Safety and Efficacy of Dexpramipexole in Eosinophilic Asthma (EXHALE): A randomized controlled trial

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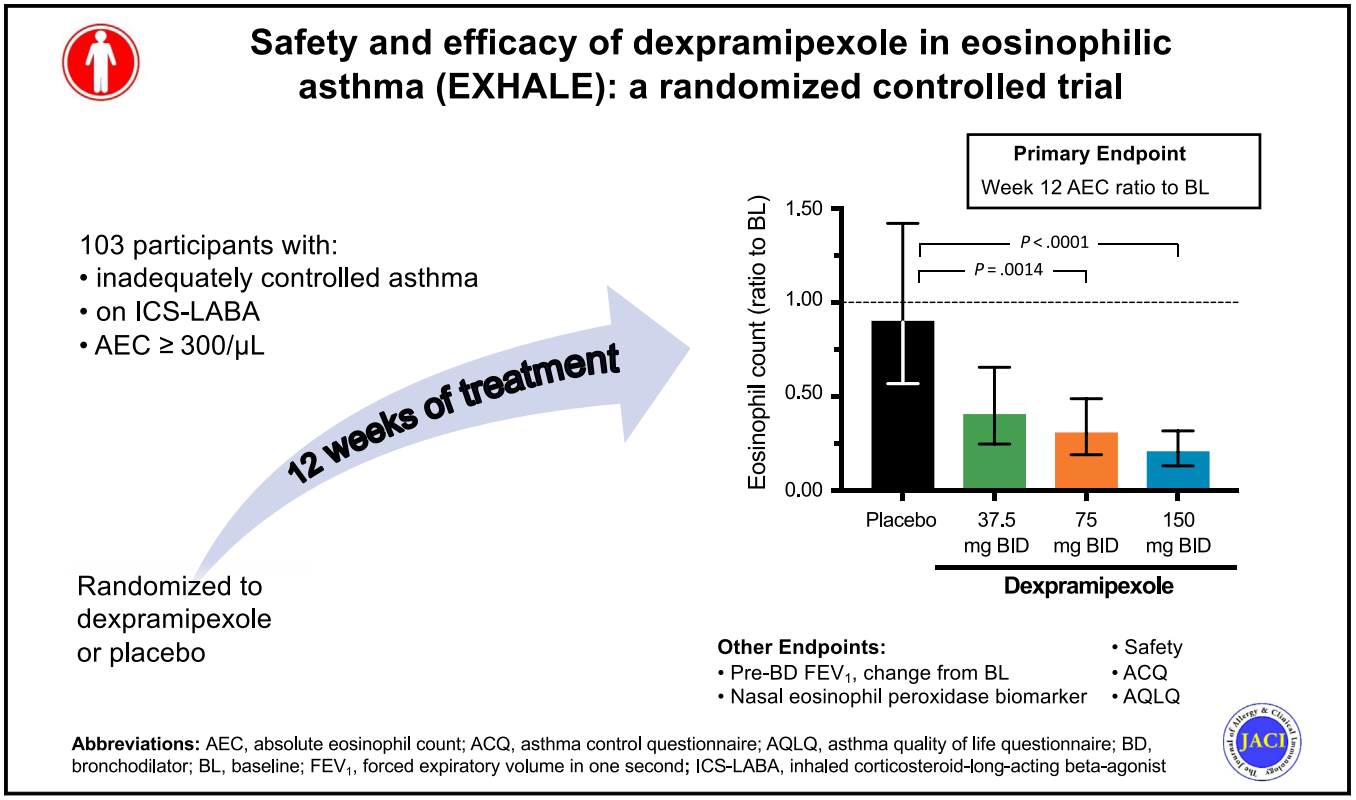
GRAPHICAL ABSTRACT



Background: There is a need for new and effective oral asthma therapies. Dexpramipexole, an oral eosinophil-lowering drug, has not previously been studied in asthma.

Objective: We sought to evaluate the safety and efficacy of dexpramipexole in lowering blood and airway eosinophilia in subjects with eosinophilic asthma.

Methods: We performed a randomized, double-blind, placebo-controlled proof-of-concept trial in adults with inadequately controlled moderate to severe asthma and blood absolute eosinophil count (AEC) greater than or equal to 300/μL. Subjects were randomly assigned (1:1:1:1) to dexpramipexole 37.5, 75, or 150 mg BID (twice-daily) or placebo. The primary

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end point was the relative change in AEC from baseline to week 12. Prebronchodilator FEV_1 week-12 change from baseline was a key secondary end point. Nasal eosinophil peroxidase was an exploratory end point.

Results: A total of 103 subjects were randomly assigned to dexpramipexole 37.5 mg BID (N = 22), 75 mg BID (N = 26), 150 mg BID (N = 28), or placebo (N = 27). Dexpramipexole significantly reduced placebo-corrected AEC week-12 ratio to baseline, in both the 150-mg BID (ratio, 0.23; 95% CI, 0.12-0.43; $P < .0001$) and the 75-mg BID (ratio, 0.34; 95% CI, 0.18-0.65; $P = .0014$) dose groups, corresponding to 77% and 66% reductions, respectively. Dexpramipexole reduced the exploratory end point of nasal eosinophil peroxidase week-12 ratio to baseline in the 150-mg BID (median, 0.11; $P = .020$) and the 75-mg BID (median, 0.17; $P = .021$) groups. Placebo-corrected FEV_1 increases were observed starting at week 4 (nonsignificant). Dexpramipexole displayed a favorable safety profile.

Conclusions: Dexpramipexole demonstrated effective eosinophil lowering and was well tolerated. Additional larger clinical trials are needed to understand the clinical efficacy of dexpramipexole in asthma. (J Allergy Clin Immunol 2023;■■■:■■■-■■■.)

Key words: *Clinical trial, phase 2, pulmonary function tests, eosinophil peroxidase*

Abbreviations used

ACQ: Asthma Control Questionnaire
AE: Adverse event
AEC: Absolute eosinophil count
ALS: Amyotrophic lateral sclerosis
ANC: Absolute neutrophil count
AQLQ: Asthma Quality of Life Questionnaire
BD: Bronchodilator
BID: Twice daily
COVID-19: Coronavirus disease 2019
CRSwNP: Chronic rhinosinusitis with nasal polyps
EPX: Eosinophil peroxidase
FENO: Fractional exhaled nitric oxide
GINA: Global Initiative for Asthma
GM: Geometric mean
HES: Hypereosinophilic syndrome
ICS: Inhaled corticosteroid
IL-5R: IL-5 receptor
LSM: Least-squares mean
MMRM: Mixed-effect model for repeated measures

Asthma is a chronic inflammatory respiratory disease affecting 300 million to 400 million people around the world.[1] In developed countries, approximately 40% of individuals with asthma are considered to have moderate to severe asthma as per the Global Initiative for Asthma (GINA) step classification.[2,3] In the past decade, biologic therapies targeting type 2 inflammation have been a major advance in the treatment of severe asthma. Broader use of these drugs is limited by their parenteral administration and requirement for subspecialist care.[4,5] In contrast to these recent advances with biologics, no new class of oral asthma medication has become available in the past quarter-century. Thus, the clinical development of mechanistically targeted oral therapies for asthma is a priority.

Dexpramipexole is the non–dopaminergic R(+) enantiomer of the approved dopamine agonist drug S(−) pramipexole.[6,7] In contrast to the S(−) enantiomer, dexpramipexole effectively has no dopamine agonist activity at doses used clinically.[7] During its initial clinical development in amyotrophic lateral sclerosis (ALS), dexpramipexole unexpectedly decreased blood eosinophil counts.[8] In 4 previous clinical trials with dexpramipexole, including those in ALS,[8] hypereosinophilic syndrome (HES),[9] and chronic rhinosinusitis with nasal polyps (CRSwNP),[10] dexpramipexole significantly decreased blood eosinophil counts. In addition, in both HES and CRSwNP, dexpramipexole demonstrated substantial depletion of tissue eosinophils. Evidence to date indicates that dexpramipexole inhibits eosinophil maturation.[9] The consistent eosinophil lowering seen across the aforementioned clinical trials suggests that dexpramipexole may have a similar therapeutic profile to that of anti–IL-5 and IL-5 receptor (IL-5R) biologics in asthma. Accordingly, EXHALE was a proof-of-concept trial that examined the pharmacodynamic (eosinophil lowering), clinical (spirometry, asthma control, and asthma quality of life), and safety profile of dexpramipexole, added on to standard of care, in subjects with moderate to severe eosinophilic asthma, uncontrolled on GINA steps 3 to 5 therapy.

