SYNOPSIS

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Name of Sponsor/Company	Janssen Research & Development
Name of Finished Product	
Name of Active Ingredient(s)	JNJ-39758979

Protocol No.: 39758979ASH2001

Title of Study: A Double-Blind, Randomized, Placebo-Controlled, Parallel Group Exploratory Study of the Safety and Efficacy of JNJ-39758979 in the Treatment of Adults with Persistent Asthma

EudraCT Number: 2009-012444-16

NCT No.: NCT00946569

Clinical Registry No.: CR016423

Investigators: A list of Investigators used for this study is provided in the appendices.

Study Centers: This study was conducted in 4 countries (United States, Canada, Romania, and India). A list of study centers used in this study is provided in the appendices.

Publication (Reference): None

Study Period: 28 Jul 2009 (date of first subject informed consent) – 12 Nov 2011 (date of last observation).

Phase of Development: 2

Objectives: Primary: To evaluate the safety and efficacy (in terms of improvement in pre-bronchodilator [pre-BD] forced expiratory volume in 1 second [FEV_1]) of once daily oral administration of JNJ-39758979 in the treatment of adults with persistent asthma as defined by Global Initiative for Asthma (GINA) guidelines.

Secondary: To evaluate the efficacy of JNJ-39758979 in terms of changes in forced vital capacity (FVC), forced expiratory flow at 25% to 75% of vital capacity (FEF_{25-75}), FEV_1/FVC, Asthma Daily Diary data (AM and PM peak expiratory flow rates [PEFR], extent of albuterol/salbutamol use, presence of nocturnal awakenings, Asthma Symptom Score), and worsening of asthma; and to explore the relationship between pharmacokinetics and pharmacodynamic measurements.

Exploratory: To characterize the population PK of JNJ-39758979 and to characterize the effects of JNJ-39758979 on biomarkers of disease, including induced sputum cell counts, exhaled nitric oxide (eNO) production, immunoglobulin E (IgE), and other biomarkers.

Methodology: This was a Phase 2 double-blind, placebo-controlled, parallel group study in adults with persistent asthma. After Screening, subjects entered a 2-week single-blind placebo run-in period during which FEV_1 was measured at Week -2 and Week -1. At the end of this run-in period, subjects with FEV_1 measurements that were within an acceptable range of variability (±15%) compared with FEV_1 at the start

of the run-in period were randomized 1:1 to receive JNJ-39758979 300 mg once daily or matching placebo for 12 weeks.

The primary study endpoint was the improvement in pre-BD FEV_1 as measured by percent change from baseline in pre-BD percent predicted FEV_1 value at Week 12. Secondary efficacy endpoints included spirometry measurements, Asthma Daily Diary data, worsening of asthma, and relationship between pharmacokinetics and pharmacodynamic measurements. Exploratory endpoints included change in eNO concentration, induced sputum cell counts, IgE, and other biomarkers. Plasma concentrations were measured for PK and PK/PD evaluations. An induced sputum substudy was conducted at selected sites to characterize the effects of JNJ-39758979 on induced sputum cell counts and other biomarkers in sputum and blood.

An internal Data Monitoring Committee (DMC) composed of sponsor clinicians and a biostatistician not associated with the conduct of the study reviewed the study data. Two interim analyses were performed. The first interim analysis was a safety evaluation performed when approximately 50% of subjects completed Week 8. This interim analysis included the efficacy analysis of FEV_1 as part of safety measurement of lung function. The second interim analysis was performed when approximately 90 subjects completed the Week 8 visit and was intended to provide administrative information for the planning of the Phase 2b studies.

Number of Subjects (planned and analyzed): Planned enrollment was 100 (50 subjects per treatment group) subjects; 115 subjects were randomly assigned to and received at least 1 dose of study drug (58 in the placebo group and 57 in the JNJ-39758979 group) and were included in the primary efficacy endpoint analysis and the safety analysis.

Diagnosis and Main Criteria for Inclusion: Nonsmoking male and female subjects, aged 18 to 65 years, with a medically confirmed diagnosis of persistent asthma according to Expert Panel Report 3 (EPR-3) and GINA guidelines for at least 6 months and a chest x-ray without clinically significant abnormalities performed within the past 6 months were eligible for inclusion. Subjects also had to have an FEV_1 of 55-85% predicted measured > 6 hours after the most recent use of a bronchodilator at screening and randomization, evidence of FEV_1 reversibility at screening as demonstrated by an increase in FEV_1 of at least 12% and 200 mL 15 to 30 minutes after administration of 4 puffs (360 mcg) of albuterol/salbutamol via a metered-dose inhaler (MDI) or 2.5 mg albuterol/salbutamol nebulized solution, and a score of ≥1.5 on the Asthma Control Questionnaire (ACQ).

