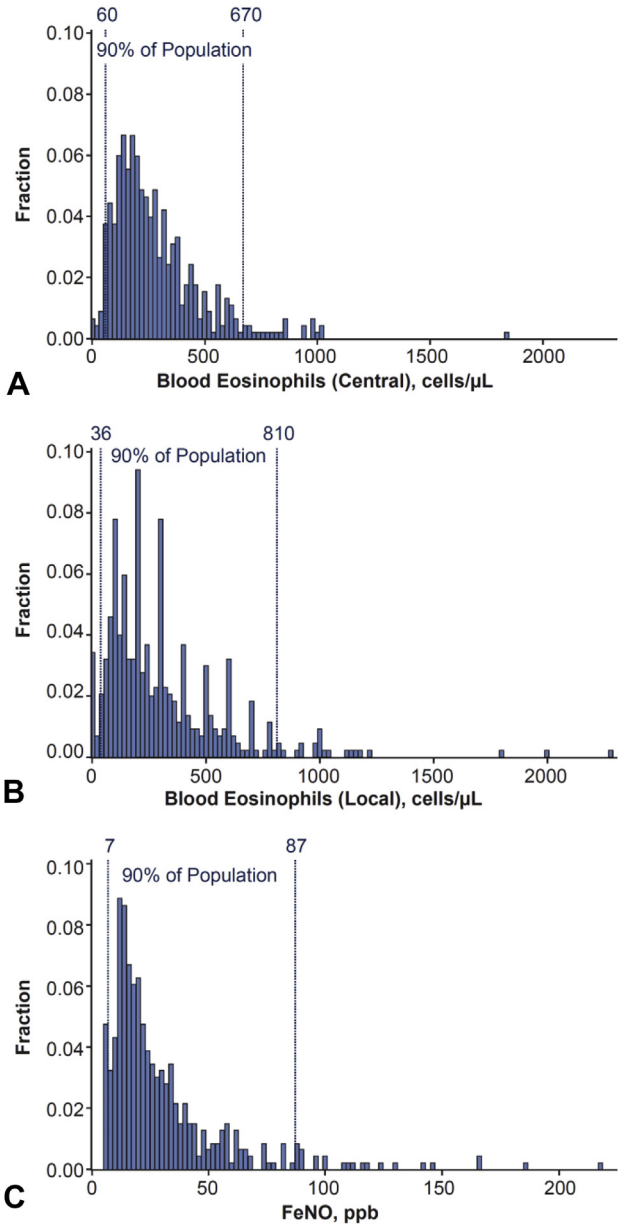

FIGURE E1. Histograms of baseline biomarker measurements: (**A**) blood eosinophil count by central laboratory measurements, (**B**) blood eosinophil count by local laboratory measurements, and (**C**) FeNO. *FeNO*, Fractional exhaled nitric oxide; *ppb*, parts per billion.