METHODS

Study design

EXHALE was a randomized, double-blind, parallel-group, placebo-controlled phase 2 proof-of-concept study to assess the efficacy of dexpramipexole in moderate to severe eosinophilic asthma, uncontrolled on standard-of-care GINA steps 3 to 5 therapy. After informed consent and initial laboratory and spirometry screening, subjects entered a 2-week run-in phase with open-label twice-daily placebo dosing, which was dispensed in a smart bottle (AdhereTech, New York, NY). During the run-in, placebo tablet adherence of 85% or more over 12 days or longer was required for eligibility. Eligible participants were randomized. They then entered the primary assessment phase, during which they received twice-daily dosing of study drug or placebo for 12 weeks (see Fig E1 in this article's Online Repository at www.jacionline.org). Following the primary assessment phase, participants stopped taking the study drug and entered a 12-week washout (eosinophil recovery phase). Individual sites were designated to have subjects return at either week 16 or week 18, 4 to 6 weeks after stopping the study drug. Thus, data points noted as "week 16/18" are composed of determinations within that broader time window. The study was conducted at 35 sites in the United States. Study procedures took place after approval by a centralized institutional review board (Advarra) or the local institutional review board. Written informed consent was obtained from all participants. The study was registered with ClinicalTrials.gov (NCT04046939), and the study protocol and statistical analysis plan are posted on that site.

Participants

Eligibradle participants were aged 18 to 74 years, with a diagnosis of moderate to severe asthma on the basis of GINA 2018 guidelines of asthma for 12 months or longer duration,[2] requiring

daily treatment with at a minimum low-dose inhaled corticosteroid (ICS) in combination with a long-acting β2-agonist on a stable dose for at least 1 month before screening. Other key inclusion criteria at screening included prebronchodilator (pre-BD) FEV_1 less than 80% and greater than or equal to 40% predicted, with BD reversibility of 12% or more, and screening absolute eosinophil count (AEC) greater than or equal to 300/μL. Complete entry criteria are reported in the Online Repository at www.jacionline.org. For randomization and blinding information, see the Online Repository.

Procedures

Subjects' eligibility was assessed during screening and confirmed at the baseline visit. Study drug (dexpramipexole or matching placebo) was self-administered twice daily by participants. Subjects were asked to withhold their morning asthma medication when pre-BD spirometry was scheduled. Spirometry was performed according to the American Thoracic Society/European Respiratory Society guidelines.[11] Data from this study were used in a journal article examining urine eosinophil–derived neurotoxin as a biomarker in eosinophil-associated disorders.[12] Additional procedures, including nasal eosinophil peroxidase (EPX),[13,14] are detailed in the Online Repository at www.jacionline.org.

Outcomes

The primary end point was the relative change in blood AEC from baseline to week 12. Secondary efficacy end points were the change from baseline to week 12 in pre-BD FEV_1, post-BD FEV_1, the 6-item Asthma Control Questionnaire (ACQ-6) score, and the Asthma Quality of Life Questionnaire (AQLQ) score. Protocol-defined exploratory end points included change from baseline to week 12 in nasal EPX, blood basophils, and fractional exhaled nitric oxide (FENO). Safety was assessed by the incidence and severity of treatment-emergent adverse events (AEs), defined as an AE that starts (or increases in severity) during or after the first dose of randomized study drug and within 30 days of the last dose of the study drug. Potential clinically significant laboratory findings from baseline to 30 days after the last dose of the study drug were also evaluated and reported.

Statistical analysis

The statistical analysis plan was finalized before study unblinding. Sample size was calculated using the methodology for a 2-sample *t* test. It was calculated that 19 subjects per study arm could provide approximately 84% power if there was a reduction of 85% in blood eosinophils within the dexpramipexole group and 10% in the placebo group. After assuming a dropout rate of 20%, this yielded the 25 subjects per study arm target used for the study.

AEC was analyzed on a $\log_{10}$ scale, with estimates transformed back to the original scale to present estimated geometric mean (GM) ratios for treatment effects and the ratio of GM of treatment effects versus placebo along with 95% CI, the same approach used to analyze eosinophils in the mepolizumab program.[15,16] A mixed-effect model for repeated measures (MMRM) was used for the analysis of change in AEC and pre-BD FEV_1; fixed-effect variables included baseline, GINA treatment steps 3 to 5, treatment, visit, Treatment-by-Visit interaction, and Baseline-by-Visit interaction, and random effect included subjects.

To control the type 1 error for the primary and key secondary end points, a closed hierarchical test sequence was used:

1. The primary end point (AEC change from baseline) was first tested in the 150-mg BID (ie, twice-daily) group.
2. It was followed by AEC change from baseline in the 75-mg BID group.
3. This was then followed by the week-12 pre-BD FEV_1 in the pooled 75- and 150-mg BID groups. The groups were pooled to increase the sample size and statistical power of this end point.
4. Lastly, this was followed by AEC change from baseline in the 37.5-mg BID group.

Once one of these key secondary end points failed to achieve a *P* value of less than .05, end points lower in the hierarchy could not be formally tested or declared statistically significant. Statistical testing for the other secondary end points was performed at the .05 level without adjustment (nominal values). Data analysis was performed using the SAS statistical software package version 9.4 (SAS, Cary, NC). The safety population included all subjects who were randomized and received at least 1 dose of the study drug. The primary analysis was conducted on data from the efficacy population, which was a modified intent-to-treat sample consisting of all subjects who received at least 1 dose of the study drug and had at least 1 postrandomization evaluation for at least 1 of the efficacy end points.

A prespecified exploratory analysis of change in week-12 pre-BD FEV_1 versus change in week-12 AEC was performed using the Spearman rank-correlation test. Change in pre-BD FEV_1 was evaluated in 2 exploratory subgroup analyses. In a *post hoc* analysis, dexpramipexole treatment arms were pooled and divided into high and low (≥50% and <50% AEC reduction) responder subgroups, on the basis of the reduction in AEC from baseline to week 12. Changes in the nasal EPX ratio were analyzed using the Wilcoxon rank-sum test.

The coronavirus disease 2019 impact

Pulmonary function testing, nasal EPX sampling, and FENO were paused starting March 20, 2020, as per professional society guidance[17] and were reinitiated on a site-by-site basis starting on May 15, 2020. This resulted in some subjects not having pre-BD spirometry data at every visit. Further details on coronavirus disease 2019 (COVID-19) impact are available in the Online Repository at www.jacionline.org, including an accounting of pre-BD spirometry FEV_1 values and subject numbers for each visit and study arm reported in Table E1 (in the Online Repository available at www.jacionline.org)

RESULTS

Disposition

Between August 15, 2019, and August 28, 2020, 534 participants were screened for eligibility, of which 103 were randomized into 1 of 4 treatment groups: dexpramipexole 37.5 mg BID (N = 22), 75 mg BID (N = 26), 150 mg BID (N = 28), or placebo (N = 27) (Fig 1). Screening was stopped when the projected target of 25 subjects per arm (100 total) was reached. Ninety-

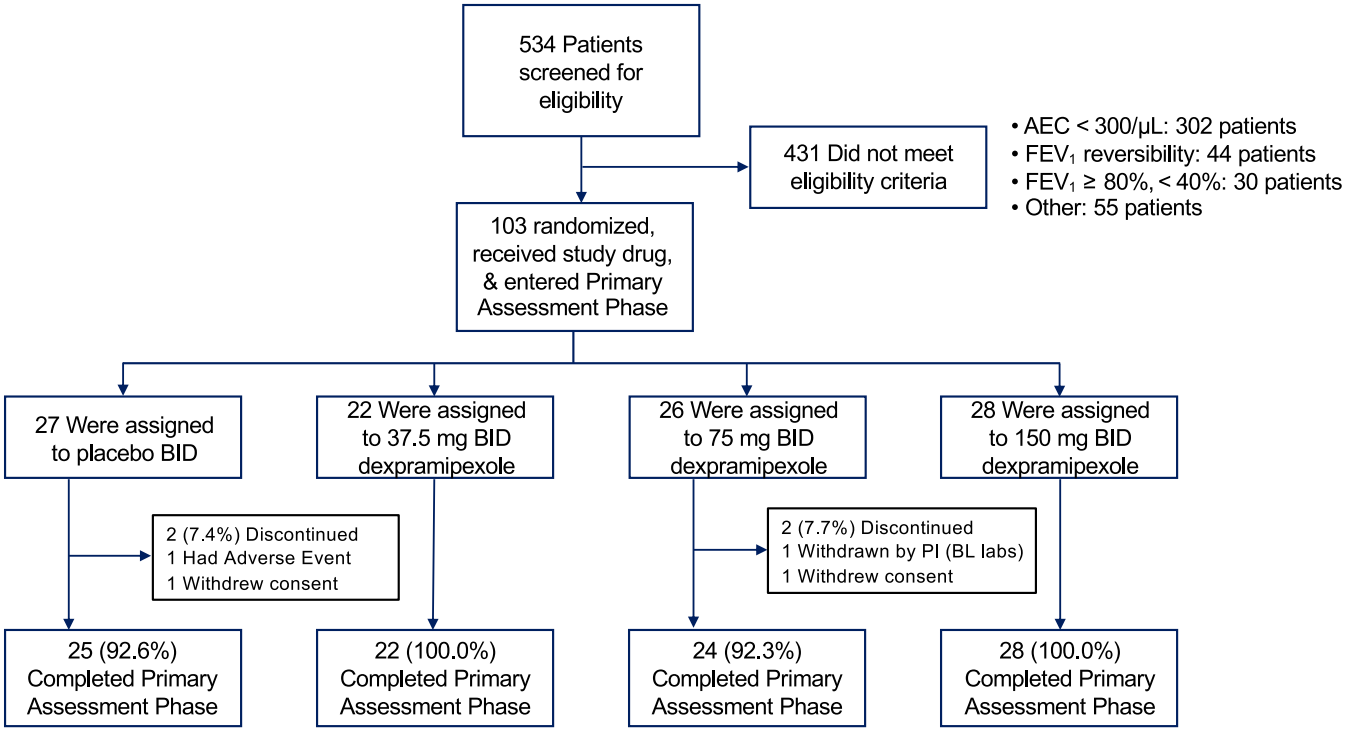

FIG 1. Trial profile. *PI,* Principal investigator.