Test Product, Dose and Mode of Administration, Batch No.: The JNJ-39758979 tablets supplied for this study were oval shaped (6.35 mm x 14.4 mm) standard convex tablets containing 100 mg of active and microcrystalline cellulose, mannitol, crospovidone, and magnesium stearate. Lot number: A01493

Reference Therapy, Dose and Mode of Administration, Batch No.: The excipients for the matching placebo tablets were mannitol, microcrystalline cellulose, crospovidone, and magnesium stearate. Lot number: A01492

Duration of Treatment: After screening, subjects entered a 2-week single-blind placebo run-in period. At the end of the run-in period, subjects with FEV_1 measurements that were within an acceptable range of variability (±15%) compared with FEV_1 at the start of the run-in period were randomized to receive treatment with either JNJ-39758979 300 mg once daily or matching placebo once daily. The treatment period lasted 12 weeks, followed by a termination visit that occurred approximately 5 weeks after the Week 12 visit.

Criteria for Evaluation:

- Pharmacokinetics: plasma concentrations of JNJ-39758979

- Pharmacodynamics: serum samples for inflammatory biomarkers
- Efficacy: Efficacy evaluations included FEV_1, FVC, FEF_{25-75}, FEV_1/FVC, Asthma Daily Diary
- Safety: Assessment of adverse events (AEs) and clinical laboratory results, vital sign measurements, and ECGs

Statistical Methods: Categorical data are summarized using counts and percentages. Continuous variables are summarized using descriptive statistics. Comparisons between treatment groups were performed using analysis of covariance (ANCOVA), t-test, Wilcoxon rank-sum test, chi-square tests, or Fisher's exact test, depending on the nature of the data.

Sample Size Determination: Approximately 100 subjects (50 per group) were planned to be randomized into the study. Assuming a standard deviation (SD) of 15% for the primary endpoint, FEV_1 percent change from baseline, a sample size of 50 subjects per group would have 80% power to detect 8.5% improvement over placebo, at a 2-sided 0.05 alpha level. The standard deviation of 15% was observed in a similarly designed asthma study of another compound that was recently conducted by the sponsor.

RESULTS:

STUDY POPULATION

In total, 115 subjects were randomly assigned to and received at least 1 dose of study drug; 58 in the placebo group and 57 in the JNJ-39758979 group. Ninety-six subjects completed the study.

Of the 19 subjects who discontinued from the study prematurely, 10 received placebo and 9 received JNJ-39758979. The most common reason for discontinuing from the study prematurely in both treatment groups was worsening of asthma (9% and 7% in the placebo and JNJ-39758979 groups, respectively). Three subjects (1 in the placebo group and 2 in the JNJ-39758979 group) withdrew from the study due to an AE.

Baseline demographics were comparable across treatment groups; 52.2% subjects were female and 47.8% subjects were male; the mean age of subjects was 37.3 years. The majority (61.7%) of subjects were white (followed by 33.0% Asian). Subjects in the placebo group had a slightly longer history of having asthma (18.6 years) than subjects in the JNJ-39758979 group (15.9 years). FEV_1, Asthma Symptom Score, ACQ, β-agonist use, and percentage of atopic subjects based on medical history were similar in both treatment groups. A higher number of subjects in the placebo group (24 subjects, 41.4%) used corticosteroids within the past year compared with the JNJ-39758979-treated group (19 subjects, 33.3%).

In total, 48 subjects had a protocol deviation during the study, 23 in the placebo group and 25 in the JNJ-39758979 group. Overall, the numbers and types of protocol deviations were similar between treatment groups.

EFFICACY RESULTS

The primary endpoint was percent change from baseline in pre-BD percent predicted FEV_1 value at Week 12. JNJ-39758979-treated subjects demonstrated no statistically significant difference in percent change from baseline in pre-BD percent-predicted FEV_1 compared with placebo subjects (placebo-adjusted least squares [LS] mean percent change from baseline= 3.2; p= 0.230). Based on this result, all other statistical tests with significance results ($p < 0.05$) was considered nominal.

