CLINICAL STUDY REPORT SYNOPSIS

Document No.: EDMS-PSDB-6423263:2.0

Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development	
Name of Finished Product	Not applicable	
Name of Active Ingredient(s)	1-[7-(4-bromo-2,6-dimethylphenyl)-2,5-dimethyl-7*H*-pyrolo[2,3-d] pyrimidin-4-yl]-4-piperidine-methanol hydrochloride	

Protocol No.: R317573DEP2002

Title of Study: A Double Blind, Placebo- and Active-Controlled, Randomized, Sequential Group, Multiple Dose Study to Examine the Effect of the CRF1-Receptor Antagonist R317573 on 7.5% CO_2-Inhalation Induced Anxiety in Healthy Subjects

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Publication (Reference): Not applicable

Study Period: Clinical Conduct: 16 October 2006 to 2 February 2007 | **Phase of Development:** 2a

Objectives:

The primary objective of this study was:

- To determine whether R317573, after multiple dosing over one week in healthy male or female subjects, reduced the intensity of anxiety symptoms induced by breathing air with 7.5% carbon dioxide (CO_2) over 20 minutes.

Secondary objectives were:

- To assess the influence of R317573 on CO_2-induced changes in blood pressure, heart rate, and adrenocorticotrophic hormone (ACTH)-, vasopressin (AVP)- and cortisol plasma concentrations.
- To assess the safety and tolerability of multiple oral doses of R317573 in healthy male or female subjects.
- To assess the effect of a single oral dose of lorazepam (2 mg) on the intensity of anxiety symptoms induced by breathing air with 7.5% CO_2 over 20 minutes, as a reference active control.
- To assess potential relationships between the R317573 pharmacokinetic profile and the pharmacodynamic effects, safety and tolerability of R317573.

Methodology:

- Double-blind, randomized, placebo- and active-controlled, sequential group, multiple dose study.
- A minimum of 32 healthy subjects (i.e., Cohort 1) was planned to participate in the study. Depending on the outcome, additional cohorts (n=24) could be included (see Table).

R317573 Dosing Schedule

Cohort	Dosage Regimen (o.d.)	Tablets Administered per Dosing
1	40 mg	4 tablets of 10 mg
2[a,*]	100 mg	2 tablets of 50 mg
3[b,*]	20 mg	2 tablets of 10 mg
4[c,*]	10 mg	1 tablet of 10 mg

[a] If the 40 mg o.d. dose cohort did not show a relevant PD effect and no safety concerns.
[b] If the 40 mg o.d. dose cohort showed a relevant PD effect and no safety concerns.
[c] If the 40 and 20 mg o.d. dose cohorts showed a relevant PD effect and no safety concerns.
[*] These cohorts were not executed.
PD = pharmacodynamic.

- In each cohort, subjects were randomly assigned to one of the following treatments:
  - R317573: R317573 o.d. in the evening on Days 1 to 7 and placebo to lorazepam in the morning of Day 8 (n=12).
  - Placebo: placebo to R317573 o.d. in the evening on Days 1 to 7 and placebo to lorazepam in the morning of Day 8 (Cohort 1: n=12; other cohorts: n=8).
  - Lorazepam: placebo to R317573 o.d. in the evening on Days 1 to 7 and lorazepam 2 mg in the morning of

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Day 8 (Cohort 1: n=8; other cohorts: n=4).

- The study consisted of a screening evaluation (21 to 2 days before first dose administration), a double-blind treatment phase (8 days) and a follow up examination (4 to 7 days after the last dose administration). The maximum duration of the study for each subject was approximately 5 weeks.
- The subjects were not hospitalized during the double-blind treatment phase. They visited the research center on a daily basis for dinner, dosing and the trial assessments. However, the subjects remained in the research center from the time before dinner on Day 7, until complete recovery from the CO_2-challenge test on Day 8.

Number of Subjects (planned and analyzed): Thirty-two subjects were actually randomized, dosed and analyzed (i.e., only Cohort 1 was executed).