six percent of subjects overall and 97% of dexpramipexole-treated subjects completed the primary assessment phase on the study drug. Subjects with more than 90% study drug adherence during the primary assessment phase represented 96%, 91%, 92%, and 96% of the placebo, 37.5-mg BID, 75-mg BID, and 150-mg BID groups, respectively.

Demographic and baseline characteristics

Demographic parameters were balanced across treatment groups, and the baseline clinical characteristics were representative of a population with moderate to severe eosinophilic asthma (Table I). The overall median age was 44 years, and most subjects were White (73.8%) and female (52.4%). Overall, 76% of subjects were receiving medium- to high-dose ICS plus long-acting β-agonist (GINA steps 4 and 5) to control their asthma. Overall, 20% of participants fulfilled the European Respiratory Society/American Thoracic Society definition of severe asthma.[18] Baseline clinical characteristics were similar between treatment groups.

Efficacy

Eosinophil lowering was observed starting at weeks 4 to 6 (Fig 2, *A*). The primary efficacy end point, week -12 placebo-corrected AEC ratio to baseline, was 0.23 (95% CI, 0.12-0.43; $P < .0001$) in the 150-mg BID group, 0.34 (95% CI, 0.18-0.65; $P = .0014$) in the 75-mg BID group, and 0.45 (95% CI, 0.23-0.87; $P = .019$) in the 37.5-mg BID group, corresponding to 77%, 66%, and 55% reductions, respectively (Table II). A statistically significant dose response was observed as indicated by log-linear dose-response analysis (Table II). At week 12, the study drug was stopped, and the AEC gradually returned to pretreatment levels by week 20 (Fig 2, *A*). Dexpramipexole 150 mg BID lowered basophils by 44% ($P = .029$) and 29% ($P = .048$) at week 12, as determined by flow cytometry and automated differential, respectively (see Table E2 in this article's Online Repository at www.jacionline.org).

In subjects with severe asthma, nasal EPX is highly correlated to sputum eosinophil count and has emerged as a minimally invasive means to assess airway eosinophilia.[14] In the present study, nasal EPX week-12 ratio to baseline was assessed as an exploratory end point. The reduction of nasal EPX was the greatest for the 150-mg BID group (median ratio, 0.11; interquartile range, 0.00-0.94; $P = .020$) and the 75-mg BID group (median ratio, 0.15; interquartile range, 0.00-0.71; $P = .021$), corresponding to 89% and 85% reductions, respectively (Fig 2, *B*). At week 12, nasal EPX ratio to baseline was highly correlated with blood AEC lowering (Fig 2, *C*).

Week-12 pre-BD FEV_1 in the pooled 75- and 150-mg BID groups was a key secondary end point in the hierarchical testing scheme and did not achieve statistical significance, at which point formal statistical testing ceased (Table E1). Despite the lack of statistical significance in the pooled 75- and 150-mg BID groups, increases in pre-BD FEV_1 were observed, with varying magnitude and significance across the study groups and visits (Fig 3, *A*; Table E1). For example, in the 150-mg BID group, the placebo-corrected least-squares mean (LSM) change from baseline was 81.9 mL (95% CI, −83.8 to 248; $P = .33$) at week 4; 271 mL (95% CI, 71.8 to 470; $P = .0083$) at week 8; 182 mL (95% CI, −35.5 to 400; $P = .10$) at week 12; and 240 mL (95% CI, 32.0 to

TABLE I. Baseline characteristics of the intent-to-treat population

Characteristic	Placebo (N = 27)	Dexpramipexole 37.5 mg BID (N = 22)	Dexpramipexole 75 mg BID (N = 26)	Dexpramipexole 150 mg BID (N = 28)
Age (y), mean ± SD	45.8 ± 12.9	46.6 ± 13.4	44.5 ± 15.5	44.6 ± 12.5
Sex, n (%)				
Male	10 (37.0)	11 (50.0)	12 (46.2)	16 (57.1)
Female	17 (63.0)	11 (50.0)	14 (53.8)	12 (42.9)
Race, n (%)				
White	21 (77.8)	17 (77.3)	16 (61.5)	22 (78.6)
Black or African American	4 (14.8)	4 (18.2)	6 (23.1)	6 (21.4)
Asian	1 (3.7)	1 (4.5)	2 (7.7)	—
Other*	1 (3.7)	—	2 (7.7)	—
Body mass index (kg/m2), mean ± SD	34.3 ± 12.7	31.7 ± 7.4	33.44 ± 10.7	32.1 ± 7.0
Eosinophil count (per μL), GM (± SD)	382 (297-491)	404 (251-650)	374 (279-502)	438 (303-633)
Serum IgE (IU/mL), mean ± SD	279 ± 327	289 ± 316	619 ± 986	618 ± 2092
Age at asthma onset (y), n (%)				
<18	18 (66.7)	16 (72.7)	19 (76.0)	22 (78.6)
≥18	9 (33.3)	6 (27.3)	6 (24.0)	6 (21.4)
ICS dose, n (%)				
Low-dose ICS + LABA	10 (37.0)	8 (36.4)	4 (15.4)	3 (10.7)
Medium-dose ICS + LABA	14 (51.9)	9 (40.9)	15 (57.7)	19 (67.9)
High-dose ICS + LABA	3 (11.1)	5 (22.7)	7 (26.9)	6 (21.4)
Pre-BD FEV_1 (mL), mean ± SD	2050 ± 566	1980 ± 577	2030 ± 555	2110 ± 506
Pre-BD FEV_1 (% predicted)	62.7 ± 7.55	59.0 ± 10.8	63.6 ± 9.50	62.3 ± 10.3
Reversibility (%)	19.9 ± 16.8	16.9 ± 10.8	18.7 ± 10.2	21.9 ± 15.1
Total 6-item ACQ score, mean ± SD	2.3 ± 0.8	2.3 ± 0.9	1.9 ± 0.7	2.1 ± 0.9
History of nasal polyps, n (%)	5 (18.5)	2 (9.1)	0 (0)	2 (7.1)
FENO (ppb), mean ± SD	34 ± 22.5	49 ± 52	35 ± 27	31 ± 23
Subjects with ≥1 asthma exacerbation in previous year,† n (%)	6 (22.2)	1 (4.5)	5 (19.2)	7 (25.0)

Some percentages do not add up to 100 because of rounding.
LABA, Long-acting β_2-agonist; *ppb*, parts per billion.
*Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, or other.
†One or more asthma exacerbations requiring systemic corticosteroids in the previous year. ICS dose strength was as per GINA 2019 guidelines.[2]

448; $P = .024$) at week 16/18 (nominal P values). As per protocol, the study drug was stopped at week 12; however, improvements in FEV_1 were durable through week 16/18, as seen in Fig 3 and Tables E1 and E3.

A prespecified analysis of pre-BD FEV_1 week-12 change from baseline correlated with week-12 AEC change from baseline yielded a correlation coefficient of 0.58 in the pooled 75- and 150-mg BID groups (Fig 4). Similar correlations were not seen between basophil and FEV_1 changes. Similarly, a *post hoc* analysis of pre-BD FEV_1 was performed in a subgroup consisting of pooled dexpramipexole subjects (all dose groups) with greater than or equal to 50% eosinophil lowering versus those with less than 50% eosinophil lowering at week 12 (Fig 3, *B*). Larger FEV_1 improvements were consistently found in the eosinophil-high responder subgroup (≥50% AEC reduction) than in the subgroup with less than 50% AEC reduction.

A *post hoc* analysis of pre-BD FEV_1 in each dexpramipexole group averaged across all study visits (week 4 through week 16/18) was performed (see Table E3 in this article's Online Repository at www.jacionline.org). Averaged over all study visits, the 150-mg BID group yielded a placebo-corrected change from baseline of 183 mL (95% CI, 20.3-350; $P = .029$, nominal value).

