SYNOPSIS

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Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	"To be determined"
Name of Active Ingredient(s)	JNJ-40929837

Protocol No.: 40929837ASH2001

Title of Study: A Randomized Double-blind, Placebo-and Active-controlled, Crossover Study to Evaluate the Efficacy of JNJ-40929837 for the Treatment of Asthma Using a Bronchial Allergen Challenge (BAC) Model

EudraCT Number: 2010-022437-28

NCT No.: NCT01241422

Clinical Registry No.: CR017533 - NCT01241422

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Study Center(s): GBR and DEU

Publication (Reference): None

Study Period: 28 Oct 2010 to 06 Jun 2011

Phase of Development: Phase 2a

Objectives: Primary Objective: To evaluate the allergen-induced late asthmatic response (LAR), as measured by maximal percent fall in forced expiratory volume in 1 second (FEV_1), in subjects with stable mild atopic asthma after treatment with JNJ-40929837 compared to placebo.

Secondary Objective: (1) to compare the effects of JNJ-40929837 and placebo on allergen-induced early asthmatic response (EAR), as measured by maximal percent fall in FEV_1, (2) to compare the effects of JNJ-40929837 and placebo on allergen-induced EAR and LAR, as measured by area under the FEV_1/time curves, (3) to evaluate the safety of JNJ-40929837, (4) to characterize the pharmacokinetic/pharmacodynamic (PK/PD) relationship of JNJ-40929837 and sputum Leukotriene B_4 (LTB_4) (sputum substudy).

Exploratory Objective: (1) to compare the effects of JNJ-40929837 and placebo on allergen-induced: airway hyperresponsiveness (AHR) to methacholine (MCh) challenge, sputum eosinophil and neutrophil counts (sputum substudy only), and exhaled nitric oxide (eNO) levels; (2) to characterize the PK/PD relationship of JNJ-40929837 to the EAR and LAR.

Methodology: This was a randomized, double-blind, placebo- and active-controlled, multicenter, 3-period crossover study in approximately 18 adult subjects with stable, mild, atopic asthma who were demonstrated to have both an EAR and LAR to allergen during the screening period. Subjects were to receive study drug for 7 days in each treatment period separated by washout periods of at least 14 days.

A substudy was to be performed with at least 12 subjects who could produce an adequate sputum sample at screening. During the treatment periods, these subjects were to undergo sputum induction for analysis of cell counts, RNA, and other biomarkers in the sputum.

Screening: Eligibility for the study was assessed over 3 screening visits. Screening during Visit 1 was to include physical examination, medical history, routine laboratory tests, spirometry, and prick skin testing. At Visit 2, MCh challenge was to be performed to determine baseline sensitivity to MCh, and subjects' ability to produce sputum was to be evaluated to determine if they could participate in the sputum substudy. Subjects who continued to meet eligibility criteria were to proceed to Visit 3. At Visit 3, subjects' ability to demonstrate both an EAR and LAR in response to bronchial allergen challenge (BAC) was assessed using the allergen that either produced the largest diameter wheal after prick skin testing and/or was judged by the investigator to be most appropriate based on clinical symptoms reported by patients on past exposure to these allergens. Subjects who met all eligibility criteria after completing all screening procedures were to be randomized to 1 of 6 treatment sequences to balance a 3-treatment, 3-period crossover study.

Treatment and Follow-up: After a washout period of 2 to 4 weeks, the first treatment period was to be initiated. On Day 1 of each treatment period, subjects were to undergo eNO measurement, spirometry, and sputum induction, followed by administration of their first dose of assigned study drug and telemetry monitoring and hourly ECG sampling through 4 hours after the first dose. Subjects were to take the study drug at home until they returned to the clinic on Day 5 for spirometry, eNO measurement, and sputum induction. After an overnight stay at clinic on Day 5, eNO and BAC were to occur 2 hours after dosing, with spirometry measured until 10-hours post-BAC to assess both EAR and LAR on Day 6. Exhaled NO testing was to be repeated at 11 hours post-BAC. On Day 7 (approximately 24 hours post-BAC), eNO measurement, spirometry, MCh challenge, and sputum induction were to be performed.

