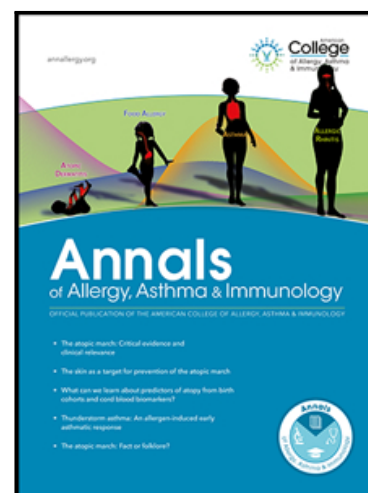


Accepted Manuscript

A Phase 2a Study of Toreforant, a Histamine H₄ Receptor Antagonist, in Eosinophilic Asthma

Alexa P. Kollmeier , Elliot S. Barnathan , Christopher O'Brien , Bin Chen , Yichuan (Karen) Xia , Bei Zhou , Matthew J. Loza , Philip E. Silkoff , Michelle Ge , Robin L. Thurmond

PII: S1081-1206(18)30632-X
DOI: <https://doi.org/10.1016/j.anai.2018.08.001>
Reference: ANAI 2659



To appear in: *Annals of Allergy, Asthma Immunology*

Received date: 18 June 2018
Revised date: 25 July 2018
Accepted date: 6 August 2018

Please cite this article as: Alexa P. Kollmeier , Elliot S. Barnathan , Christopher O'Brien , Bin Chen , Yichuan (Karen) Xia , Bei Zhou , Matthew J. Loza , Philip E. Silkoff , Michelle Ge , Robin L. Thurmond , A Phase 2a Study of Toreforant, a Histamine H₄ Receptor Antagonist, in Eosinophilic Asthma, *Annals of Allergy, Asthma Immunology* (2018), doi: <https://doi.org/10.1016/j.anai.2018.08.001>

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Authors: ¹Alexa P. Kollmeier, MD; ¹Elliot S. Barnathan, MD; ¹Christopher O'Brien, MD, PhD; ^{*2}Bin Chen, PhD; ¹Yichuan (Karen) Xia, PhD; ¹Bei Zhou, PhD; ¹Matthew J. Loza, PhD; ^{*3}Philip E. Silkoff, MD; ^{*4}Michelle Ge, PhD; ¹Robin L. Thurmond, PhD

Affiliations: ¹Janssen Research & Development, LLC; ²Bayer AG; ³Third Pole Therapeutics, Inc; ⁴Genocea Biosciences, Inc; ^{*}Employed by Janssen Research & Development, LLC at the time the study was conducted

Corresponding author:

Alexa Kollmeier

Janssen Research & Development, LLC

3210 Merryfield Row, San Diego, CA, 92121, USA

Telephone number: 858-320-3460

Fax number: 858-784-3013

E-mail address: akollmei@its.jnj.com

Funding source: Janssen Research & Development, LLC provided funding and guidance for the study design and execution; the collection, analysis, and interpretation of data; the writing of the report; and the decision to submit the article for publication.

Registry information: This study is registered at ClinicalTrials.gov, registration number NCT01823016.

Word count: Abstract: 255; Manuscript: 2780

Figure/Table count: Tables: 4; Figures: 3

Author disclosures: APK, ESB, CO, YX, BZ, MJL, and RLT are employed by and own stock in Janssen Research & Development, LLC. BC, PES, and MG were employed by Janssen Research & Development, LLC at the time the study was conducted.

Author contributions: APK, ESB, CO, BC, YX, BZ, MJL, PES, MG, and RLT all contributed to conception and design of study, data generation, analysis and interpretation of data, and preparation/critical revision of manuscript.