In the dexpramipexole 150-mg BID group, incremental, but nonsignificant, improvements relative to placebo were observed for the 6-item ACQ score (Table III), the AQLQ score, and FENO (see Tables E4 and E5 in this article's Online Repository at www.jacionline.org).

The enrolled subject population, with uncontrolled asthma despite GINA step 3 to 5 therapy, had generally milder disease than that enrolled in recent phase 3 asthma trials.[19,20] To examine spirometry in a more severe population, a *post hoc* analysis of pre-BD FEV_1 in the subgroup on GINA step 4 and 5 therapy was performed, which showed a similar FEV_1 improvement as that seen in the intent-to-treat population (see Fig E2 in this article's Online Repository at www.jacionline.org).

Safety

Overall, dexpramipexole was found to be safe and well tolerated. Of 76 dexpramipexole-treated subjects, 74 (97%) completed the primary assessment phase on the study drug (Fig 1). Treatment-emergent AEs assessed during the primary assessment phase and for 30 days after were reported by 31.8%, 46.2%, and 42.9% of subjects in the 37.5-, 75-, and 150-mg BID dexpramipexole groups, respectively, compared with 33.3% in the placebo group (Table IV).

No serious AEs or deaths were observed. Most AEs in the dexpramipexole arms were of mild to moderate severity. Three AEs rated as severe were observed, none of which was considered drug-related by investigators: 2 AEs in the 75 -mg BID group

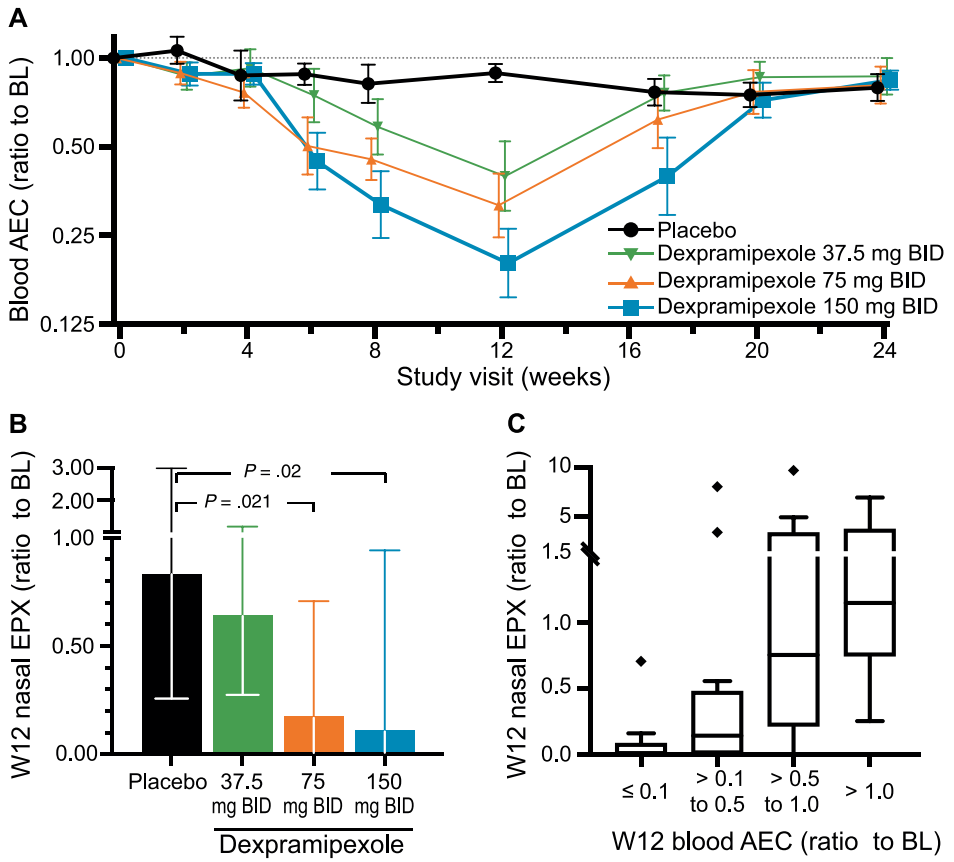

FIG 2. Eosinophil pharmacodynamic biomarkers of response. **A**, Blood AEC ratio to baseline (BL) shown across all study visits. AEC ratio is presented as the GM; error bars represent SE. **B**, Week-12 (W12) nasal eosinophil peroxidase ratio to baseline. Nasal EPX ratios are presented as median values, interquartile range; *P* values calculated using the Wilcoxon rank-sum test. **C**, Nasal EPX week-12 ratio to baseline vs blood AEC week-12 ratio to baseline; Tukey plot shown for the 3 dexpramipexole arms combined, categorized by subjects with AEC week-12 ratio to baseline less than or equal to 0.1 (n = 11), more than 0.1 to 0.5 (n = 16), more than 0.5 to 1.0 (n = 16), and more than 1.0 (n = 8).

TABLE II. Primary end point and relative change in blood AEC from baseline to week 12

	Placebo (N = 25)	Dexpramipexole 37.5 mg BID (N = 22)	Dexpramipexole 75 mg BID (N = 24)	Dexpramipexole 150 mg BID (N = 28)
Baseline eosinophil count	382	404	374	438
Week-12 ratio to baseline, LSM	0.90	0.40	0.31	0.21
Ratio vs placebo (95% CI)		0.45 (0.23-0.87)	0.34 (0.18-0.65)	0.23 (0.12-0.43)
P value vs placebo		.019*	.0014	<.0001
Log-linear dose-response trend	<.0001			

Estimates are LSMs from the MMRM performed in the modified intent-to-treat population.
*Testing in the closed hierarchical testing scheme was stopped for a nonsignificant end point before reaching the 37.5-mg BID group; therefore, this result cannot be considered statistically significant within the hierarchical testing scheme.

(7.7%), including 1 episode of anaphylaxis (hives and asthma worsening after pokeweed exposure) and 1 episode of recurrent sinusitis, and 1 AE of back pain in the 150-mg BID group (3.6%). Moreover, the pattern of specific AEs did not appear to be dose-related. The only AE that led to discontinuation of the study drug occurred in a placebo subject who reported arm pain.

Treatment-emergent laboratory findings included 4 cases of neutropenia (nadir absolute neutrophil counts [ANCs] of 900-1490/μL) that were evenly divided among the 4 study groups, including placebo (see Table E6 in this article's Online Repository at www.jacionline.org). Of these, 1 subject in the dexpramipexole 150-mg BID group had a single ANC of 1310/μL