Exploratory analyses of the primary endpoint were performed for the predefined subgroups of the intent-to-treat (ITT) analysis set based on demographic features, geographic location, baseline disease characteristics, and concomitant medications. Although the majority of the subgroup analyses showed no significant difference in percent change in pre-BD percent predicted FEV_1 compared with placebo, in

3 subgroups with baseline eosinophilic inflammation, JNJ-39758979 treatment was associated with a nominally significant improvement in pre-BD FEV_1. These subgroups were defined as either baseline eNO > 60 ppb (n= 31, placebo-adjusted LSmean percent change from baseline=12.5, p= 0.009), baseline sputum eosinophils ≥ 3% (n= 11, placebo-adjusted LSmean percent change from baseline=21.4, p= 0.032), or baseline blood eosinophils ≥ $0.25x10^9$/L (n= 57, placebo-adjusted LSmean percent change from baseline=9.1, p= 0.019).

In the baseline eNO < 20 ppb subgroup, treatment with JNJ-39758979 was associated with a reduction in pre-BD percent predicted FEV_1 compared with placebo; however, this was not statistically significant (placebo-adjusted LSmean percent change from baseline= -6.0, p= 0.152).

When spirometry was analyzed with the modified ITT population, the placebo-adjusted LSmean percent change from baseline in pre-BD FEV_1 was -9.6% (n= 23, p= 0.058) in the eNO < 20 ppb subgroup, 9.9% (n= 31, p= 0.041) in the eNO > 60 ppb subgroup, 21.4% (n= 11, p= 0.032) in the sputum eosinophils ≥3% subgroup, and 7.7% (n= 57, p= 0.045) in the blood eosinophils ≥ $0.25x10^9$/L subgroup.

Treatment with JNJ-39758979 was associated with a nominally significant improvement in post-BD percent predicted FEV_1 at Week 12 compared with placebo (placebo-adjusted LSmean percent change from baseline= 4.8, p= 0.010).

Treatment with JNJ-39758979 was associated with a trend for improvement in pre-BD percent predicted FVC at Week 12 compared with placebo (placebo-adjusted LSmean percent change from baseline= 3.1, p=0.087). There was no difference in post-BD percent predicted FVC in JNJ-39758979-treated subjects compared with placebo-treated subjects at Week 12 or at Week 4.

There was no difference in pre-BD percent predicted FEF_{25-75} in JNJ-39758979-treated subjects compared with placebo-treated subjects at Week 12. In comparison with subjects who received placebo, JNJ-39758979-treated subjects showed a trend for improvement in post-BD percent predicted FEF_{25-75} (placebo-adjusted LSmean percent change from baseline= 9.2, p= 0.052) at Week 12.

There was no difference in pre-BD percent predicted FEV_1/FVC in JNJ-39758979-treated subjects compared with placebo-treated subjects at Week 12. In comparison with subjects who received placebo, JNJ-39758979-treated subjects showed a trend for improvement in post-BD percent predicted FEV_1/FVC (placebo-adjusted LSmean percent change from baseline 2.4, p= 0.060) at Week 12.

Asthma Daily Diary: Treatment with JNJ-39758979 was associated with a trend for improvement in the Asthma Symptom Score at Week 12 compared with placebo (placebo-adjusted LSmean percent change from baseline -0.309, p= 0.062). The onset of the improvement in the Asthma Symptom Score was evident by a trend for improvement at Week 3 of treatment and appeared to be maintained over the treatment period with significance at Weeks 5, 7, 10, and 11.

Treatment with JNJ-39758979 in the baseline sputum eosinophils ≥3% subgroup was associated with a trend for improvement in the Asthma Symptom Score at Week 12 compared with placebo treatment (placebo-adjusted LSmean percent change from baseline -1.456, p= 0.081). Treatment with JNJ-39758979 in the baseline blood eosinophils ≥ $0.25x10^9$/L subgroup was associated with a trend for improvement in the Asthma Symptom Score at Week 12 compared with placebo treatment (placebo-adjusted LSmean percent change from baseline -0.428, p= 0.064). Treatment with JNJ-39758979 in the eNO > 60 ppb subgroup was directionally consistent with these subgroups but was more weakly associated with an improvement in the Asthma Symptom Score at Week 12 compared with placebo treatment (placebo-adjusted LSmean percent change from baseline -0.446, p= 0.199).

Worsening of Asthma: In the JNJ-39758979 treatment group, 7% of subjects reported worsening of asthma events compared with 12% of subjects in the placebo group. The median time to worsening of asthma event was 23 days and 57 days in the JNJ-39758979 and placebo treatment groups, respectively.