Subjects were to return for a follow-up visit approximately 14 days after the end of Treatment Period 3.

Number of Subjects (planned and analyzed): Planned: Approximately 18 subjects were planned to be enrolled in the study to ensure at least 14 subjects completed the study. Analyzed: A total of 22 subjects were randomly assigned to receive the study drug; 15 subjects completed the study while remaining 7 subjects were withdrawn.

Diagnosis and Main Criteria for Inclusion: Subjects in good health between 18 to 55 years of age, who had stable, mild atopic asthma, were enrolled in the study. At screening, each subject was to have a positive prick skin test to at least 1 of the challenge agents (house dust mite [*Dermatophagoides pteronissinus* with protease activity (Der p1)], mixed grass pollen, or cat dander) and demonstrate an allergen-induced EAR of ≥20% reduction in FEV_1 and LAR of ≥15% reduction in FEV_1. Subjects who met these criteria and produced an adequate sputum sample at screening were to be enrolled into a sputum substudy. Women who were pregnant, lactating, actively seeking pregnancy, or who were not using adequate contraception if of childbearing potential, were to be excluded from participation.

Test Product, Dose and Mode of Administration, Batch No.: JNJ-40929837 was to be supplied as white to off-white, 50 mg tablets for oral administration with approximately 240 mL of non-carbonated water (Batch No.: 50459C, Expiration date: 18 August 2011)

Reference Therapy, Dose and Mode of Administration, Batch No.: Montelukast was supplied as "000" grey, opaque, hard-gelatin, 10-mg capsules (over encapsulated, enteric coated tablets) (Batch No.: 10F25/G034, Expiration date: March 2013); matching placebo tablets, identical in shape, size, appearance and excipient composition (Batch No.: 50461C, Expiration date: 02 September 2014); and matching placebo capsules were supplied as "000" grey, opaque, hard-gelatin capsules (Batch No.: 09J28/G001, Expiration date: November 2011) with microcrystalline cellulose as excipient. These reference therapies were supplied for oral administration with approximately 240 mL of non-carbonated water.

Duration of Treatment: The study consisted of 3-periods and subjects received study drug for 7 days in each treatment period separated by washout periods of at least 14 days.

Criteria for Evaluation:

EFFICACY EVALUATIONS:

Spirometry: A complete set of spirometry parameters was to be obtained at the start of each screening visit as well as prior to first dose (on Day 1), and 2-hours postdose each on the day before the BAC (Day 5), the day of BAC (Day 6), and the day post-BAC (Day 7).

Bronchial-Allergen Challenge: Subjects were to be skin tested with Der p1, mixed grass pollen, and cat dander followed by a screening challenge with incremental nebulized doses of one of these allergens until an EAR occurred. Further they were assessed with periodically repeated FEV_1 measurements to determine if an LAR was able to be demonstrated. Subjects who passed screening were to undergo allergen challenge during each treatment period with the same allergen used during screening but administered as a bolus.

Methacholine Challenge: Methacholine sensitivity was to be assessed at baseline and 24 hours after each treatment period allergen challenge. The Day 7 MCh occurred during the treatment period, since the last day of the treatment period was Day 7. Methacholine was to be administered in incremental doses by nebulization until a ≥20% fall in FEV_1 compared to the FEV_1 after saline administration at baseline was demonstrated, defining PC_{20} (provocative concentration causing a ≥20% fall in FEV_1).

Sputum Induction (Substudy): Subjects having a pre-induction FEV_1 >70% underwent sputum induction using hypertonic saline. Sputum was collected for cell counts (primarily eosinophils and neutrophils) and LTB_4 levels as well as other soluble biomarkers. A minimum of 12 subjects were to be enrolled in the sputum substudy.

Exhaled Nitric Oxide (eNO): Exhaled nitric oxide levels were assessed using NIOX™ equipment prior to the start of each treatment period as well as before and after (11 hours and 24 hours) each BAC.