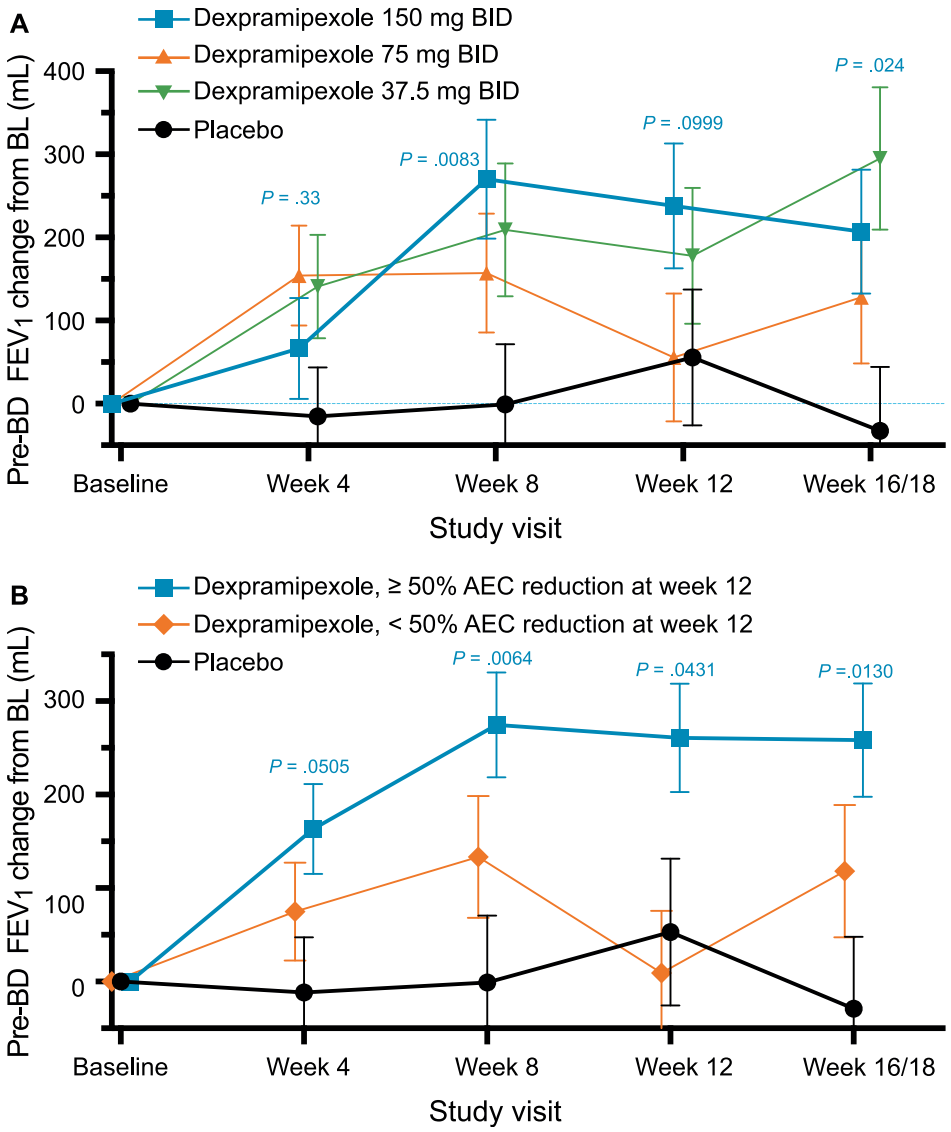

FIG 3. Change from baseline in lung function in the efficacy population. **A**, LSM pre-BD FEV_1 change from baseline in the 4 study arms. **B**, LSM pre-BD FEV_1 change from baseline in subgroups consisting of pooled dexpramipexole study arms with week-12 AEC reduction from baseline of greater than or equal to 50% and less than 50%, and placebo. *$P < .05$; **$P < .01$. In Fig 3, *A*, *P* values are shown for the 150-mg BID arm vs placebo; in *B*, *P* values are shown for the eosinophil-high responder subgroup vs placebo. These *P* values were not multiplicity-controlled analyses and therefore are nominal. Error bars represent SE. Pre-BD FEV_1 subject numbers for each arm and visit are provided in Table E1.

concurrent with an uncomplicated case of COVID-19. The COVID-19 AE was judged unrelated to the study drug by the investigator.

DISCUSSION

In the EXHALE phase 2 proof-of-concept study, the oral eosinophil-lowering drug dexpramipexole significantly reduced blood eosinophil counts in a dose-dependent manner in subjects with moderate to severe eosinophilic asthma, uncontrolled on standard-of-care GINA step 3 to 5 therapy. Blood eosinophil lowering was accompanied by significant reductions in nasal EPX, a biomarker of airway eosinophilia.

The magnitude of blood eosinophil and nasal EPX lowering seen in the dexpramipexole 150-mg BID group was comparable with the blood and sputum eosinophil lowering seen with anti–IL-5 biologics, such as mepolizumab.[15,16,21] The weight of evidence indicates that the therapeutic benefit of anti–IL-5/5R therapy is conferred through lowering blood and airway eosinophils, rather than by downregulating eosinophil activation or modifying gene transcription.[22-25] The current results demonstrating comparable eosinophil lowering as that produced by anti–IL-5 therapies suggest that dexpramipexole may have the potential to deliver clinical benefit in asthma similar to that seen with eosinophil-lowering biologics.

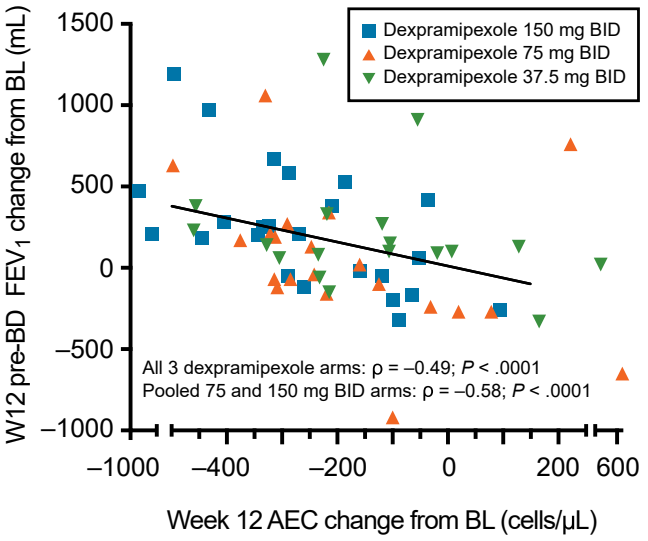

FIG 4. Correlation between eosinophil lowering and lung function improvement. Week-12 AEC change from baseline vs week-12 pre-BD FEV_1 change from baseline. Each symbol represents a unique subject as per the key shown. Spearman correlation coefficients are shown for the groups listed. Week-12 pre-BD FEV_1 subject numbers are provided in Table III.

This study is notable for its use of nasal EPX, a noninvasive biomarker of eosinophil activation and airway eosinophilia, which is highly correlated with sputum eosinophil count.[13,14] A clear dose-dependent response was seen, with EPX depletion in both the 75- and the 150-mg BID groups, generally comparable with the tissue and sputum eosinophil lowering observed with anti–IL-5/5R biologics.[15,26,27] EPX has been identified as a potential mediator of mucus plugging and airflow obstruction in severe asthma, ultimately leading to air trapping and decreases in FEV_1.[28,29]

EXHALE was a proof-of-concept study that was powered for the eosinophil lowering primary end point but had a sample size substantially less than that needed to reliably power an FEV_1 improvement of 100 mL or higher. Despite this, clinically meaningful increases in pre-BD FEV_1 were evident in the highest 150-mg BID group (Table III). Unlike the clear dose-dependent AEC results, pre-BD change in FEV_1 did not demonstrate a dose-dependent response. This finding is in line with previous dose-ranging clinical trials of anti–IL-5/5R biologics that have similarly not observed dose-dependent FEV_1 improvements.[15,30] These FEV_1 findings are further substantiated by the demonstration that in dexpramipexole-treated subjects, week-12 increases in FEV_1 were correlated with eosinophil lowering, as shown in both the eosinophil responder (Fig 3, *B*) and the correlation (Fig 4) analyses. To our knowledge, these preliminary correlations in this proof-of-concept study between the magnitude of eosinophil reduction and FEV_1 improvement represent new findings. These findings demonstrate the link between eosinophil reduction and clinical benefit.

Available evidence indicates that dexpramipexole lowers eosinophils by inhibiting their maturation[9] and is the subject of active investigation. The additional finding of dexpramipexole lowering basophils (Table E2) is consistent with this mechanism of action because basophils and eosinophils share a common hematopoietic progenitor.[31] It has not been studied whether this broader activity across both eosinophils and basophils translates into clinical efficacy in more traditional allergic diseases, such as allergic rhinitis.

Blood eosinophil lowering began between weeks 4 and 6 of treatment (Fig 2, *A*), similar to the kinetics seen in previous clinical trials.[8,10] This delay in eosinophil lowering is consistent with dexpramipexole inhibiting the maturation of an early eosinophil progenitor as per a "conveyor belt" model of hematopoiesis.[9,32] Similar time frames are required to generate eosinophils in $CD34^+$ progenitor and induced pluripotent stem cell cultures.[33,34] Furthermore, the lack of rapid blood eosinophil lowering is further evidence that dexpramipexole does not act on mature eosinophils. Despite this lag in eosinophil lowering, increases in FEV_1 were seen as early as week 4, at which time point blood eosinophils were largely unchanged (Fig 3, *B*; Tables E1 and E3). Future studies are needed to determine whether this apparent early increase in FEV_1 at week 4 is replicable. Conversely, the durability of FEV_1 improvements through week 16/18, 4 to 6 weeks after stopping the study drug, likely reflects the delayed kinetics of eosinophil recovery.

Dexpramipexole has been well tolerated in previous trials, with more than 1200 subjects exposed to dexpramipexole, including 888 subjects with ALS,[35] 20 with CRSwNP,[10] and 10 with HES.[9] The current results in eosinophilic asthma provide additional evidence that dexpramipexole is safe and well tolerated.

A limitation of this study is its sample size and duration, which were sufficiently powered for the eosinophil-lowering end point, but not for clinical end points of FEV_1, ACQ-6 score, or AQLQ score. This underscores the need for new asthma end points that are clinically relevant, yet adequately powered for proof-of-concept trials. In addition, the study population on GINA step 3 to 5 therapy had milder disease than that enrolled in recent phase 3 asthma trials and may not reflect a population with severe asthma. Although the FEV_1 data in EXHALE are encouraging, additional larger clinical trials are needed to definitively evaluate dexpramipexole's effect on these clinical outcomes.

The development of parenterally administered immunologically targeted asthma drugs over the past decade has been a major advancement. However, this abundance of biologic options is contrasted with the paucity of oral therapeutic options. As a well-tolerated oral drug, dexpramipexole may provide an alternative to current injected biologic therapies.