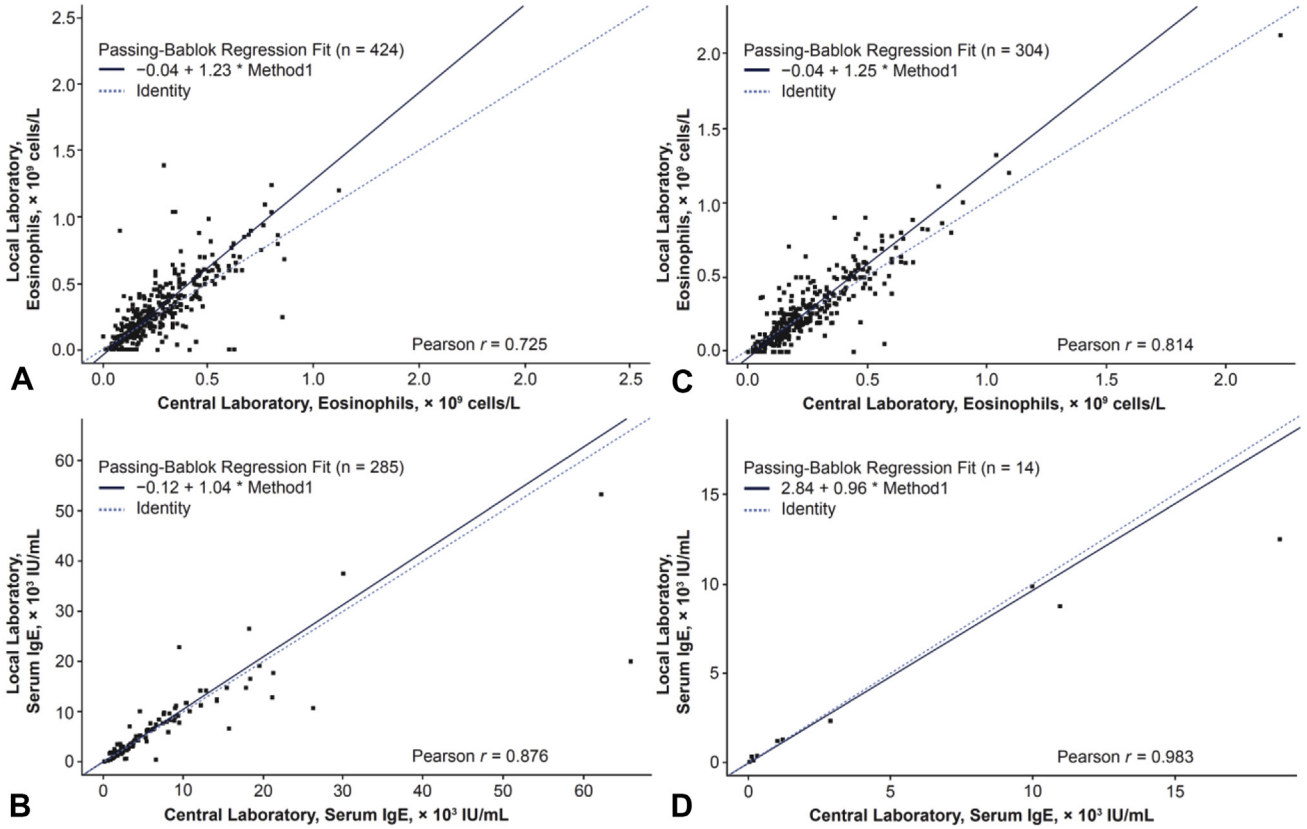

FIGURE E2. Correlation between local and central laboratory measurements at week 26 for (**A**) blood eosinophil count and (**B**) serum IgE and at week 52 for (**C**) blood eosinophil count and (**D**) serum IgE.

TABLE E1. Enrollment by country

Patients enrolled, n (%)	Periostin high* (n = 242)	Periostin low* (n = 223)	Total population (N = 465)
Belgium	17 (7.0)	14 (6.3)	31 (6.7)
Bulgaria	4 (1.7)	6 (2.7)	10 (2.2)
Canada	12 (5.0)	20 (9.0)	32 (6.9)
Denmark	9 (3.7)	2 (0.9)	11 (2.4)
Germany	4 (1.7)	8 (3.6)	12 (2.6)
Hungary	22 (9.1)	28 (12.6)	50 (10.8)
Italy	12 (5.0)	5 (2.2)	17 (3.7)
Latvia	13 (5.4)	15 (6.7)	28 (6.0)
The Netherlands	1 (0.4)	4 (1.8)	5 (1.1)
Russian Federation	51 (21.1)	31 (13.9)	82 (17.6)
Spain	9 (3.7)	9 (4.0)	18 (3.9)
United Kingdom	15 (6.2)	15 (6.7)	30 (6.5)
United States	73 (30.2)	66 (29.6)	139 (29.9)

*Periostin-high and periostin-low subgroups comprised patients with baseline periostin ≥50 and <50 ng/mL, respectively.