PHARMACOKINETIC RESULTS

In this study, subjects received multiple doses of 300 mg daily with food for 12 weeks. The mean (SD) of predose or trough JNJ-39758979 concentrations in plasma were 160.89 (108.85), 185.29 (149.88), 193.56 (168.99), and 166.37 (145.65) ng/mL at Weeks 1, 2, 4, and 12, respectively. It appeared that pharmacokinetic steady state was achieved by Week 2; the mean trough concentrations in females were 17% to 41% lower than males.

PHARMACODYNAMIC RESULTS

Exploratory PD biomarkers were evaluated for the ITT population at each scheduled visit and included eNO, total IgE, antigen specific IgE (cat dander, common ragweed, house dust mite, mold oak, timothy grass, etc), and induced sputum cell counts (eosinophils, macrophages, polymorphonuclear cells, lymphocytes, total WBC, bronchial epithelial cells, total cell count, total nonsquamous and squamous cells) in subjects participating in the substudy.

Exhaled Nitric Oxide Concentration: Compared with placebo, JNJ-39758979 had no significant effect on eNO over the treatment period overall and specifically at Week 12 versus baseline in the overall population or in pre-specified subgroups with eosinophilic inflammation at baseline.

IgE: Antigen-specific IgE average was calculated as the numerical average of IgE-specific antigens (cat dander, common ragweed, house dust mite, mold, oak, timothy grass, etc.) for subjects who had positive baseline measurements (values ≥ 2). Treatment with JNJ-39758979 for 12 weeks had no effect on antigen-specific IgE average or total IgE.

Induced Sputum Cell Counts: In total, 50 subjects were enrolled into the sputum induction substudy and 42 subjects had an acceptable baseline and at least 1 acceptable post-baseline sputum sample. Sputum results and additional exploratory analyses on biomarkers are independently reported in a biomarker technical report.

SAFETY RESULTS

JNJ-39758979 therapy was generally well tolerated except for an excess of nausea (37% versus 7%) and vomiting (16% versus 2%) compared with placebo. There were no treatment-emergent SAEs and no deaths reported.

Treatment-emergent AEs were reported in 43 (75%) and 40 (69%) of subjects who received JNJ-39758979 and placebo, respectively. In subjects who received JNJ-39758979, 21 (37%) subjects reported nausea and 9 (16%) subjects reported vomiting, compared with 4 (7%) subjects reporting nausea and 1 (2%) subject reporting vomiting in the placebo-treated subjects. Nausea occurred more often in female (17/28, 61%) compared with male (4/29, 14%) subjects.

There were generally no changes in hematology and chemistry laboratory measurements in JNJ-39758979-treated subjects compared with subjects who received placebo.

There were a greater number of subjects in the JNJ-39758979 treatment group (27 subjects, 47%) who had no urine protein at baseline and then had urine protein detected at any point after baseline compared with the placebo group (17 subjects, 29%). There were no other major differences between the 2 groups for other urinalysis parameters or for serum creatinine levels.

There were no effects on vital sign measurements or ECG assessments in either treatment group.

STUDY LIMITATIONS

No notable study limitations were identified by the Sponsor.

CONCLUSIONS

In 115 adult (aged 18 to 65 years) subjects with uncontrolled persistent asthma using only short-acting β_2-agonists:

- JNJ-39758979 (n= 57) did not demonstrate superior efficacy to placebo (n= 58), as measured by percent change from baseline in pre-BD percent predicted FEV_1 at Week 12.
- JNJ-39758979 was associated with a nominally significant improvement as measured by percent change from baseline in post-BD percent predicted FEV_1 compared with placebo.
- Treatment with JNJ-39758979 was associated with a trend for improvement in the Asthma Symptom Score at Week 12.
- In prespecified subgroup analyses, JNJ-39758979 treatment was associated with significant improvement in pre-BD percent predicted FEV_1 at Week 12 in 3 subgroups with eosinophilic inflammation, defined as eNO > 60 ppb, sputum eosinophils $\geq 3\%$, or blood eosinophils $\geq 0.25 \times 10^9$/L.
- Treatment with JNJ-39758979 was associated with a trend for improvement in the Asthma Symptom Score in the subgroups of sputum eosinophils $\geq 3\%$ or blood eosinophils $\geq 0.25 \times 10^9$/L.
- The dose of 300 mg JNJ-39758979 was generally safe and well tolerated over 12 weeks of daily administration with the exception of nausea and vomiting.

The results from this study warrant further investigation in asthma patients with eosinophilic inflammation, as measured by sputum eosinophils, eNO, and/or blood eosinophils.

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