SYNOPSIS

Name of Sponsor/Company:	Fake Pharmaceuticals, Inc.
Name of Finished Product:	Pretendlukast
Name of Active Ingredient:	Pretendlukast
Protocol No: FPI308	
Title of Study: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Pretendlukast in Adult Patients with Asthma who are on Beta-2-adrenoreceptor Agonists	
Phase of Development: III	
Principal Investigator: Wayne Breatheright, MD, PhD, University of Arizona 127 participating investigative sites in North and South America (Appendix 16.1.4)	
Publications: None	
Study Period: 22 January 2011 to 18 October 2012	
Objectives ***Primary:*** • To evaluate the efficacy of pretendlukast for the treatment of asthma in adult patients, as measured by change in trough percent of predicted forced expiratory volume in one second (FEV1) from baseline to Week 36 ***Secondary:*** • To evaluate the efficacy of pretendlukast as measured by change in trough percent of predicted peak expiratory flow rate (PEFR) from baseline to Week 36 • To evaluate the efficacy of pretendlukast as measured by change in total score on Asthma Control Questionnaire (ACQ) from baseline to Week 36 • To evaluate the efficacy of pretendlukast as measured by percentage of subjects demonstrating asthma exacerbation within 45 days • To evaluate the safety of pretendlukast • To assess the plasma pharmacokinetics (PK) of pretendlukast • To evaluate the time to first asthma exacerbation	
Methodology: This was a multicenter, double-blind, placebo-controlled trial evaluating the safety and efficacy of pretendlukast versus placebo in adult patients with asthma on beta-adrenoreceptor agonists. Subjects were randomized in a 1:1 allocation to 50 mg daily oral pretendlukast versus matching placebo capsule. Pulmonary function testing was performed at Weeks 1, 2, 4, and every 4 weeks thereafter. Subjects were followed for 36 weeks for treatment failure, defined as an exacerbation of symptoms of asthma requiring emergent or unscheduled visit or hospitalization for asthma, or other exacerbation of asthma requiring systemic corticosteroid therapy. The ACQ was administered at baseline and every 4 weeks thereafter through Week 36. Symptoms and signs of asthma, vital signs, weight, adverse events (AEs) and clinical laboratory findings were assessed at Weeks 1, 2, 4, and every 4 weeks thereafter. Medication compliance was assessed using subject diaries and capsule counts at each visit. An interim analysis of safety was conducted after the first 75 subjects were randomized and completed the Week 4 visit, at which time 23 subjects had completed Week 36 evaluations. The Data Monitoring Committee recommended that the study continue as planned.	
Number of Subjects: The study plan was to enroll 570 subjects to ensure at least 520 evaluable subjects	

(260 per treatment arm). A total of 572 subjects were randomized and 532 completed the study.

Diagnosis and Main Criteria for Inclusion: Patients >18 years of age with asthma confirmed by National Heart Lung and Blood Institute 2007 guidelines who were currently taking beta-adrenoreceptor agonists and had screening FEV1 between 40% and 70% of individual predicted value were eligible. Patients could not have use oral or inhaled corticosteroids within 90 days prior to randomization and could not have been treated for a respiratory tract infection within 30 days prior to randomization. Patients were excluded for pregnancy, history of chronic lung disease other than asthma, acute illness, history of smoking, use of another experimental treatment for asthma within 120 days prior to randomization, or history of adverse reaction to a leukotriene receptor antagonist.

Test Product, Dose and Mode of Administration, Batch No: A 50-mg oral dose of **s**tudy drug (pretendlukast or placebo) was administered daily within 30 minutes after breakfast. Batch numbers were PLK203944 (pretendlukast) and PLG334337 (placebo).

Duration of Treatment: 36-week double-blind treatment period

Criteria for Evaluation

Efficacy: Efficacy was evaluated using pulmonary function testing, ACQ scores, and incidence of and time to exacerbation of asthma.

The efficacy population included all randomized subjects.

Safety: Safety evaluations included AEs, vital signs, clinical laboratory parameters, weight, and concomitant medications. AEs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) version 11.0 and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The safety population included all randomized subjects who received at least one dose of study drug (pretendlukast or placebo).

Pharmacokinetics: PK sampling to evaluate plasma levels of pretendlukast was performed in the first 28 subjects enrolled at each of 4 preselected clinical sites, to allow assessment of PK parameters in approximately 50 subjects on active treatment.

Statistical Methods

Primary Efficacy Analysis: The primary efficacy endpoint for this study was the change in trough individual percent of predicted FEV1, defined as the percent of predicted FEV1 at Week 36, obtained at least 23 hours after the last dose of study drug, minus the percent of predicted FEV1 at baseline within 24 hours before the first dose of study drug. Subjects without a baseline FEV1 or Week 36 FEV1 were excluded from the primary analysis.

A sensitivity analysis was performed, including all randomized subjects with a baseline FEV1 and calculating the change in trough FEV1 as the last FEV1 obtained during the study minus the FEV1 at baseline within 24 hours before the first dose of study drug. Subjects without a baseline FEV1 were excluded from the analysis.