INTRODUCTION

Histamine appears to play a role in the pathophysiology of asthma. In patients with allergic asthma, there is an increase in histamine in bronchoalveolar lavage fluid that is negatively correlated with airway function.¹⁻⁶ In addition, histamine levels rapidly increase in the plasma of antigen-challenged patients,⁷ and plasma histamine levels are lowered by effective management of asthma.⁸

Results from clinical studies suggest that histamine 1 and histamine 2 receptor antagonists are not effective in the treatment of asthma.⁹⁻¹¹ However, data in preclinical asthma models support the study of histamine 4 receptor (H₄R) antagonists in the treatment of asthma.¹²⁻¹⁷ Treatment of mice with an H₄R antagonist prior to an allergen challenge significantly reduced the number of eosinophils and lymphocytes in the bronchoalveolar lavage fluid and reduced lung inflammation, which equated with improvements in lung function.¹³⁻¹⁵ H₄R antagonists have also been shown to reduce interleukin (IL)-5, IL-4, and IL-13 levels in lung and bronchoalveolar lavage fluid¹³⁻¹⁵ and to inhibit the differentiation of T-helper type 2 (Th2) cells in vivo.^{15,18}

These results led to the hypothesis that the H₄R is involved in the differentiation and activation of Th2 cells, which is considered a central mechanism underlying eosinophilic asthma, a cellular phenotype of asthma found in approximately 50% of patients with asthma.¹⁹ In conjunction with the standard of care, Th2-targeted therapies have improved lung function and reduced severe asthma exacerbations in patients with moderate-to-severe eosinophilic asthma,²⁰⁻²² a population with significant unmet medical need.

Toreforant is a novel, orally bioavailable, selective histamine H₄R antagonist²³ with encouraging efficacy results and a reasonable safety profile in a Phase 2a study in patients with rheumatoid arthritis.²⁴ Results from H₄R antagonist preclinical studies¹²⁻¹⁷ and a post hoc analysis in a study of patients with uncontrolled asthma treated with an H₄R antagonist chemically distinct from toreforant²⁵ suggested that H₄R antagonists may be effective in patients with eosinophilic asthma. Here, we report the results of a Phase 2a study to prospectively establish proof of concept for toreforant in patients with eosinophilic, persistent asthma that was inadequately controlled despite current treatment.

63 METHODS

64 Study Design

65 This was a Phase 2a, multicenter, randomized, double-blind, parallel-group,
66 placebo-controlled, proof-of-concept study designed to assess the safety and efficacy of
67 orally administered toreforant in adults with eosinophilic, persistent asthma that was
68 inadequately controlled despite current treatment. The study was conducted in
69 accordance with the ethical principles that have their origin in the Declaration of Helsinki
70 and that are consistent with Good Clinical Practices and applicable regulatory
71 requirements. Patients provided written consent to participate in the study. The study
72 protocol was reviewed and approved by an Institutional Review Board or Independent
73 Ethics Committee.

74 The screening phase of the study lasted for approximately 4 weeks, followed by
75 a 24-week, placebo-controlled treatment phase and a subsequent 4-week, follow-up
76 phase (end of study visit at Week 28) (Figure 1). At least 160 patients were to be
77 randomized in a 1:1 ratio to receive either placebo or 30 mg toreforant once daily
78 through Week 24 then followed for 4 weeks. The 30-mg dose was expected to provide
79 exposures that exceed the predicted efficacious concentration in patients with asthma
80 based on preclinical animal models.²³ Randomization was stratified according to the
81 intensity of background asthma medication use at randomization and country/site. The
82 sample size calculation was based on the primary endpoint, the change from baseline in
83 prebronchodilator (preBD) percent-predicted forced expiratory volume in 1 second
84 (FEV₁) at Week 16. Based on previous asthma studies, the standard deviation (SD) of
85 both toreforant and placebo groups was assumed to be 13.5%. To detect a clinically

meaningful treatment difference of 6% absolute change in preBD percent predicted FEV₁ (equivalent to 150 mL when 100% FEV₁ is 2.5 L) using a 2-sided t-test at an alpha level of 0.05, 160 patients (with 80 patients in each treatment group) would provide 80% power.

Eligible patients were ≥ 18 and ≤ 75 years of age and had eosinophilic (defined as having blood eosinophils ≥ 300 cells/ μ L and/or fractional exhaled nitric oxide [FENO] concentration ≥ 35 parts per billion), persistent asthma that was inadequately controlled despite treatment with inhaled corticosteroids $\pm$ a long-acting beta-2-agonist $\pm$ montelukast. Patients had to have BD reversibility ($\geq 12\%$ relative change and ≥ 200 mL change in FEV₁ postbronchodilator [postBD]) and were excluded if they smoked. Study agent was discontinued in the event of 2 severe asthma exacerbations or a single exacerbation requiring hospitalization or treatment with systemic corticosteroids for >30 days. A severe asthma exacerbation was defined as requiring the use of systemic corticosteroids (as tablets, suspension, or injection) for $\geq$ three consecutive days (courses of systemic corticosteroids separated by $\geq$ seven days were considered as separate severe exacerbation events), administration of a depot preparation of systemic corticosteroids, hospitalization, or prolongation of hospitalization. Safety data were reviewed on a routine basis by an unblinded independent data monitoring committee.