DISCLOSURE STATEMENT

This work was funded by Knopp Biosciences, LLC, which participated in the study design; the collection, analysis, and interpretation of data; the writing of the report; and the decision to submit the report for publication.

Disclosure of potential conflict of interest: S. Siddiqui has provided advisory services for Knopp Biosciences, GlaxoSmithKline, Novartis, AstraZeneca, CSL Behring, ERT Medical, Owlstone Medical, Mundiphrama, Chiesi, and Boehringer Ingelheim. M. E. Bozik, D. G. Archibald, S. I. Dworetzky, R. Killingsworth, J. L. Mather, and C. Prussin are former employees of Knopp Biosciences and own stock or stock options in Knopp Biosciences. R. A. Panettieri has been a speaker and/or advisor for and/or has received research funding from Knopp Biosciences, AstraZeneca, Equillium, Evelobio, Genentech, Johnson & Johnson, Medimmune, Maven, Novartis, Optikira, the Research Institute of Fragrance Materials, Sanofi/Regeneron, and Theravance. W. W. Busse reports consultant fees from AstraZeneca,

TABLE III. Secondary end points, baseline to week 12

Variable	Placebo	Dexpramipexole 37.5 mg BID	Dexpramipexole 75 mg BID	Dexpramipexole 150 mg BID
No. of subjects randomized	27	22	26	28
Pre-BD FEV_1 (mL)				
No. of subjects analyzed	17	18	21	24
Change from baseline, LSM	55.7	178	55.5	238
Difference vs placebo, LSM (95% CI)		123 (−105 to 350)	−0.2 (−221 to 221)	182 (−35.5 to 400)
P value vs placebo		.29	1.00	.10
Post-BD FEV_1 (mL)				
No. of subjects analyzed	20	18	22	23
Change from baseline, LSM	−5.5	93.2	−0.7	176
Difference vs placebo, LSM (95% CI)		98.7 (−105 to 302)	4.7 (−192 to 202)	181 (−16 to 378)
P value vs placebo		.34	.96	.072
Six-item ACQ score				
No. of subjects analyzed	25	22	24	28
Change from baseline, LSM	−0.39	−0.42	−0.44	−0.66
Difference vs placebo, LSM (95% CI)		−0.028 (−0.56 to 0.51)	−0.046 (−0.58 to 0.48)	−0.26 (−0.77 to 0.25)
P value vs placebo		.92	.86	.31

Estimates are LSMs from the analysis models performed in the modified intent-to-treat population. The analysis of pre-BD FEV_1 and 6-item ACQ score used an MMRM analysis. The analysis of post-BD FEV_1 used an analysis of covariance. Spirometry was paused during the initial phase of the COVID-19 pandemic, resulting in a variance between the number of subjects randomized and analyzed, as detailed under the "COVID-19 impact" subheading in the Results section and in Table E1 in the Online Repository at www.jacionline.org.

TABLE IV. Treatment-emergent AEs

Adverse event	Placebo (N = 27) nS* (%)	Dexpramipexole 37.5 mg BID (N = 22) nS (%)	Dexpramipexole 75 mg BID (N = 26) nS (%)	Dexpramipexole 150 mg BID (N = 28) nS (%)
Serious AEs	0	0	0	0
Any AE	9 (33.3)	7 (31.8)	12 (46.2)	12 (42.9)
Preferred term				
Asthma	2 (7.4)	2 (9.1)	—	2 (7.1)
Nasopharyngitis	1 (3.7)	3 (13.6)	—	1 (3.6)
Pain in extremity	1 (3.7)	—	2 (7.7)	—
Skin laceration	—	1 (4.5)	1 (3.8)	1 (3.6)
Upper respiratory tract infection	1 (3.7)	—	2 (7.7)	—
Acute sinusitis	—	—	1 (3.8)	1 (3.6)
Back pain	—	—	—	2 (7.1)
Bronchitis	—	1 (4.5)	—	1 (3.6)
Dry mouth	—	—	1 (3.8)	1 (3.6)
Headache	1 (3.7)	—	1 (3.8)	—
Nausea	—	—	2 (7.7)	—
Neutropenia	—	—	1 (3.8)	1 (3.6)
Otitis externa	—	—	1 (3.8)	1 (3.6)
Rash	—	1 (4.5)	1 (3.8)	—
Sinusitis	1 (3.7)	—	1 (3.8)	—
COVID-19 test result positive	—	—	—	2 (7.1)

Treatment-emergent AEs were defined as those with an onset date or increase in severity on or after the first day of randomized study drug and within 30 d of taking the last dose of the study drug. AEs are shown for any preferred term with >1 subject in the safety population.
*No. of subjects (nS) with AEs.

Genentech, GlaxoSmithKline, Novartis, Regeneron Pharmaceuticals, Inc, and Sanofi. S. E. Wenzel has been an advisor for and/or has received research funding from Aer Therapeutics, AstraZeneca, Knopp Biosciences, Regeneron, and Sanofi. The rest of the authors declare that they have no relevant conflicts of interest.

Clinical implications: In this study, dexpramipexole demonstrated dose-dependent eosinophil lowering and substantial improvements in FEV_1. As a well-tolerated oral drug, dexpramipexole may provide an alternative to current injected biologic therapies.

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PROTOCOL ENTRY CRITERIA

Inclusion criteria

To be eligible to participate in this study, candidates must meet the following criteria:

1. Signed informed consent.
2. Male or female aged 18 to 74 years at the time of providing consent.
3. Willing to practice 1 highly effective method of contraception or 2 protocol-acceptable methods of contraception in tandem, from the time of informed consent through 1 month (female participants) or 3 months (male participants) after taking the last dose of the study drug.
4. Physician diagnosis of asthma for 12 months or more (relative to baseline) on the basis of the GINA 2018 guidelines.
5. Asthma requiring treatment with, at a minimum, low-dose ICSs in combination with a long-acting β_2-agonist (GINA steps 3-5), on a stable dose for at least 1 month before screening. Subjects using other controller options without long-acting β_2-agonist are not eligible for the study.
6. BD reversibility, as evidenced by greater than or equal to 12% and greater than or equal to 200 mL improvement in FEV_1 15 to 25 minutes following inhalation of albuterol at screening.
7. Pre-BD FEV_1 greater than or equal to 40% and less than 80% of predicted at screening and baseline.
8. AEC greater than or equal to 0.30×10^9/L at the screening visit. May be repeated once if the initial value is between 0.25×10^9/L and 0.29×10^9/L; the second AEC must be greater than or equal to 0.30×10^9/L.
9. Seven-item ACQ score greater than or equal to 1.5 at screening.
10. Negative pregnancy test result at baseline.
11. Adherence greater than or equal to 85% with twice-daily placebo taken during the run-in period (minimum 12 days of adherence data), as documented by the smart bottle.

Exclusion criteria

Candidates will be excluded from study entry if any of the following has been documented at baseline:

1. Asthma considered by the site investigator as unstable at baseline.
2. Treatment for an asthma exacerbation within 8 weeks before baseline visit.
3. Current diagnosis of allergic bronchopulmonary aspergillosis, eosinophilic granulomatosis with polyangiitis, eosinophilic gastrointestinal diseases, hypereosinophilic syndrome, or lung diseases (eg, chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis), which may confound interpretation of this trial's findings.
4. Infection of the upper or lower respiratory tract, including paranasal sinuses and middle ear within the 4 weeks before baseline.
5. Treatment with systemic corticosteroids in the 8 weeks before screening.
6. Treatment with an investigational drug in the previous 30 days or 5 half-lives before baseline, whichever is longer.
7. Treatment with mAb therapy, including benralizumab, dupilumab, mepolizumab, reslizumab, omalizumab, or TNF inhibitors, within 5 half-lives before baseline.
8. Treatment with pramipexole within 4 weeks of baseline.
9. Treatment with selected drugs known to have a substantial risk of neutropenia.
10. Planned surgical procedures during the conduct of the study.
11. History of malignancy. Subjects with basal cell carcinoma, localized squamous cell carcinoma of the skin, or *in situ* carcinoma of the cervix are not excluded, provided that the subject is in remission and curative therapy was completed 12 months or more before screening. Subjects with other malignancies are not excluded, provided that the subject is in remission and curative therapy was completed 5 years or more before screening.
12. Known history of HIV infection.
13. Active hepatitis B or C infection. Subjects with a history of hepatitis C with undetectable viral load for 1 year or longer are not excluded.
14. Renal dysfunction, defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73m^2 at screening (using the Chronic Kidney Disease Epidemiology Collaboration formula).
15. History of unstable or severe cardiac, hepatic, or renal disease, or other medically significant illness.
16. Medical or other condition likely to interfere with subject's ability to undergo study assessments, adhere to visit schedule, or comply with study requirements.
17. Helminth infection within 6 months before baseline.
18. Use of any smoke or inhaled nicotine delivery device within 1 year before screening or a smoking history of 10 pack years or more.
19. Known or suspected alcohol or other substance abuse.
20. Known or suspected nonadherence with study dosing schedule.
21. Unwillingness or inability to follow the procedures outlined in the protocol, including throat or nasal swab.
22. ANC less than 2.0×10^9/L at screening, or any documented history of ANC less than 2.0×10^9/L.
23. History of long QT syndrome or arrhythmia.
24. Electrocardiogram (ECG) showing prolongation of QT-corrected interval, calculated using Fridericia heart rate correction formula, greater than 450 ms at the screening visit or predose at baseline. The interval calculated as the mean of triplicate determinations.
25. Clinically important abnormalities in resting ECG at screening or baseline, including any of the following:
    - PR interval greater than 210 ms;
    - QRS greater than 110 ms;
    - Heart rate less than 45 bpm or greater than 100 bpm (average of 3 assessments).
26. Pregnant or breast-feeding women.

