# Oral Dexpramipexole Efficacy in Lowering Blood Eosinophils in Patients with Moderate to Severe Uncontrolled Eosinophilic Asthma

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## Introduction

Dexpramipexole is an oral investigational drug that lowers blood and tissue eosinophils by inhibiting eosinophil maturation. Dexpramipexole has been shown to significantly lower eosinophils in 4 previous clinical trials in over 1000 subjects with ALS, eosinophilic chronic rhinosinusitis with nasal polyps, and hypereosinophilic syndrome.

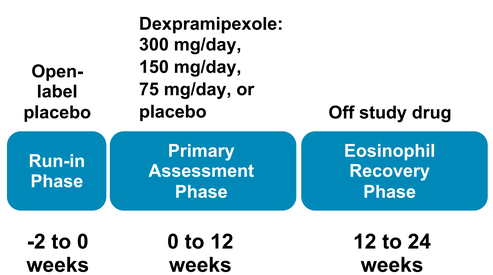
## Objectives

The EXHALE trial aimed to investigate dexpramipexole dose-dependent eosinophil lowering and to examine clinical efficacy, safety, and tolerability in adults with moderate-severe eosinophilic asthma.

## Study Design/Methods

• EXHALE was a randomized, double-blind, placebo-controlled trial of dexpramipexole in eosinophilic asthma, NCT04046939 (Figure 1).
**Key inclusion criteria:**
• Age 18-75 years, GINA steps 3-5, on daily inhaled corticosteroid plus long-acting beta agonist.
• Pre-bronchodilator FEV1 <80% & ≥40% predicted, with reversibility ≥12% and ≥200 mL (at Screening).
• Absolute eosinophil count (AEC) ≥300/μL (at Screening).
• Asthma control questionnaire-7 (ACQ-7) ≥1.5 (at Screening).
• Adherence ≥85% by Smart Bottle during the open-label placebo Run-in Phase.
**Endpoints:**
Primary Endpoint
• Change in blood absolute eosinophil count from baseline (BL) to Week 12 (W12)
Secondary Endpoints
• Change in pre-bronchodilator (pre-BD) FEV1, from BL to Week 12
• Incidence and severity of AEs, changes in vital signs, clinical laboratory safety tests, physical examination, body weight, and ECGs
**Statistics:**
Change from baseline in AEC and FEV1 were analyzed with a mixed-effect model for repeated-measures with terms for baseline, Global Initiative for Asthma (GINA) treatment steps 3-5 , treatment, visit, treatment by visit interaction, and baseline by visit interaction as fixed effects, and subject as a random effect. Absolute eosinophil count was analyzed on the log10 scale with estimates transformed back to the original scale to present estimated geometric means for treatment effects and ratio of geometric means (GM) of treatment effects versus placebo along with 95% CI. The data in this poster reflect an analysis performed after the last subject completed the Week 12 primary outcome visit. As such, data from time points after Week 12 may reflect small differences from the final data set.

## Fig. 1 EXHALE study design




## Results

### Table 1 Baseline demographics and clinical characteristics

• 534 subjects were screened, of which 103 subjects were randomized and received study drug. Of those, 99 subjects (96%) completed the primary assessment phase on drug. 74 of 76 (97%) of dexpramipexole-treated subjects completed the primary assessment phase on drug.

| Demographics | Statistic | Placebo (N = 27) | 75 mg/day dexpramipexole (N = 22) | 150 mg/day dexpramipexole (N = 26) | 300 mg/day dexpramipexole (N = 28) |
|---|---|---|---|---|---|
| **Age (years)** | Mean | 45.8 | 46.6 | 44.5 | 44.6 |
| **Sex** | | | | | |
| Female | n (%) | 17 (63.0) | 11 (50.0) | 14 (53.8) | 12 (42.9) |
| **Race** | | | | | |
| White | n (%) | 21 (77.8) | 17 (77.3) | 16 (61.5) | 22 (78.6) |
| Black or African American | n (%) | 4 (14.8) | 4 (18.2) | 6 (23.1) | 6 (21.4) |
| Asian | n (%) | 1 (3.7) | 1 (4.5) | 2 (7.7) | --- |
| **Ethnicity** | | | | | |
| Hispanic or Latino | n (%) | 2 (7.4) | 3 (13.6) | 3 (11.5) | 3 (10.7) |
| **Blood AEC (per μL)** | Geo Mean | 382 | 404 | 374 | 438 |
| **Pre-Bronchodilator FEV1 (L)** | Mean | 2.05 | 1.98 | 2.03 | 2.11 |
| **Pre-BD FEV1 (% predicted)** | Mean | 61.0 | 59.8 | 60.3 | 60.9 |
| **Inhaled corticosteroid dose** | | | | | |
| **Low** | n (%) | 10 (37.0) | 8 (36.4) | 4 (15.4) | 3 (10.7) |
| **Medium** | n (%) | 14 (51.9) | 9 (40.9) | 15 (57.7) | 19 (67.9) |
| **High** | n (%) | 3 (11.1) | 5 (22.7) | 7 (26.9) | 6 (21.4) |
| **Total ACQ-6 score** | Mean | 2.30 | 2.28 | 1.94 | 2.13 |
| **Hx of nasal polyps** | n (%) | 5 (18.5) | 2 (9.1) | 0 (0) | 2 (7.1) |