TABLE E2. Change from baseline in serum periostin, blood eosinophil count (central laboratory measurements), FeNO, and serum IgE (local laboratory measurements) at week 26 and week 52

Change from baseline, median (IQR)	Week 26	Week 52
Serum periostin (ng/mL)	−0.9 (−5.5 to 2.7) n = 431	−0.8 (−5.7 to 4.1) n = 419
Blood eosinophil count (central) (cells/μL)	−10 (−90 to 50) n = 424	−10 (−90 to 40) n = 400
FeNO (ppb)	0 (−6 to 8) n = 432	0 (−6 to 7) n = 426
Serum IgE (local) (IU/mL)	0.0 (−14.4 to 25.0) n = 413	0.0 (−19.8 to 31.0) n = 396

FeNO, Fractional exhaled nitric oxide; *IQR*, interquartile range; *ppb*, parts per billion.

TABLE E3. Biomarker phenotypes

	Patients with available blood eosinophil count and FeNO measurements at baseline (n = 449)	
Patients with phenotype, n (%)	Including skin allergen test results	Excluding skin allergen test results
Type 2-high	393 (87.5)	354 (78.8)
• Blood eosinophils ≥150 cells/μL **and/or**		
• FeNO ≥25 ppb **and/or**		
• Positive skin allergen test		
Type 2-low	12 (2.7)*	95 (21.2)
• Blood eosinophils <150 cells/μL **and**		
• FeNO <25 ppb **and**		
• Negative skin allergen test		

FeNO, Fractional exhaled nitric oxide; *ppb*, parts per billion.
*A total of 44 patients (9.8%) had blood eosinophils <150 cells/μL and FeNO <25 but either had unknown skin allergen test results (14 patients) or had not had the test performed (30 patients).

TABLE E4. Rate of asthma exacerbations per patient-year in subgroups defined by baseline blood eosinophil count and FeNO

Rate of asthma exacerbations per patient-year*	Blood eosinophils <300 cells/μL (n = 291)	Blood eosinophils ≥300 cells/μL (n = 158)	Total (n = 449)†
FeNO <25 ppb (n = 257)	0.35	0.57	0.39
FeNO ≥25 ppb (n = 192)	0.52	0.67	0.60
Total (n = 449)†	0.40	0.63	

FeNO, Fractional exhaled nitric oxide; *ppb*, parts per billion.
*Unadjusted exacerbation rates were estimated as the total number of exacerbations observed over 52 weeks divided by the total patient-weeks. Annualized rates were calculated as the number of events/week × 52 weeks.
†Patients with missing baseline blood eosinophil count or FeNO were excluded from this analysis.

TABLE E5. Overview of adverse events

Patients with ≥1 event, n (%)	Periostin high* (n = 242)	Periostin low* (n = 223)	Total population (N = 465)
Any AEs	74 (30.6)	71 (31.8)	145 (31.2)
Serious AEs	12 (5.0)	5 (2.2)	17 (3.7)
Other AEs of interest†	25 (10.3)	20 (9.0)	45 (9.7)
Study assessment-related AEs	6 (2.5)	13 (5.8)	19 (4.1)
AEs leading to discontinuation	1 (0.4)	0	1 (0.2)
Deaths	1 (0.4)	0	1 (0.2)

AE, Adverse event.
*Periostin-high and periostin-low subgroups comprised patients with baseline periostin ≥50 and <50 ng/mL, respectively.
†Other AEs of interest were defined as malignancies; respiratory infections, including acute bronchitis, allergic bronchitis, bronchiectasis, organizing pneumonia, pneumonia, and pleurisy; other infections, including parasitic infections (such as helminthic and protozoan); opportunistic infections and Listeria monocytogenes infections; newly diagnosed diabetes mellitus; cataracts; bone fractures; dental operations; anaphylaxis, anaphylactoid, and hypersensitivity events; and pregnancies.