METHODS

Statistical analysis

Log-linear dose-response analysis. Within the MMRM model, a contrast was created to test the AEC treatment effect at

week 12 for log-linear dose response for dose on the log scale. For this analysis, a value of 1 was added to all the dose levels to allow for the $\log_{10}$ transformation of the placebo dose of "0."

Randomization and blinding

Subjects enrolled into the primary assessment phase were randomly allocated in a 1:1:1:1 ratio to receive dexpramipexole 37.5, 75, 150 mg BID, or placebo, using a central, automated interactive system incorporating a permuted blocked randomization, stratified by study site (Medidata Rave RTMS). Dexpramipexole and placebo tablets were identical in appearance. Subjects, investigators, and staff remained blinded to the treatment allocation. Because of the potential for hematology laboratory results to unblind to study drug allocation, AEC, absolute basophil count, total white blood cell count, and white blood cell percentage differential results were blinded to the aforementioned parties but were monitored by an unblinded safety physician for safety. Other hematology results were not blinded to the investigators and staff.

Procedures

Subjects' eligibility was assessed during screening and confirmed at the baseline visit. The study drug (dexpramipexole or matching placebo) was self-administered twice daily by participants. The study drug was dispensed in a smart bottle, which reminded subjects to take their study drug via lights, audible chimes, and text message reminders, and on the opening of the container uploaded date and time to a server. Adherence during the study was monitored in real time using the smart bottle. At weeks 4, 8, and 12, study drug adherence was calculated on the basis of returned pill counts. Subjects were asked to withhold their morning asthma medication at screening, baseline, and weeks 4, 8, 12, and 16/18 when pre-BD spirometry was scheduled.

Spirometry was performed according to the American Thoracic Society/European Respiratory Society guidelines[E1] using Global Lung Function Initiative reference values.[E2] FENO was measured using a NIOX Vero Device (Circassia USA, Morrisville, NC) according to published procedures.[E3] The ACQ was completed at the start of each visit. The 32-question AQLQ was completed at baseline and week 12. Twelve-lead ECGs were performed in triplicate at screening, baseline, and weeks 4, 8, and 12, with central evaluation by a qualified cardiovascular physician.

Safety laboratories, including complete blood cell counts and automated differential, were performed in a central laboratory (Labcorp Drug Development, Inc, Indianapolis, Ind). AEC and basophil counts were obtained from the automated differential. Basophils were additionally enumerated using baseline and week-12 samples using flow cytometry, by gating on $CD123^{+}$, $HLA\text{-}DR^{negative}$ cells. Nasal EPX samples were obtained and analyzed as previously described.[E4,E5] Briefly, a cotton applicator was placed 1 to 2 cm in the inferior nares and passed in and out of the nares 5 times, and then the process was repeated with the same swab on the contralateral side. The swab tip was then frozen and stored at −80° C. At the end of the trial, samples were analyzed. EPX was quantitated using a sandwich ELISA, modified with new capture and detection clones MM25_420.1 and MM25_82.2, respectively (Mayo Clinic Scottsdale, Ariz). Total protein in the EPX samples was quantitated using a bicinchoninic acid protein assay (Pierce BCA Protein Assay Kit, Thermo Fisher, Rockford, Ill). The EPX-to-protein ratio was used to normalize the EPX for the quantity of sample, yielding values in nanogram EPX per milligram of protein.

COVID-19 impact

Pulmonary function testing, nasal EPX collection, and nitric oxide determination were paused starting March 20, 2020, as per the American Thoracic Society guidance[E6] and were reinitiated on a site-by-site basis starting on May 15, 2020, depending on local conditions and individual sites' ability to adhere to COVID-19 safety guidelines. This resulted in some subjects not having pre-BD spirometry, nasal EPX, or FENO data for some visits. A detailed accounting of pre-BD spirometry FEV_1 values and subject numbers for each visit and study arm is provided in Table E1.

To minimize the impact of lost FEV_1 data during the study, the 7-item ACQ was replaced with the 6-item ACQ as the primary assessment of asthma symptom control. Because a dexpramipexole effect on FEV_1 was not expected as early as the week-4 visit, subjects who were missing both the week-8 and week-12 pre-BD FEV_1 because of COVID-19 were to be excluded from the primary analysis of FEV_1. All of the aforementioned decisions were documented in the statistical analysis plan before formal database lock and treatment group unblinding. The results of the analysis of FEV_1 on the full efficacy population versus excluding subjects missing week-8 and week-12 spirometry were very similar. Therefore, the FEV_1 analysis on the full efficacy sample is presented to be more consistent and comparable with what has been presented by other asthma studies.

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- GINA steps 4–5 standard of care asthma therapy
- AEC ≥ 300/μL
- FEV1 < 80%, ≥ 40% predicted
- ACQ-7 ≥ 1.5
- Albuterol reversibility ≥ 12%, 200 mL

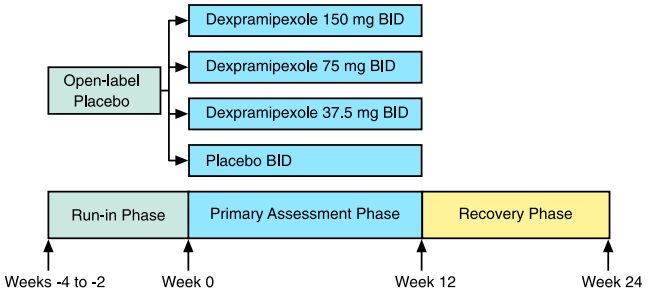

FIG E1. Trial design and flow.

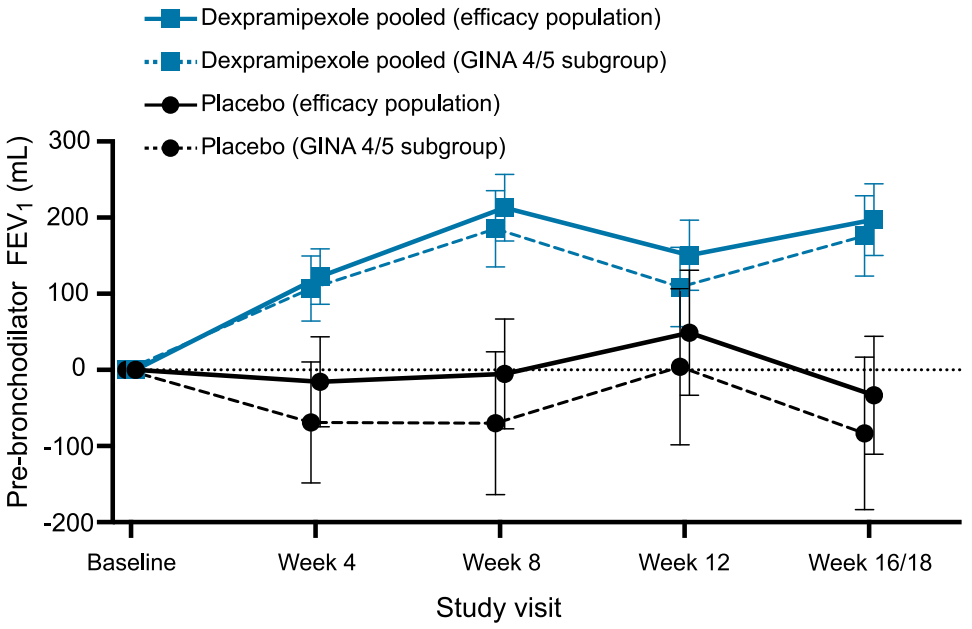

FIG E2. FEV_1 change from baseline in GINA step 4/5 subjects. LSM pre-BD FEV_1 change from baseline in the placebo and pooled dexpramipexole study arms. Bold lines represent the efficacy population and dashed lines represent the subgroup on GINA step 4 or 5 therapy. Error bars represent SE.