Study Assessments

Efficacy assessments included preBD and postBD spirometry and patient-reported outcomes including Asthma Control Questionnaire (ACQ), daily asthma symptom diaries, and asthma exacerbations. Biomarker assessments included evaluation of serum C-reactive protein (CRP), immunoglobulin E (IgE), CCL17/TARC,

and CCL26/eotaxin-3; cell differentials; blood lymphocyte flow cytometry; and FENO. Safety was monitored by adverse event reporting, spirometry, electrocardiograms (ECGs), and laboratory assessments, including analyses of clinical chemistry and hematology and urinalysis. ECGs at approximate time of maximum plasma concentration (2 hours after dosing) were performed at steady state (Week 2). Peak flow and asthma symptoms were recorded twice daily at home using electronic devices. Careful monitoring for renal toxicity with frequent chemistry, urinalysis, and urine protein evaluations was also conducted.

Statistical Analyses

Efficacy

All efficacy analyses were performed on the modified intent-to-treat analysis set, which included all randomized patients who received at least one dose of study agent and had at least one posttreatment efficacy measurement. The baseline measurement for spirometry assessments was defined as the average of all valid pretreatment assessments. The baseline measurement for other assessments was generally defined as the closest measurement taken prior to the first administration of study agent.

The primary endpoint was the change from baseline in preBD percent-predicted FEV₁ at Week 16. Extensive subgroup analyses on the primary endpoint were also planned in subgroups defined by baseline demographic characteristics, baseline disease characteristics, and previous treatment to identify potential population subgroups more clinically responsive to treatment. The major secondary endpoints included change from baseline in the following parameters at Week 16: postBD percent-

131 predicted FEV₁ and the patient-reported outcome asthma assessments ACQ, weekly
132 average of Daytime Asthma Diary Symptom Score, weekly average of Nighttime
133 Asthma Diary Symptom Score, and weekly average of number of puffs in a day that
134 rescue medication was used. Number of severe exacerbations was also predefined as
135 another endpoint.

136 Both treatment failure rules, which assigned unfavorable values to the period
137 when patients took certain prohibited medications, and a last observation carried
138 forward approach, which used the last available posttreatment measurement as the
139 Week 16 value, were applied to the primary endpoint unless otherwise specified.
140 Patients who did not withhold short-acting beta agonist and/or long-acting beta-2
141 agonist windows at Week 16 were to have their last observation carried over when
142 these medications were withheld.

143 The primary and major secondary endpoints were analyzed by using an analysis
144 of covariance (ANCOVA) model, which included treatment and intensity of background
145 asthma medication at baseline (ie, the stratification factor for randomization) as fixed
146 factors and baseline as a covariate. Treatment effects were estimated based on the
147 least-square (LS) mean of the difference. The study was considered positive if the
148 primary analysis achieved statistical significance at the 0.05 level. If non-normality was
149 observed, appropriate nonparametric tests were to be used to evaluate the differences
150 between treatments. A negative binomial regression model was applied to compare the
151 difference in the number of severe asthma exacerbations between treatments.

152 *Biomarkers*

153 Changes in biomarkers were compared between the toreforant and placebo
154 groups to evaluate the significance of pharmacodynamic responses. A contrast dataset
155 for within-patient changes in biomarkers was generated from log₂-transformed data,
156 with the difference between the specified time points and baseline calculated for each
157 patient and time point (ie, log₂ transform of ratio of time X over baseline). General linear
158 model analyses were performed with the treatment group variable as the fixed factor,
159 with estimates set as comparisons between the active treatment group and placebo,
160 with contrast coefficients of +1 and -1, respectively. Missing or failed measurements
161 were kept as missing values.

162 *Safety*

163 Safety analyses were based on the actual treatment received. Treatment-
164 emergent adverse events were summarized by treatment group and Medical Dictionary
165 for Regulatory Activities system organ class and preferred terms. All reported adverse
166 events with onset on or after the first study agent administration were included in the
167 analysis.