PHARMACOKINETIC EVALUATIONS

Blood samples were to be collected for the measurement of plasma concentrations of JNJ-40929837. Plasma samples also were to be analyzed to document the presence of circulating metabolites and to evaluate other analytes related to the effects of the drug or biomarkers related to asthma.

PHARMACODYNAMIC EVALUATIONS

Pharmacodynamics was to be determined from ex vivo ionophore-stimulated LTB_4 production. Serum biomarkers to be analyzed were to include cytokines, chemokines, eosinophilic cationic protein (ECP), myeloperoxidase (MPO), Immunoglobulin E (IgE), and high sensitivity C-Reactive protein (hsCRP). Blood samples were to be collected for RNA expression profiling.

For subjects in the sputum substudy, induced sputum was to be collected at times specified and analyzed for LTB_4. RNA expression profiling could be performed on sputum cells.

Urine samples were to be collected as specified and analyzed for urine creatinine, LTE_4, and LTE_4/creatinine ratio.

PHARMACOGENOMIC EVALUATIONS

An optional pharmacogenomic blood sample (10 mL) was to be collected to allow for pharmacogenomic research (where local regulations permit).

SAFETY EVALUATIONS

Safety assessments were to include reports of adverse events (AEs), clinical laboratory tests, vital signs, 12-lead ECGs, telemetry, and spirometry. At-home measurement of peak expiratory flow rates (PEFRs),

use of rescue medication, and nocturnal awakenings due to asthmatic symptoms constituted the daily diary provided to subjects for evaluation of asthma. PEFR is the greatest rate of airflow that can be achieved during forced expiration, beginning with lungs fully inflated.

Statistical Methods:

Sample Size: A total of approximately 18 subjects (3 per sequence) were to be randomized into the study (12 subjects in sputum substudy) in order to have at least 14 subjects complete the study. Eighteen subjects provided approximately 90% power and 14 subjects provided approximately 80% power to detect 10% difference in LAR over placebo, at a 2-sided 0.05 alpha level using paired t-test. This assumed that the LAR after placebo treatment is 17.8 ± 13.8% (mean ± SD) and the response to JNJ-40929837 would be the same as that reported after montelukast treatment (7.8 ± 9.9%).

Efficacy parameters: Descriptive statistics for the efficacy endpoints were to be presented by treatment. Comparisons of JNJ-40929837 to placebo and montelukast to placebo were to be performed at each timepoint using mixed-effect analysis of covariance (ANCOVA) model to analyze the change from baseline in efficacy endpoints. A mixed effect, ANCOVA model that included treatment, sequence and period as fixed factors, subjects nested within sequence as a random factor and LAR collected during screening as a baseline covariate was used to perform the primary endpoint analysis. Missing values were not imputed. The secondary endpoint variables of EAR, area under the curve from 0 to 2 hours (AUC_{0-2}) and area under the curve from 3 to 10 hours (AUC_{3-10}) was to be summarized by treatment period and compared using the ANCOVA model in the same manner as the primary endpoint.

Pharmacokinetics: Plasma concentrations of JNJ-40929837 were to be summarized by treatment and timepoint using descriptive statistics.

Pharmacodynamics: All PD measurements were to be summarized by timepoint and treatment using descriptive statistics.

Safety: The safety analyses were to include the incidence of AEs, clinical laboratory tests, vital signs, ECGs, and physical exams. These safety parameters were to be summarized by treatment.

RESULTS:

STUDY POPULATION:

A total of 22 subjects were randomly assigned to and received at least 1 dose of the study drug; 15 subjects completed the study treatment. Seven subjects were withdrawn from study; 5 (22.7%) were discontinued due to AEs, and 1 (4.5%) subject each was discontinued due to withdrawal of consent and protocol violation. An equal number of men and women (11 [50%] each) were enrolled in the study; median age of the subjects was 27 years; majority were white (18 [82%]); and 8 (36%) subjects were skin test positive for animal dander and 7 (32%) subjects each were skin test positive for grass and house dust mite. Major protocol deviations were reported in 3 subjects.