Diagnosis and Main Criteria for Inclusion:

- Healthy male and female subjects, aged between 18 and 45 years.
- Body mass index between 18 and 28 kg/m^2.
- Show a significant response to a 20-minute CO_2 inhalation administered during screening, defined as a total score above or equal to 20 points in the Panic Symptom Inventory (PSI) taken just after inhalation to assess peak effect.
- Non-smoker or smoking less than 5 cigarettes per day.
- Without clinically significant laboratory abnormalities, vital signs, 12-lead ECG or significant illnesses.
- Female subjects only: postmenopausal (for at least 12 months), surgically sterile, abstinent, or practicing an effective method of birth control.

Test Product, Dose and Mode of Administration, Batch No.:

- The oral formulation of R317573 was supplied as 10-mg (free base equivalent) immediate release oral tablets. Bulk Lot Number: 05L05/F008.
- Lorazepam was provided as hard gelatin capsules (red cap / red body, size 0), containing respectively 2 tablets of Temesta® (lorazepam) 1-mg oral immediate release tablets and sugar spheres. Johnson & Johnson Pharmaceutical Research and Development performed the over-encapsulation. Bulk Lot Number: 06H03/F320.
- The CO_2, O_2 and N_2 used in the gas mixture were commercially available medical gases supplied by the BOC Group, Worsley, United Kingdom. During the CO_2-inhalation test a gas mixture (7.5% CO_2, 21% O_2, 71.5% N_2) or piped air was delivered via a nasal-oral exercise face mask attached to a 500 L bag.

Reference Therapy, Dose and Mode of Administration, Batch No.:

- Placebo to R317573 was supplied as matching placebo tablets (i.e., with the same ingredients, but without active compound). Bulk Lot Number: 06C06/F010.
- Placebo to lorazepam was provided as hard gelatin capsules (red cap / red body, size 0), containing sugar spheres only. Bulk Lot Number: 06F26/F094.

Duration of Treatment: Eight days.

Criteria for Evaluation:

Pharmacokinetics:

Pharmacokinetic analyses of the plasma concentrations were undertaken after each cohort on unblinded data to estimate peak plasma concentration and systemic exposure of R317573 and its acid metabolite (R337676). Based on the individual plasma concentration-time data, using the actual sampling times, the following pharmacokinetic parameters of R317573 and its acid metabolite were estimated in all subjects receiving the last dose of R317573 on Day 7: peak plasma concentration (C_{max}), predose plasma concentration ($C_{predose}$), and time to peak plasma concentration (t_{max}).

Pharmacodynamics:

A CO_2-challenge test was executed on Day 1 (before the first dosing of R317573/placebo) and on Day 8 (approximately 12 to 15 hours after the last dosing with R317573/placebo, time matched with Day 1 challenge). The response of the subjects to the CO_2-challenge test and the study medication was assessed by:

- Psychometric testing using the Spielberger State Anxiety Inventory (SSAI), the PSI, the General Anxiety Disorder Criteria inventory (GAD-C) and Visual Analogue Scales (VAS) for anxiety related symptoms.
- Assessment of plasma concentrations of ACTH, AVP and cortisol.
- Assessment of changes in vital signs (blood pressure, pulse rate, respiratory rate) during the CO_2-challenge

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test.

Safety:

Safety was assessed by adverse events inquiry, clinical laboratory analysis (hematology, biochemistry, urinalysis, thyroid stimulating hormone [TSH]), vital signs, 12-lead ECG, and physical examination.

Pharmacogenomics:

- A 10 mL blood sample was collected from subjects who consented to the pharmacogenomic component of the study. Subject participation in pharmacogenomic research was optional.
- No genes were genotypes in this study. DNA samples will be maintained for future research, according to subject's informed consent.