168 RESULTS

169 Patient Disposition and Disease Characteristics

170 A total of 165 patients were randomized (83 to the placebo group and 82 to the
171 toreforant group) from 04 September 2013 (first patient randomized) and followed until
172 23 July 2015 (last patient, last visit) (Figure 2). A total of 32 patients discontinued the
173 study; 21.7% from the placebo group and 17.1% from the toreforant group. More
174 patients in the placebo group than in the toreforant group discontinued the study due to
175 adverse events (4.8% vs 2.4%, respectively). Four patients (4.8%) from each group
176 discontinued the study because they experienced two severe asthma exacerbations.

177 Demographic characteristics were similar between groups with respect to age,
178 body mass index, and race. In both groups, about half of the patients were female
179 (55.4% in the placebo group and 48.8% in the toreforant group) and most were white
180 (96.4% in the placebo group and 89.0% in the toreforant group) (Table 1). Baseline
181 disease characteristics were generally similar between groups, although no hypothesis
182 testing was conducted, and were consistent with moderate-to-severe, persistent,
183 uncontrolled asthma. The placebo group had numerically higher mean Nighttime
184 Asthma Diary Symptoms Scores compared with the toreforant group (0.39 vs 0.19,
185 respectively). More patients in the toreforant group than in the placebo group used
186 systemic steroids (28.0% vs 15.9%, respectively) and had an asthma-related
187 emergency room visit (9.8% vs 3.7%, respectively) in the past 12 months.

188 Efficacy

189 There was no significant difference between groups in the primary endpoint,
190 preBD percent-predicted FEV₁. The LS mean of the change from baseline in this
191 endpoint at Week 16 was 3.83% (standard error [SE] 1.155%) for the placebo group
192 and 3.64% (SE 1.151%) for the toreforant group (difference in LS means, -0.19%; $P =$
193 .90) (Table 2). Furthermore, there was no significant change from baseline in the preBD
194 percent-predicted FEV₁ at any time point (Figure 3). Preplanned subgroup analyses on
195 patients who only met FENO criteria also did not show a significant difference with
196 toreforant ($n = 27$) compared with placebo ($n = 26$) on the primary endpoint (estimated
197 treatment difference at Week 16 was 3.20%, $P = .2051$). There was no significant
198 treatment benefit observed in any of the other subgroups tested (data not shown).

199 Similarly, there was no significant difference between groups at Week 16 in the
200 changes from baseline in the major secondary endpoints of postBD FEV₁, ACQ,
201 Daytime and Nighttime Asthma Diary Symptom Scores, number of puffs in a day that
202 rescue medication was used, and number of severe asthma exacerbations ($P \geq .30$)
203 (Table 3). The data at Week 24 were similar to the data at Week 16 (data not shown).

204 Biomarkers

205 No pharmacodynamic changes in clinical biomarkers and serum analytes were
206 observed at Week 16 (data not shown). Toreforant treatment was not associated with
207 decreases in eosinophilic or type 2 inflammation biomarkers (FENO, blood B cells,
208 serum CRP, IgE, serum CCL17/TARC, and serum CCL26/eotaxin-3), and there was no
209 association of biomarkers with clinical response.

210 Safety

211 Mean duration of treatment was 148.26 (SD 46.51) days in the placebo group
212 and 155.76 (SD 33.78) days in the toreforant group. The most common adverse event
213 in both groups was asthma, which occurred more frequently in the toreforant group than
214 in the placebo group (29.3% vs 24.4%, respectively). Headache and upper respiratory
215 tract infection also occurred more frequently in the toreforant group than in the placebo
216 group (9.8% vs 1.2% and 11.0% vs 7.3%, respectively) (Table 4).

217 Discontinuations of study treatment due to one or more adverse events were
218 more common in the placebo group than in the toreforant group (9.8% vs 7.3%,
219 respectively), and 2.4% of patients in each group had a dose interruption due to one or
220 more adverse events. Two patients in the placebo group and five patients in the
221 toreforant group experienced an asthma-related emergent healthcare visit. Overall,
222 there were no clinically concerning changes in hematology, chemistry, or urinalysis
223 values, ECGs, or vital signs over time. No deaths or serious adverse events were
224 reported at any time point.