EFFICACY RESULTS:

Primary Endpoint:

LAR

In comparison with placebo treatment, JNJ‑40929837 treatment did not demonstrate a statistically significant improvement in LAR (p=0.630). The placebo-subtracted least square (LS) mean (standard error [SE]) was 0.955 (1.9584). Conversely, montelukast demonstrated a statistically significant improvement in LAR (p=0.014) when compared to placebo treatment. The placebo-subtracted LS mean (SE) was -5.050 (1.9149).

Secondary Endpoints:

EAR

In comparison with placebo treatment, JNJ‑40929837 treatment did not demonstrate a statistically significant improvement in EAR (p=0.963). The placebo-subtracted LS mean (SE) was 0.124 (2.6630). Conversely, montelukast demonstrated a statistically significant improvement in EAR (p<0.001) when compared to placebo treatment. The placebo-subtracted LS mean (SE) was -11.801 (2.6101).

Change in Predicted (%) FEV_1 from Period 1 Pretreatment to Day 5 of each Treatment Period

In comparison with placebo treatment, JNJ‑40929837 treatment did not demonstrate a statistically significant change in % predicted FEV_1 from Period 1 pretreatment to Day 5 of each period (p=0.382). The placebo-subtracted LS mean (SE) was 1.60 (1.8878). Similar to JNJ-40929837, montelukast did not demonstrate a statistically significant change (p=0.090). The placebo-subtracted LS mean (SE) was 3.09 (1.8850).

AUC_{0-2} of FEV_1

In comparison with placebo treatment, JNJ‑40929837 treatment did not demonstrate a statistically significant improvement in AUC_{0-2} (p=0.371). The placebo-subtracted LS mean (SE) was -2.989 (3.2925). Conversely, montelukast demonstrated a statistically significant improvement in AUC_{0-2} (p<0.001) when compared to placebo treatment. The placebo-subtracted LS mean (SE) was -23.547 (3.2255).

AUC_{3-10} of FEV_1

In comparison with placebo treatment, JNJ‑40929837 treatment did not demonstrate a statistically significant improvement in AUC_{3-10} (p=0.749). The placebo-subtracted LS mean (SE) was -4.617 (14.3053). Conversely, montelukast demonstrated a statistically significant improvement in AUC_{3-10} (p=0.006) when compared to placebo treatment. The placebo-subtracted LS mean (SE) was -41.832 (13.9560).

Exploratory Endpoints:

Of the 22 randomized subjects, 13 subjects were enrolled in the sputum substudy. However those available in the placebo, JNJ-40929837 and montelukast treatment with both pre-BAC sample and post-BAC samples are 10, 7, and 6 respectively, and those available in the placebo, JNJ-40929837 and montelukast treatment with pre-BAC (Day 5) samples are 10, 10, and 9 respectively. Neither JNJ-40929837 nor montelukast demonstrated a statistically significant difference from placebo in change in sputum eosinophil or neutrophil counts.

JNJ-40929837 treatment did not demonstrate a statistically significant difference in percent change from baseline at Day 7 after BAC in PC_{20} (p=0.887), however, montelukast was significantly different than placebo (p=0.035). Neither JNJ-40929837 nor montelukast demonstrated a statistically significant difference from placebo in change in eNO levels.

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS:

Pharmacokinetics:

Individual plasma concentrations indicated that subjects were appropriately exposed to JNJ-40929837 after receiving 50 mg doses of JNJ-40929837. Other PK analyses were planned (eg, circulating metabolites), but not performed at this time.

Pharmacodynamics:

In comparison with placebo, JNJ-40929837 showed a significant decrease in sputum LTB_4 levels from pretreatment (period baseline) to Day 5 and from pretreatment to Day 7, but no significant effect on LTB_4 levels from pre-allergen challenge (Day 5) to post-allergen challenge at Day 7 while montelukast showed no significant effect. Following JNJ-40929837 administration, LTB_4 concentrations decreased within 2 hours postdose and remained suppressed throughout the 7 day dosing period. In contrast, LTB_4 concentrations remained relatively unchanged throughout the administration of montelukast or placebo. In comparison with placebo, JNJ-40929837 showed an increase in urinary LTE_4/creatinine ratios from pretreatment (period baseline) to Day 5, while montelukast showed a decrease.