Statistical Methods:

Interim Analyses

- To aid decisions on the doses of subsequent cohorts, descriptive summaries of the psychometric assessment data and cortisol, AVP and ACTH concentration data was produced by treatment group and provided to the study team in such a way that the treatment regimen for any individual subject could not be determined.

Pharmacokinetic Analyses

- Pharmacokinetic analyses were performed using descriptive statistics only, and presented per dose for R317573 and R337676.

Pharmacodynamic and Efficacy Analyses

- Unless otherwise specified all pharmacodynamic parameters were presented by treatment group and time using summary statistics. Statistical analyses were performed comparing each R317573 dose to placebo and lorazepam to placebo.
- Since only an improvement (comparison) in scores for active compound versus placebo was of interest and since this was a non-pivotal study, analyses of the psychometric assessments were 1-sided with a significance level of 10%. Analyses of the other parameters were 2-sided with a significance level of 5%.
- Mixed effects modeling (ANCOVA) was used to analyze the data, with the baseline value from the Day 1 predose procedure and sex added as covariates. Estimates for means and contrasts were provided along with 95% confidence intervals.
- Response parameters for the ANCOVA models were the measurements at peak CO_2, both corrected and uncorrected for peak air measurements.

Pharmacokinetic/Pharmacodynamic Analyses

- The influence of plasma concentrations of R317573 (and its acid metabolite) on the dynamic responses (ACTH, AVP and cortisol, vital signs, psychometric tests) subsequent to the CO_2-challenge was analyzed graphically. A suitable pharmacokinetic/pharmacodynamic (PK/PD) model was to be applied to describe the exposure-effect relationship.
- Because only 1 cohort (i.e., Cohort 1) was tested, no PK/PD analyses were performed.

Safety Analyses

- The safety analyses were performed using descriptive statistics only. All subjects receiving at least one dose of study treatment (R317573, placebo or lorazepam) were included in the safety analysis.

SUMMARY - CONCLUSIONS

PHARMACOKINETICS:

- After 1 week of 40 mg o.d. dosing, the 2-hour post dosing plasma concentrations reached 45.2 ± 18.9 ng/mL and 1,755 ± 708 ng/mL for R317573 and R337676, respectively
- The mean R317573 plasma concentration immediately before CO2 inhalation on Day 8 was 13.5 ± 3.82 ng/mL, which is similar to the pre-injection value of 14.4 ± 5.06 ng/mL observed in the R317573 40 mg o.d. group in the CCK-4 challenge study on Day 8.

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SUMMARY - CONCLUSIONS (continued)

PHARMACOKINETICS (continued):

- Mean plasma concentrations of R317573 and R337676 are presented in the table below:

Mean Plasma Concentrations of R317573 and R337676

			R317573		R337676	
Day	Time	N	Mean (ng/mL)	SD	Mean (ng/mL)	SD
7	0 h	12	9.32	2.79	1,533	695
	1 h	11	34.1	19.8	1,578	743
	1.5 h	12	39.5	12.7	1,650	615
	2 h	12	45.2	18.9	1,755	708
8	before CO_2	12	13.5	3.82	1,672	643
	0.5 h after CO_2	12	12.6	3.44	1,655	713
	1 h after CO_2	12	12.5	3.21	1,560	663

h = hour; SD = standard deviation.

PHARMACODYNAMICS:

- CO_2-challenge resulted in expected increases in anxiety on multiple parameters.
- Statistical analyses (ANCOVA) comparing the peak responses to CO_2 inhalation on Day 8 versus Day 1, and including for the responses to 'air' (per protocol analysis) showed that:
  - The expected effects of lorazepam did not emerge from the analysis.
  - Effects of R317573 were seen on a few isolated symptoms in the PSI.
  - Differences in response, most notably to the ‘air’ challenge, occurred on Day 1 (baseline, before treatment) between the groups. This confounded the interpretation of any treatment effects, including the expected effects of lorazepam.
- Post hoc analyses (ANCOVA) comparing the peak responses to CO_2 inhalation on Day 8 versus Day 1 of VAS, but without including responses to 'air' testing Day 8 versus Day 1 post challenge responses showed that:
  - Lorazepam had the expected effect on VAS, affecting 6 out of 11 scales (alert, fearful, nervous, relaxed, tense, and worried).
  - Forty milligram R317573 o.d. for 7 days had an effect on 3 VAS scales (decrease in anxious, nervous and worried) without sedation (alert).
- Post hoc analyses (ANCOVA) comparing peak responses to CO_2 inhalation on Day 8 versus Day 1 of PSI, but without including responses to 'air' showed that:
  - Lorazepam blunted responses to 6 out of 34 symptoms compared to placebo.
  - Forty milligram R317573 o.d. for 7 days blunted responses to 7 out of 34 symptoms compared to placebo.
- Compared to placebo, administration of 40 mg R317573 o.d. for 7 days had no significant effects on plasma ACTH, AVP and cortisol levels. Continuous vital signs were also not affected.

SAFETY RESULTS:

- Twenty-eight (87.5%) subjects reported at least 1 treatment-emergent adverse event, 10 (83.3%) in the placebo group, 12 (100%) in the R317573 group, and 6 (75%) in the lorazepam group. The most common adverse events were headache (placebo 33.3%, R317573 25.0%, lorazepam 37.5%), nausea (placebo 16.7%, R317573 16.7%, lorazepam 12.5%), fatigue (placebo 16.7%, R317573 8.3%, lorazepam 12.5%), and somnolence (placebo 25.0%, R317573 0%, lorazepam 12.5%). Overall, the incidence of adverse events was similar between the different treatment groups.
- Treatment-emergent effects on liver enzymes, i.e., increases in ALT, AST and/or GGT, were observed in 2 subjects in the placebo group, 1 subject in the R317573 40 mg o.d. group, and no subjects in the lorazepam group.
- Only one subject (in the lorazepam group) displayed clinically significantly elevated liver enzymes, which, however, were not treatment-emergent. This subject's ALT levels were elevated, starting before dosing on Day 1 and lasting until Follow-Up, ranging from 2.7 × the upper limit of normal (ULN) on Day 1 and decreasing to 1.2 × ULN at Follow-Up. The subject's AST levels were also significantly elevated on Day 1 (1.4 × ULN) and Day 3 (1.1 × ULN). These elevated liver enzymes were reported as a mild adverse event that

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was not related to the study medication.

- There were no clear, consistent treatment- or time-related changes in mean laboratory parameters (biochemistry, hematology, urinalysis) and vital signs. All ECGs were considered clinically normal and no subjects had QTc intervals of more than 450 milliseconds during the study.
- One subject, who participated in the placebo group of Cohort 1, chose to withdraw from the study on Day 5 (before the Day 5 dosing). This subject reported several mild treatment-emergent adverse events (i.e., irritability, excessive sleep, reduced concentration, and fatigue) that started within 1 to 2 days after the first dose administration. The investigator considered these adverse events of very likely relationship to the study medication. All adverse events had resolved before the Follow-Up examination, which occurred on Day 10. Seven days after the Follow-Up visit, the subject was involved in a traffic accident, which resulted in the death of the subject (aortic rupture). This incident was recorded as a serious adverse event that was not related to study medication.

CONCLUSION:

- Healthy volunteers dosed with 40 mg R317573 o.d. showed blunting of anxiogenic effects of the CO_2-challenge; i.e., 3 out of 11 VAS scales improved compared to placebo. Moreover, there was no evidence of sedation (i.e., no reduction in alertness) during or following the challenge, as was seen with lorazepam.
- The R317573 plasma concentrations observed during the CO_2-challenge on Day 8 were consistent with observations in previous studies with similar dosing.
- R317573 administered orally as 40 mg o.d. for 7 consecutive days was safe and well tolerated by healthy male and female subjects in this study.

Issue Date of the Clinical Study Report: 24 July 2007

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