225

226 DISCUSSION

227 This study assessed the efficacy and safety of once-daily oral administration of
228 the H₄R antagonist toreforant in patients with uncontrolled, eosinophilic, persistent
229 asthma. In a previous Phase 2a study,²⁵ treatment with another H₄R antagonist
230 (JNJ-39758979) in patients with uncontrolled asthma using only short-acting beta-2-
231 agonists resulted in nominally significant improvements in preBD FEV₁ in subsets of
232 patients with elevated exhaled nitric oxide, sputum eosinophils, or blood eosinophils at
233 baseline (post hoc analyses). The development of JNJ-39758979 was terminated due to
234 safety issues.²⁶ In the prospective study presented here, which included only patients
235 with blood eosinophils ≥ 300 cells/ μ L and/or FENO concentration ≥ 35 parts per billion on
236 inhaled corticosteroids $\pm$ a long-acting beta-2-agonist $\pm$ montelukast, the H₄R antagonist
237 toreforant failed to demonstrate a statistically significant difference from placebo in the
238 primary endpoint of change from baseline preBD percent-predicted FEV₁ at Week 16 in
239 the overall population and in any of the subgroups tested. These results were consistent
240 across the major secondary endpoints of the study. Furthermore, consistent with the
241 lack of clinical efficacy observed in this trial, there was also a lack of significant
242 pharmacodynamic effects on clinical biomarkers and serum analytes.

243 There were, however, several notable differences between this study and the
244 previous H₄R antagonist study in asthma. First, the chemical properties of toreforant are
245 distinct from those of the H₄R antagonist previously evaluated in uncontrolled, untreated
246 asthma (JNJ-39758979).²⁵ Differences in pharmacology and biodistribution between the
247 two classes could potentially affect the biological and clinical impact of the different
248 antagonists tested. It is also possible that the toreforant dose chosen was simply

inadequate to achieve near-complete inhibition of H₄R. The dose chosen was likely to be close to the maximum dose that would be safe in a general asthma population, given that much higher doses of toreforant were associated with modest increases in QT interval in a Phase 1 study.²³ The percent receptor occupancy that might be needed to see a clinically meaningful effect is unknown, but pharmacokinetic/pharmacodynamic modeling would suggest that this dose likely did not provide much more than 50% inhibition at steady state in the pharmacodynamic assay used in the Phase 1 study.²³ The dose of the other H₄R antagonist (JNJ-39758979 300 mg once daily) tested in the previous Phase 2a study²⁵ was likely sufficient to provide >90% inhibition in the pharmacodynamic assay.¹⁷

Another major difference between the studies is that the patients in the first study were not using asthma controller medications (eg, inhaled corticosteroids), whereas the patients in this study had uncontrolled asthma despite being on background inhaled corticosteroids ± long-acting beta-2-agonist ± montelukast. It is possible that the pathophysiology driving the disease is different in these two populations and that the H₄R plays a role only in the former. It is also possible that the effects of inhaled corticosteroids and long-acting beta-2-agonists overlap with those of H₄R antagonism, in which case toreforant would be redundant in this study population.

Notably, for a range of reasons, demonstration of benefit in moderate-to-severe asthma populations predominantly treated with inhaled corticosteroid/long-acting beta-2-agonist combinations has proven challenging for therapeutic candidates and marketed asthma therapies alike.²⁷⁻²⁹ However, we believe the eosinophilic asthma population targeted in this study was an appropriate population in which to assess

toreforant. Similarly, despite some improvements seen in the placebo group in measures such as ACQ, rescue use, and symptom scores, based on the totality of the data, we believe the results are interpretable and not confounded.

The results of the current study indicate that, although generally safe and well tolerated, toreforant failed to provide therapeutic benefit in this population of patients with uncontrolled, eosinophilic, persistent asthma, most of whom were treated with inhaled corticosteroids and long-acting beta-2-agonists. Based on these data, further clinical study of toreforant in the treatment of asthma has been discontinued. However, given that dosing of toreforant may have been insufficient to provide full inhibition of H₄R in vivo and the fact that efficacy was seen with another H₄R antagonist in a slightly different asthma population, it remains to be seen if substantial or complete blockade of the H₄R might provide benefit in certain asthma populations. In light of potential dose limitations for toreforant, evaluation of agents allowing higher dosing may be needed to definitively demonstrate efficacy or inefficacy of H₄R blockade in persistent eosinophilic asthma.