### Fig. 2 Primary endpoint, change in eosinophil count

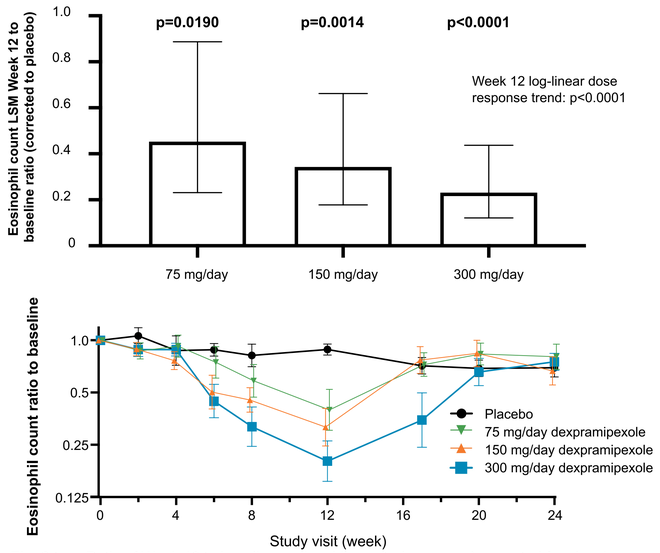



**Fig. 2 top:** Ratio of Week 12 to baseline eosinophil counts (geo mean) corrected for placebo. Data shown are least square mean (LSM) values, derived using a mixed-effects model with repeated measures. Error bars represent 95% confidence intervals, p values vs. placebo.
**Fig. 2 bottom**: Ratio of eosinophil counts to baseline value. Error bars represent standard error.

### Fig. 3 Pre-BD FEV1, change from baseline

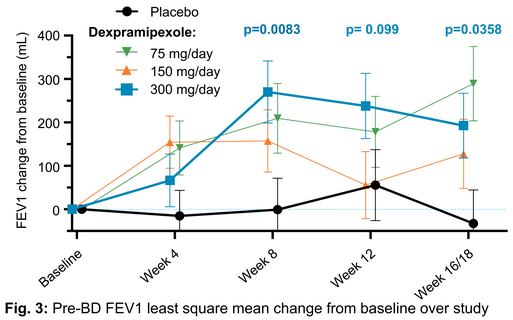



**Fig. 3:** Pre-BD FEV1 least square mean change from baseline over study visits, using a mixed-effects model with repeated measures. Error bars represent standard error, p values shown for 300 mg/day arm vs. placebo.

### Table 2 Pre-BD FEV1 pooled analyses across study arms & visits

| Study arms | Visits | ΔFEV1 vs Placebo (mL) LSM (SEM) | P-value vs Placebo |
|---|---|---|---|
| **75 mg/day** | **Weeks 4, 8, 12, & 16/18 pooled** | **205** (86.5) | **0.0198** |
| **150 mg/day** | **Weeks 4, 8, 12, & 16/18 pooled** | **128** (84.6) | **0.1337** |
| **300 mg/day** | **Weeks 4, 8, 12, & 16/18 pooled** | **182** (83.2) | **0.0309** |
| **75, 150, & 300 mg/day pooled** | **Week 4** | **139** (68.0) | **0.0448** |
| **75, 150, & 300 mg/day pooled** | **Week 8** | **213** (83.4) | **0.0123** |
| **75, 150, & 300 mg/day pooled** | **Week 12** | **99** (92.4) | **0.285** |
| **75, 150, & 300 mg/day pooled** | **Week 16/18** | **236** (89.0) | **0.0094** |
| **75, 150, & 300 mg/day pooled** | **Weeks 4, 8,12, & 16/18 pooled** | **172** (69.0) | **0.0145** |

Pre-BD FEV1 placebo-corrected change from baseline, pooling data across study arms and/or visits, as noted. Data shown are least square mean values, derived using a mixed-effects model with repeated measures.