Pharmacokinetics/Pharmacodynamics

The PK/PD relationship between plasma JNJ-40929837 concentrations and sputum LTB_4 was planned for evaluation but the analyses were not performed. Instead, a PK/PD analysis of plasma JNJ-40929837 concentrations vs. plasma LTB_4 was conducted. Analysis of exposure response relationships between individual ex vivo LTB_4 plasma concentration data vs. JNJ-40929837 plasma concentration data resulted in an estimated EC_{50} of 4.2 ng/mL. The mean plasma concentrations after oral administration of 50 mg JNJ-40929837 observed were in vast excess of the estimated EC_{50}, suggesting substantial inhibition of LTB_4 production throughout the study. Exploratory PK/PD analyses of plasma JNJ-40929837 concentrations vs. EAR and LAR were planned, but not performed.

IgE

Small mean decreases in serum IgE levels from study baseline were seen with both JNJ-40929837 (-0.21 nmol/L) and montelukast (-0.19 nmol/L) compared with placebo (-0.08 nmol/L).

SAFETY RESULTS:

JNJ-40929837 therapy was generally well tolerated. There were no treatment-emergent serious AEs or deaths reported in the study. Treatment-emergent AEs were reported in 12 (70.6%) subjects when treated with JNJ-40929837 as compared with 11 (57.9%) subjects when treated with placebo and 10 (55.6%) subjects when treated with montelukast. Four (23.5) subjects when treated with JNJ-40929837 reported headache as compared with 4 (21.1%) and 3 (16.7%) subjects when treated with placebo and montelukast, respectively. Five subjects discontinued due to AEs. The events which led to the discontinuation of study drug were asthma and dyspnea (when treated with JNJ-40929837), allergic respiratory disease, bronchospasm, and influenza-like illness (when treated with placebo), and tonsillitis (when treated with montelukast).There were no clinically meaningful changes in hematology, chemistry laboratory measurements with JNJ-40929837 treatment compared with placebo and montelukast treatments.

There were no effects on vital sign measurements or physical examination abnormalities in subjects receiving JNJ-40929837 compared with placebo. On ECG evaluations, those receiving JNJ-40929837 demonstrated a nominally statistically significant increase in heart rate at 2 out of 5 time points compared with placebo. There were no effects on other ECG parameters of JNJ 40929837 compared with placebo. Mean change from baseline analyses did not show an increase in QTcF when considering all data from JNJ-40929837 treatment periods together. Three (17.6%) subjects when treated with JNJ-40929837 and 1 (5.6%) subject when treated with montelukast reported with borderline increase (>430 ms, ≤450 ms in males; >450 ms, ≤460 ms in females) in the QTcB values. One (5.6%) subject when treated with montelukast was reported with prolonged QTcB value while no subject had prolonged QTcB after JNJ-40929837 administration.

STUDY LIMITATIONS: No notable study limitations were identified by the sponsor.

CONCLUSION(S):

JNJ-40929837 did not reduce the allergen-induced LAR and also did not have an effect on the early asthmatic response or MCh sensitivity despite evidence of target engagement as demonstrated by a reduction in plasma and sputum LTB_4 levels. Furthermore, JNJ-40929837 did not have significant anti-inflammatory effects since allergen-induced increases in sputum cell counts and eNO levels were not significantly attenuated.

Analysis of exposure response relationships between individual ex vivo LTB_4 plasma concentration data vs. JNJ-40929837 plasma concentration data resulted in an estimated EC_{50} of 4.2 ng/mL. The mean plasma concentrations after oral administration of JNJ-40929837 observed were in vast excess of the estimated EC_{50}, suggesting substantial inhibition of LTB_4 production throughout the study.

JNJ-40929837 was generally safe and well-tolerated. No significant prolongation of the QTcF interval was demonstrated but the effect of JNJ-40929837 on heart rate may confound this conclusion.

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