ACKNOWLEDGMENTS

Writing support was provided by Holly Capasso-Harris, PhD, of Synchrogenix, a Certara Company.

REFERENCES

1. Broide DH, Gleich GJ, Cuomo AJ, et al. Evidence of ongoing mast cell and eosinophil degranulation in symptomatic asthma airway. *J Allergy Clin Immunol.* 1991;88:637-648.
2. Casale TB, Wood D, Richerson HB, et al. Elevated bronchoalveolar lavage fluid histamine levels in allergic asthmatics are associated with methacholine bronchial hyperresponsiveness. *J Clin Invest.* 1987;79:1197-1203.
3. Jarjour N, Calhoun W, Schwartz L, Busse W. Elevated bronchoalveolar lavage fluid histamine levels in allergic asthmatics are associated with increased airway obstruction. *Am Rev Respir Dis.* 1991;144:83-87.
4. Liu MC, Bleecker ER, Lichtenstein LM, et al. Evidence for elevated levels of histamine, prostaglandin D₂, and other bronchoconstricting prostaglandins in the airways of subjects with mild asthma. *Am Rev Respir Dis.* 1990;142:126-132.
5. Wardlaw AJ, Dunnette S, Gleich GJ, Collins JV, Kay AB. Eosinophils and mast cells in bronchoalveolar lavage in subjects with mild asthma. Relationship to bronchial hyperreactivity. *Am Rev Respir Dis.* 1988;137:62-69.
6. Wenzel SE, Fowler AA, III, Schwartz LB. Activation of pulmonary mast cells by bronchoalveolar allergen challenge. In vivo release of histamine and tryptase in atopic subjects with and without asthma. *Am Rev Respir Dis.* 1988;137:1002-1008.
7. Busse WW, Swenson CA. The relationship between plasma histamine concentrations and bronchial obstruction to antigen challenge in allergic rhinitis. *J Allergy Clin Immunol.* 1989;84:658-666.

8. Akagi K, Townley RG. Spontaneous histamine release and histamine content in normal subjects and subjects with asthma. *J Allergy Clin Immunol.* 1989;83:742-749.
9. Leopold JD, Hartley JP, Smith AP. Effects of oral H1 and H2 receptor antagonists in asthma. *Br J Clin Pharmacol.* 1979;8:249-251.
10. Nogrady SG, Hahn AG. H2-receptor blockade and exercise-induced asthma. *Br J Clin Pharmacol.* 1984;18:795-797.
11. Van Ganse E, Kaufman L, Derde MP, Yernault JC, Delaunois L, Vincken W. Effects of antihistamines in adult asthma: a meta-analysis of clinical trials. *Eur Respir J.* 1997;10:2216-2224.
12. Alfon J, Ardanaz N, Gil-Torregrosa B, et al. UR-60427, a novel H4 receptor-inverse agonist that shows good efficacy in a rat asthma model. *Inflamm Res.* 2010;59(Suppl 2):S199-S200.
13. Beermann S, Glage S, Jonigk D, Seifert R, Neumann D. Opposite effects of mepyramine on JNJ 7777120-induced amelioration of experimentally induced asthma in mice in sensitization and provocation. *PLoS One.* 2012;7:e30285.
14. Cowden JM, Riley JP, Ma JY, Thurmond RL, Dunford PJ. Histamine H4 receptor antagonism diminishes existing airway inflammation and dysfunction via modulation of Th2 cytokines. *Respir Res.* 2010;11:86.
15. Dunford PJ, O'Donnell N, Riley JP, Williams KN, Karlsson L, Thurmond RL. The histamine H₄ receptor mediates allergic airway inflammation by regulating the activation of CD4⁺ T cells. *J Immunol.* 2006;176:7062-7070.