Secondary Efficacy Analysis:

- Change in PEFR was defined as change in trough individual percent of predicted PEFR at Week 36, obtained at least 23 hours after the last dose of study drug, minus the percent of predicted PEFR obtained at baseline within 24 hours before the first dose of study drug.
- Change in ACQ score was defined as total ACQ score at Week 36 minus total score at baseline.
- Asthma exacerbation was defined as an unscheduled visit to a clinic or hospital culminating in addition of oral or inhaled corticosteroids to the treatment regimen and occurring within 45 days of randomization, or other exacerbation of asthma requiring systemic corticosteroid therapy within 45 days of randomization.
- Descriptive statistics at each time point, including changes from baseline by treatment arm, were

calculated for weight and for each vital sign and laboratory parameter. AEs were summarized at each time point and followed for 30 days after the last dose of study drug.

- Individual and treatment group mean PK parameters were calculated for subjects taking pretendlukast, including peak plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), elimination half-life ($t_{1/2}$), and area under the concentration-time curve (AUC_{0-t}).
- Kaplan-Meier methodology was used to estimate medians and confidence intervals of times to first asthma exacerbation by treatment arm. Subjects not experiencing an exacerbation were censored at Week 36. Subjects discontinuing study drug were followed until Week 36. Subjects lost to follow-up were considered to have experienced an exacerbation at the time of last contact.

Summary of Results and Conclusions

Efficacy:

- Pretendlukast demonstrated statistically significant improvement over placebo in change in percent of predicted FEV1 from baseline to Week 36. Mean (standard deviation) percent of predicted FEV1 at baseline was 69% ± 29% in the pretendlukast group and 67% ± 28% in the placebo group. Mean change in percent predicted FEV1 at Week 36 was 14.8% ± 5.5% in subjects treated with pretendlukast and 2.4% ± 5.3% in subjects treated with placebo (p = 0.046).
- Pretendlukast demonstrated a trend toward improvement over placebo in the change in percent of predicted trough PEFR from baseline to Week 36. Mean baseline percent of predicted peak flow at baseline was 72% (± 22%) in the pretendlukast group and 68% ± 24% in the placebo group. Mean change in percent predicted PEFR at Week 36 was 11.8% ± 5.1% in subjects treated with pretendlukast and 2.7% ± 4.7% in subjects treated with placebo (p = 0.071).
- Mean decreases in ACQ scores at Week 36 as compared with baseline were observed in both treatment groups and were greater among subjects treated with pretendlukast. However, the difference between treatment groups was not statistically significant. Mean baseline ACQ scores were 20.3 ±13.8 in subjects treated with pretendlukast and 19.7 ±12.0 in subjects treated with placebo. Mean change in ACQ from baseline to Week 36 was -8.9 ±4.4 in subjects treated with pretendlukast and -5.1 ±4.0 in subjects treated with placebo (p = 0.371).
- The percentage of subjects in each treatment group experiencing exacerbation of asthma within 45 days after randomization was significantly lower in subjects treated with pretendlukast (10.4% ± 4.8%) than in subjects treated with placebo (22.6% ± 6.9%; p = 0.022)
- Number of days to first asthma exacerbation was not significantly between treatment groups (215 ± 28 days in pretendlukast group versus 178 ± 39 days in placebo group; p = 0.489).

Safety:

- The most common treatment-emergent AEs were headache, nausea, and upper respiratory infection. There were more neurologic adverse events in the pretendlukast group than in the placebo group (15.1% versus 9.6%), including headache, insomnia, and dizziness.
- Eleven serious adverse events (SAEs) were observed in 8 subjects: 6 SAEs in 4 subjects the pretendlukast group and 5 SAEs in 4 subjects in the placebo group. SAEs in the pretendlukast group were wrist fracture, acute hearing loss, and acute renal failure, each of which occurred in 1 subject, and congestive heart failure, cerebrovascular accident, and asthma exacerbation, all occurring in the same subject. The asthma exacerbation was the only SAE in the pretendlukast group considered related to study drug. SAEs in the placebo group were carotid aneurysm, psoriasis, and atypical pneumonia, each of which occurred in 1 subject, and gastrointestinal bleeding and anemia, both occurring in the same subject. Atypical pneumonia was the only SAE in the placebo group considered related to study drug.
- There were no deaths. Grade 3/4 AEs were uncommon in both treatment groups. Grade 3/4 AEs reported in the pretendlukast group included acute renal failure, congestive heart failure, cerebrovascular accident, hives, and thrombocytopenia (each occurred in 1 subject).

Thrombocytopenia was considered related to study drug. Grade 3/4 AEs in the placebo group included carotid aneurysm, atypical pneumonia, septic arthritis, and hepatic failure (each occurred in 1 subject). Atypical pneumonia and hepatic failure were considered related to study drug.

- Adverse events leading to study drug discontinuation in the pretendlukast group were headache (19 subjects), insomnia (6 subjects), dizziness (4 subjects), and hives (1 subject). Adverse events leading to study drug discontinuation in the placebo group were headache (4 subjects), fatigue (4 subjects), tinnitus (1 subject), and atypical pneumonia (1 subject).
- Physical examination findings, weights, vital signs, and clinical laboratory values were unremarkable.

Pharmacokinetics:

Pretendlukast plasma concentrations reached steady state at Day 10. Elimination half-life of pretendlukast was 32.1 ± 4.8 hours. Other pharmacokinetic parameters are detailed in a separate report (Appendix 14.4).

Conclusions:

Pretendlukast is superior to placebo for treatment of adults with asthma who are on beta-adrenoreceptor agonists. The magnitude of objective response as measured by changes in pulmonary function tests compares favorably with that observed with use of other leukotriene receptor antagonists. Superiority of pretendlukast was not demonstrated on the ACQ. Pretendlukast is safe and well-tolerated in this population, but may be associated with a moderately increased incidence of headache.