TABLE E1. Pre-BD FEV_1 (mL) change from baseline through week 16/18

Time point	Treatment	n	Observed raw mean	Change from baseline LSM	Difference vs placebo LSM (95% CI)	*P* value vs placebo
Analysis baseline	Placebo	26	2050			
	37.5 mg BID dexpramipexole	22	1980			
	75 mg BID dexpramipexole	25	2030			
	150 mg BID dexpramipexole	27	2080			
	Pooled 75 and 150 mg BID	48	2050			
Week 4	Placebo	23		−15.4		
	37.5 mg BID dexpramipexole	20		141	157 (−11.3 to 325)	.0671
	75 mg BID dexpramipexole	22		154	170 (4.0 to 335)	.0449
	150 mg BID dexpramipexole	23		66.5	81.9 (−83.8 to 248)	.3285
Week 8	Placebo	20		−0.8		
	37.5 mg BID dexpramipexole	15		209	210 (−1.92 to 422)	.0521
	75 mg BID dexpramipexole	21		157	158 (−42 to 359)	.1199
	150 mg BID dexpramipexole	22		270	271 (71.8 to 470)	.0083
Week 12	Placebo	17		55.7		
	37.5 mg BID dexpramipexole	18		178	123 (−105 to 350)	.2880
	75 mg BID dexpramipexole	21		55.5	−1.76 (−221 to 221)	.9987
	150 mg BID dexpramipexole	24		238	182 (−035.5 to 400)	.0999
	Pooled 75 and 150 mg BID	45		147	91 (−0.103 to 0.285)	.3528
Week 16 or week 18	Placebo	22		−32.8		
	37.5 mg BID dexpramipexole	17		295	327 (105 to 550)	.0043
	75 mg BID dexpramipexole	20		128	161 (−54.4 to 377)	.1411
	150 mg BID dexpramipexole	25		207	240 (32.0 to 448)	.0242

Estimates are LSMs calculated using an MMRM analysis. Data shown are from the original MMRM through week 12, as prespecified in the statistical analysis plan. Following the unblinding, because of the unexpected durability of pre-BD FEV_1 improvements through the week-16/18 visit, an additional MMRM analysis was carried out through week 16/18. The week-16/18 data are from that second analysis.

TABLE E2. Week-12 peripheral blood basophil counts, ratio to baseline

Time point	Treatment	n	Median (25th, 75th percentile)	Ratio to baseline, median (25th, 75th percentile)	*P* value vs placebo
Basophils by flow cytometry					
Analysis baseline	Placebo	15	14.8 (8.91, 24.4)		
	37.5 mg BID dexpramipexole	14	16.0 (4.92, 23.5)		
	75 mg BID dexpramipexole	17	16.3 (11.9, 21.2)		
	150 mg BID dexpramipexole	19	21.8 (13.5, 36.8)		
Week 12	Placebo	15	22.8 (11.0, 40.0)	0.866 (0.751, 2.45)	
	37.5 mg BID dexpramipexole	14	10.9 (6.34, 25.7)	0.910 (0.557, 1.62)	.5557
	75 mg BID dexpramipexole	17	9.58 (4.72, 18.2)	0.877 (0.243, 1.79)	.2903
	150 mg BID dexpramipexole	19	11.1 (4.93, 2.40)	0.563 (0.245, 1.10)	.0289
Basophils by automated differential					
Analysis baseline	Placebo	24	60 (45, 75)		
	37.5 mg BID dexpramipexole	22	65 (40, 90)		
	75 mg BID dexpramipexole	24	45 (35, 80)		
	150 mg BID dexpramipexole	28	60 (40, 80)		
Week 12	Placebo	24	55 (40, 80)	0.873 (0.679, 1.17)	
	37.5 mg BID dexpramipexole	22	50 (40, 70)	0.875 (0.50, 1.50)	.6533
	75 mg BID dexpramipexole	24	35 (20, 55)	0.690 (0.477, 1.00)	.1091
	150 mg BID dexpramipexole	28	30 (20, 60)	0.708 (0.250, 1.00)	.0482

Peripheral blood basophils were enumerated at baseline and week 12 using flow cytometry and automated differential, respectively. Significance vs placebo was calculated using a Wilcoxon rank-sum test.

TABLE E3. Pre-BD FEV_1 (mL) through week 16/18, averaged across pooled study arms and visits

Time point	Treatment	n*	Observed raw mean (mL)	Change from baseline LSM (mL)	Difference vs placebo LSM (95% CI) (mL)	*P* value vs placebo
Analysis baseline†	Placebo	26	2050			
	37.5 mg BID dexpramipexole	22	1980			
	75 mg BID dexpramipexole	25	2030			
	150 mg BID dexpramipexole	28	2110			
	Pooled dexpramipexole study arms	75	2040			
Week 4	Placebo	23		−15.3		
	Pooled dexpramipexole study arms	65		123	138 (3.18 to 274)	.0450
Week 8	Placebo	20		−6.45		
	Pooled dexpramipexole study arms	58		206	212 (46.3 to 378)	.0128
Week 12	Placebo	17		47.0		
	Pooled dexpramipexole	63		146	99 (−84.8 to 0.282)	.2879
Week 16/18	Placebo	22		−32.8		
	Pooled dexpramipexole study arms	62		210	243 (68.3 to 417)	.0069
Averaged across all study visits	Placebo	26		−1.89		
	37.5 mg BID dexpramipexole	22		204	206 (34.7 to 377)	.0190
	75 mg BID dexpramipexole	25		126	128 (−39.4 to 296)	.1322
	150 mg BID dexpramipexole	28		183	185 (20.3 to 350)	.0282
Pooled dexpramipexole study arms averaged across all study visits	Pooled dexpramipexole study arms	75		171	173 (36.4 to 310)	.0136

For a given time point, pre-BD FEV change from baseline LSM was analyzed using the MMRM model, with contrasts used to average across pooled dexpramipexole study arms and compared with placebo. Alternatively, for each study arm, pre-BD FEV change from baseline was analyzed using the MMRM model, with contrasts used to average across dexpramipexole study visits and compared with placebo. Lastly, within the MMRM model, all dexpramipexole study arms and visits were pooled and compared with placebo. A modified intent-to-treat analysis was used, which included all subjects who had at least 1 postrandomization evaluation for 1 of the efficacy end points.

*No. of subjects with valid observations.

†Analysis baseline is defined as the last valid value recorded before the first randomized dose.

TABLE E4. AQLQ score week-12 change from baseline

Time point	Treatment	n	Observed raw mean	Change from baseline LSM	Difference vs placebo LSM (95% CI)	*P* value vs placebo
Analysis baseline	Placebo	26	4.58			
	37.5 mg BID dexpramipexole	22	4.56			
	75 mg BID dexpramipexole	25	5.15			
	150 mg BID dexpramipexole	28	4.85			
Week 12	Placebo	26		0.376		
	37.5 mg BID dexpramipexole	22		0.531	0.154 (−0.411 to 0.720)	.5894
	75 mg BID dexpramipexole	25		0.312	−0.0642 (−0.627 to 0.499)	.8214
	150 mg BID dexpramipexole	28		0.584	0.208 (−0.338 to 0.755)	.4512

The analysis used an analysis of covariance with terms for baseline, GINA treatment step, and treatment as fixed effects; LOCF was used to impute missing week = 12 observations.
LOCF, Last Observation Carried Forward.

TABLE E5. FENO (ppb) week-12 change from baseline

Time point	Treatment	N	Observed raw mean	Change from baseline LSM	Difference vs placebo LSM (95% CI)	*P* value vs placebo
Analysis baseline	Placebo	25	34.1			
	37.5 mg BID dexpramipexole	21	49.2			
	75 mg BID dexpramipexole	24	34.8			
	150 mg BID dexpramipexole	26	31.5			
Week 12	Placebo	17		3.38		
	37.5 mg BID dexpramipexole	17		−6.79	−10.2 (−23.4 to 3.04)	.1294
	75 mg BID dexpramipexole	20		−3.14	−6.53 (−19.1 to 6.08)	.3061
	150 mg BID dexpramipexole	23		−4.86	−8.24 (−20.6 to 4.13)	.1886

Estimates are LSMs calculated using an MMRM analysis.
ppb, Parts per billion.

TABLE E6. Laboratory-defined neutropenia

Study group	Lowest ANC prerandomization (/μL)	Nadir ANC (/μL)	Clinical events associated with neutropenia	First ANC < 1500/μL (study day)	Race	Sex	Age (y)
Placebo	2310	1120	None	57	Black	Male	40
37.5 mg BID	2210	1490	None	44	Black	Female	29
75 mg BID	1980	900	None	29	Black	Female	62
150 mg BID	3650	1310	Concurrent with COVID-19 diagnosis	80	Hispanic White	Female	61

Incidence of neutropenia with an onset on or after the first day of randomized study drug and within 30 d of the last dose of the study drug. Lowest prerandomization ANC is limited to values obtained in the EXHALE study. Study day of first ANC <1500/μL are days after randomization. Clinical events associated with neutropenia noted if occurring ±10 d of an ANC <1500/μL.