16. Somma T, Cinci L, Formicola G, et al. A selective antagonist of histamine H4 receptors prevents antigen-induced airway inflammation and bronchoconstriction in guinea pigs: involvement of lipocortin-1. *Br J Pharmacol.* 2013;170:200-213.
17. Thurmond RL, Chen B, Dunford PJ, et al. Clinical and preclinical characterization of the histamine H4 receptor antagonist JNJ-39758979. *J Pharmacol Exp Ther.* 2014;349:176-184.
18. Lundberg K, Broos S, Greiff L, Borrebaeck CAK, Lindstedt M. Histamine H4 receptor antagonism inhibits allergen-specific T-cell responses mediated by human dendritic cells. *Eur J Pharmacol.* 2011;651:197-204.
19. Woodruff PG, Modrek B, Choy DR, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med.* 2009;180:388-395.
20. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med.* 2015;3:355-366.
21. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet.* 2012;380:651-659.
22. Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med.* 2013;368:2455-2466.

23. Thurmond RL, Chen B, Dunford PJ, et al. Pharmacology and clinical activity of toreforant, a histamine H₄ receptor antagonist. *Ann Pharmacol Pharm.* 2017;2:1013.
24. Thurmond RL, Greenspan A, Radziszewski W, et al. Toreforant, a histamine H₄ receptor antagonist, in patients with active rheumatoid arthritis despite methotrexate therapy: results of 2 phase II studies. *J Rheumatol.* 2016;43:1637-1642.
25. Kollmeier A, Greenspan A, Xu XL, et al. Phase 2a, randomized, double-blind, placebo-controlled, multicenter, parallel-group study of an H₄R-antagonist (JNJ-39758979) in adults with uncontrolled asthma. *Clin Exp Allerg.* 2018;Apr 23 [Epub ahead of print].
26. Murata Y, Song M, Kikuchi H, et al. Phase 2a, randomized, double-blind, placebo-controlled, multicenter, parallel-group study of a H₄ R-antagonist (JNJ-39758979) in Japanese adults with moderate atopic dermatitis. *J Dermatol.* 2015;42:129-139.
27. Erpenbeck VJ, Popov TA, Miller D, et al. The oral CRTh₂ antagonist QAW039 (fevipiprant): a phase II study in uncontrolled allergic asthma. *Pulm Pharmacol Ther.* 2016;39:54-63.
28. Hanania NA, Korenblat P, Chapman KR, et al. Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials. *Lancet Respir Med.* 2016;4:781-796.

29. Robinson DS, Campbell D, Barnes PJ. Addition of leukotriene antagonists to therapy in chronic persistent asthma: a randomised double-blind placebo-controlled trial. *Lancet*. 2001;357:2007-2011.

FIGURE LEGENDS

Figure 1. Overview of study design

DBL, database lock; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; LABA, long-acting beta-2-agonist; N, patients randomized and treated in a group; n, a subset of patients from a group.

Figure 2. Consolidated Standards of Reporting Trials (CONSORT) diagram

^aOne patient randomized to the placebo group was never treated.

^bIncludes four patients who discontinued study participation due to two asthma exacerbations.

AE, adverse event; D/C, discontinued.

Figure 3. Summary of change from baseline in preBD percent-predicted FEV₁ over time

BD, bronchodilator; FEV₁, forced expiratory volume in 1 second; N, patients randomized and treated in a group.

TABLES

Table 1. Demographic and baseline characteristics

	Placebo N = 83	Toreforant N = 82	Total N = 165
Median age, y	49.0	49.5	49.0
Female, n (%)	46 (55.4)	40 (48.8)	86 (52.1)
Race, n (%)			
White	80 (96.4)	73 (89.0)	153 (92.7)
Black	3 (3.6)	6 (7.3)	9 (5.5)
Other ^a	0	3 (3.7)	3 (1.8)
Median BMI, kg/m ²	27.6	26.6	27.4
Mean (SD) preBD FEV ₁			
%	62.63 (9.91)	62.77 (10.53)	62.70 (10.19)
L	2.09 (0.58)	2.11 (0.62)	2.10 (0.60)
Mean (SD) postBD FEV ₁			
%	76.38 (12.79)	75.50 (13.24)	75.94 (12.98)
L	2.55 (0.73)	2.54 (0.75)	2.54 (0.74)
Mean (SD) ACQ score	2.54 (0.624)	2.43 (0.512)	2.48 (0.572)
Mean (SD) Daytime Asthma Diary	0.54 (0.472)	0.42 (0.350)	0.48 (0.419)
Symptom score			
Mean (SD) Nighttime Asthma	0.39 (0.449)	0.19 (0.246)	0.29 (0.375)
Diary Symptom score			
Background asthma medication			
use, n (%)			
High-dose ICS	20 (24.1)	11 (13.6)	31 (18.9)
Montelukast	15 (18.1)	11 (13.4)	26 (15.8)
LABA	66 (79.5)	66 (80.5)	132 (80.0)
Systemic steroids, n (%)	13 (15.9)	23 (28.0)	36 (22.0)
Asthma-related ER visits, n (%)	3 (3.7)	8 (9.8)	11 (6.7)