### Fig. 4 Pre-BD FEV1 subgroup analysis, hematologic high-responders

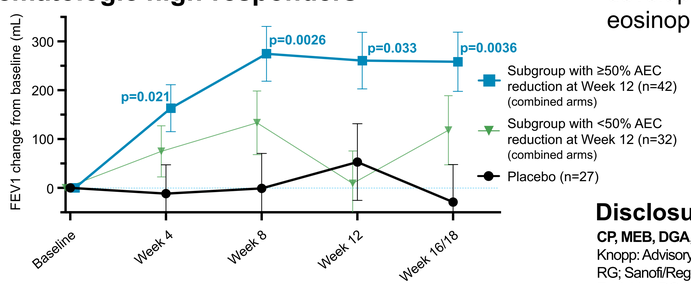



**Fig. 4:** Pre-BD FEV1 change from baseline over study visits. Dexpramipexole study arms were combined and divided into hematologic high- and low- responder subgroups based on ≥ or < 50% reduction in eosinophil count from baseline to Week 12, respectively. Data shown are least square means derived using a mixed-effects model with repeated measures. Error bars represent standard error, p values shown for the high-responder group vs. placebo.

### Table 3 Treatment-emergent adverse events

| | Placebo (N=27) | 75 mg/day dexpramipexole (N=22) | 150 mg/day dexpramipexole (N=26) | 300 mg/day dexpramipexole (N=28) |
|---|---|---|---|---|
| | Number of subjects (%) | Number of subjects (%) | Number of subjects (%) | Number of subjects (%) |
| **Overall** | 9 (33.3%) | 7 (31.8%) | 12 (46.2%) | 11 (39.3%) |
| **Serious** | --- | --- | --- | --- |
| **Leading to Discontinuation** | 1 (3.7%) | --- | --- | --- |
| **Leading to Death** | --- | --- | --- | --- |
| **Severity** | | | | |
| Mild | 7 (25.9%) | 4 (18.2%) | 6 (23.1%) | 8 (28.6%) |
| Moderate | 5 (18.5%) | 5 (22.7%) | 8 (30.8%) | 6 (21.4%) |
| Severe | | | 1 (3.8%) | |

**Treatment-emergent adverse events** from baseline to 30 days after last dose of study drug.

## Conclusions

- Dexpramipexole demonstrated highly significant, dose dependent eosinophil lowering
- Eosinophil lowering increased during the primary assessment phase and was maximal at Week 12
- Eosinophils returned to baseline in the recovery phase
- Dexpramipexole produced large-magnitude increases in FEV1 across study arms and time points
- The magnitude of FEV1 improvement was comparable to currently approved biologics
- FEV1 improvement was seen by Week 4 and was sustained 4-6 weeks after stopping drug (Week 16/18)
- Dexpramipexole was well tolerated, with adverse events evenly distributed between drug and placebo arms
- These findings strongly support continued clinical development of dexpramipexole as a first-in-class oral eosinophil-lowering drug in asthma

### Disclosures

**CP, MEB, DGA**, and **JLM** are employees of Knopp Biosciences and own stock or stock options in Knopp. **RA**: Knopp: Advisory board (AB); AstraZeneca: AB, research grant (RG), speaker (S); RIFM: AB, RG; Equillium: AB, RG; Sanofi/Regeneron: AB, S; Genentech: S, RG; Novartis: RG; Optikira: RG; Medimmune: RG; Maven: RG; Evelobio: RG; Johnson & Johnson: RG; Theravance: AB. **SS** has provided advisory services for Knopp, GSK, Novartis, Astra Zeneca, CSL Behring, ERT Medical, Owlstone Medical, Mundiphrama, Chiesi, Boehringer Ingelheim.

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### References

1. Ortega et al. N Engl J Med. 2014 Sep 25;371(13):1198-207. 2. Bleecker et al. Lancet. 2016 Oct 29;388(10056):2115-2127. 3. FitzGerald et al. Lancet. 2016 Oct 29;388(10056):2128-2141.