Asthma-related hospitalization, n	1 (1.2)	1 (1.2)	2 (1.2)
(%)			

^aThe values used for other races were for Asian and Other.

ACQ, Asthma Control Questionnaire; BD, bronchodilator; BMI, body mass index; ER, emergency room; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; LABA, long-acting beta-2-agonist; n, a subset of patients from a group; N, patients randomized and treated in a group; n, a subset of patients from a group; SD, standard deviation; y, year(s).

413 Table 2. Summary of change from baseline in preBD percent-predicted FEV₁ at Week
 414 16
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	Placebo N = 82	Toreforant N = 82
PreBD percent-predicted FEV ₁ , %		
Baseline, mean (SD)	62.84 (9.773)	62.77 (10.528)
Week 16, mean (SD)	66.59 (13.379)	66.31 (14.659)
Change from baseline, %		
Mean (SD)	3.72 (8.976)	3.53 (9.203)
LS means (SE)	3.83 (1.155)	3.64 (1.151)
Difference LS means (SE)		-0.19 (1.431)
<i>P</i> value		0.90
95% CI		-3.01, 2.64

416 BD, bronchodilator; CI, confidence interval; FEV₁, forced expiratory volume in 1 second;
 417 LS, least-square; N, patients randomized and treated in a group; SD, standard
 418 deviation; SE, standard error.

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421 Table 3. Summary of change from baseline in secondary efficacy endpoints at Week 16

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	Placebo N = 82	Toreforant N = 82
ACQ		
Mean (SD)	-0.77 (0.734)	-0.65 (0.743)
LS means (SE)	-0.77 (0.090)	-0.70 (0.090)
Difference LS means (SE)		0.07 (0.113)
P value		0.51
95% CI		-0.15, 0.30
PostBD percent-predicted FEV ₁ , %		
Mean (SD)	-1.15 (6.121)	-0.62 (6.827)
LS means (SE)	-0.72 (0.836)	-0.18 (0.820)
Difference LS means (SE)		0.54 (1.021)
P value		0.60
95% CI		-1.48, 2.55
Daytime Asthma Diary Symptom score		
Mean (SD)	-0.25 (0.406)	-0.20 (0.349)
Difference median		0.05
P value		0.79
95% CI		-0.06, 0.14
Nighttime Asthma Diary Symptom Score		
Mean (SD)	-0.20 (0.359)	-0.11 (0.228)
Difference median		0.03
P value		0.30
95% CI		0.00, 0.09
Average number of puffs in a day that rescue medication is used		

Mean (SD)	-0.86 (1.595)	-0.82 (1.856)
Difference median		0.26
<i>P</i> value		0.56
95% CI		-0.14, 0.67
Number of severe exacerbations		
Mean (SD)	0.26 (0.584)	0.33 (0.630)
Ratio of exacerbation rates		0.84
95% CI		0.45, 1.56
<i>P</i> value		0.59

ACQ, asthma control questionnaire; BD, bronchodilator; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; LS, least-square; N, patients randomized and treated in a group; SD, standard deviation; SE, standard error.

428 Table 4. Treatment-emergent adverse events in at least 5% of patients through Week
 429 28
 430

	Placebo	Toreforant
	N = 82	N = 82
Any adverse event	59 (72.0)	61 (74.4)
Asthma	20 (24.4)	24 (29.3)
Nasopharyngitis	11 (13.4)	10 (12.2)
Upper respiratory tract infection	6 (7.3)	9 (11.0)
Bronchitis	8 (9.8)	1 (1.2)
Headache	1 (1.2)	8 (9.8)
Sinusitis	6 (7.3)	3 (3.7)

431 All values are n (%).

432 N, patients randomized and treated in a group; n, a subset of patients from a group.

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