CLINICAL STUDY REPORT SYNOPSIS

Document No.: EDMS-PSDB-6492850:2.0

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.: R317573DEP2001

Title of Study: A Double blind, Placebo Controlled, Randomized, Sequential Group, Multiple Dose Study of the Efficacy of the CRF1-Receptor Antagonist R317573 on CCK-4 Induced Anxiety in Healthy Male Subjects

Principal Investigator: R.G. Tiessen, M.D. Ph.D. - Pharmaceutical Research Associates, [redacted] The Netherlands

Publication (Reference): Not applicable

Study Period: Clinical Conduct: 24 May 2006 to 27 February 2007 | **Phase of Development:** 2a

Objectives:

The primary objective of this study was:

- To determine whether R317573, after multiple dosing over one week, reduced the intensity of an anxiogenic reaction induced by the intravenous (i.v.) administration of 40 µg cholecystokinin-tetrapeptide (CCK-4).

The secondary objectives of this study were:

- To assess the influence of R317573 on CCK-4 induced changes in blood pressure, pulse rate, respiratory rate and adrenocorticotropic hormone (ACTH), cortisol, insulin and glucose plasma concentrations.
- To assess the effects of R317573 on anticipatory anxiety.
- To assess the safety and tolerability of multiple oral doses of R317573.
- To assess potential relationships between the R317573 pharmacokinetic profile and the pharmacodynamic effects, safety and tolerability of R317573.

Methodology:

- Double-blind, randomized, placebo-controlled, sequential group, multiple dose study.
- A minimum of 24 subjects (i.e., Cohort 1) was planned to participate in the study. Depending on the outcome, additional cohorts (Cohort 3 and Cohort 4: n=24, Cohort 5: n=16) could be included.
- In each cohort, subjects were to be randomly assigned to treatment with R317573 (n=12) or placebo (Cohorts 1, 3 and 4: n=12; Cohort 5: n=4), according to the following schedule:

R317573 Dosing Schedule

Cohort	Dosage Regimen	Tablets Administered per Dosing
1	100 mg b.i.d.	2 tablets of 50 mg
5[a]	200 mg o.d.	1 tablet of 200 mg
3[b]	40 mg o.d.	4 tablets of 10 mg
4[c]	20 mg o.d.	2 tablets of 10 mg

[a] If the 100 mg b.i.d. dose cohort showed a relevant PD efficacy and no safety concerns.
[b] If the 200 mg o.d. dose cohort showed a relevant PD efficacy and no safety concerns.
[c] If the 40 mg o.d. dose cohort showed a relevant PD efficacy and no safety concerns. This cohort was not executed.
PD = pharmacodynamic.

- The study consisted of a screening evaluation (21 to 4 days before first dose administration), a 3-day preparation phase (Day -3 to Day -1), 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.

Number of Subjects (planned and analyzed): Minimally 24 and maximally 88 subjects were planned to participate in the study (i.e., Cohorts 1, 5, 3 and 4 [Cohort 4 was not executed]). One subject in the placebo group of Cohort 3 did not show up in the clinic at the start of the preparation phase (i.e., Day -3). This subject was not replaced. Therefore, 63 subjects (instead of 64) were actually randomized, dosed and analyzed (i.e., Cohorts 1, 5 and 3).

SYNOPSIS (CONTINUED)

Diagnosis and Main Criteria for Inclusion:

- Healthy male subjects, aged between 18 and 45 years.
- Body mass index between 18 and 28 kg/m^2.
- Without clinically significant laboratory abnormalities, vital signs, 12-lead electrocardiogram (ECG) or significant illnesses.
- Subjects with an insignificant response to the first CCK-4 challenge test (Day -1) were excluded from the study. For Cohort 1 this was defined as not having a score ≥ 2 for fear/anxiety/apprehension in the panic symptom score (PSS) and/or not having a score of ≥ 1 on at least 4 of the 18 symptoms in the PSS. For Cohorts 3 and 5 an insignificant response to the CCK-4 challenge was defined as not having a total PSS score ≥ 20.

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

- The oral formulation of R317573 was supplied as 10-mg, 50-mg or 200-mg (free base equivalent) immediate release oral tablets. Bulk Lot Numbers: 05L05/F008 (10 mg), 05L07/F007 (50 mg) and 06B27/F006 (200 mg).
- CCK-4 was delivered in 6R vials containing 50 µg lyophilized powder (Bulk Lot Number: AC0589). Five milliliter normal saline (Bulk Lot Number: 5465C11) was added to the lyophilized powder. Before administration 4 mL (40 µg CCK-4) of the solution was withdrawn from the vial into a syringe. The CCK-4 was administered as a bolus injection over a maximum of 10 seconds via a cannula inserted in the arm of the subject.

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 Numbers: 06C06/F010 (placebo for R317573 10 mg tablets), 06A16/F010 (placebo for R317573 50 mg tablets) and 06B21/F009 (placebo for R317573 200 mg tablets).

Duration of Treatment: In Cohort 1, subjects received R317573 or placebo twice daily from Day 1 to Day 7, and as a single dose in the morning of Day 8. In Cohorts 3 to 5, subjects were to be dosed with R317573 or placebo once daily from Day 1 to Day 7.

Criteria for Evaluation:

Pharmacokinetics:

- Preliminary pharmacokinetic analyses of the plasma concentrations were undertaken after each dose escalation step on blinded 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 from Cohort 1 (100 mg b.i.d.) receiving the last morning dose of R317573 on Day 8: peak plasma concentration ($C_{max)}$, predose plasma concentration ($C_{predose}$), time to peak plasma concentration (t_{max}), and the area under the concentration time curve from 0 hours to 3 hours after dosing (AUC_{0-3h}). For Cohort 5 (200 mg o.d.) and Cohort 3 (40 mg o.d.), only the plasma concentrations determined before dosing, and at 2 hours and 14 hours after dosing (i.e., just before the CCK-4 injection) were reported.
- On Day 7 urine samples were analyzed to determine concentrations of R317573 and its acid metabolite (Cohort 1 only), and reported as the amount excreted during a dosing interval (Ae_{12h}, %).
- The presence of glucuronides of R317573 and R337676 was explored in selected plasma and urine samples (Cohort 1 only). The results from these experiments will be reported separately from this study report.

Pharmacodynamics and Efficacy Analyses:

A CCK-4 challenge test was performed on Day -1 (baseline) and Day 8. The response of the subjects to the CCK-4 challenge and the study medication was assessed by:

- Psychometric testing using the Spielberger State Anxiety Inventory (SSAI), PSS, visual analog scales (VAS) for anxiety, and the Stanford Sleepiness Scale.
- The assessment of plasma concentrations of ACTH and cortisol.
- The assessment of changes in vital signs (blood pressure, pulse rate, respiratory rate) during the CCK-4 challenge test.

Safety:

Safety was assessed by adverse events inquiry, clinical laboratory analysis (hematology, biochemistry, urinalysis,

SYNOPSIS (CONTINUED)

thyroid stimulating hormone [TSH], insulin and glucose, vital signs, 12-lead ECG, and physical examination.

Pharmacogenomics:

- One pharmacogenomic blood sample (10 mL) was collected from subjects who had given separate written informed consent, to allow for pharmacogenomic analysis, as necessary.
- No genes were genotyped in this study.

Statistical Methods:

Interim Analyses

- To aid decisions on the doses of subsequent cohorts, descriptive summaries of the psychometric assessment data were 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. The details of the interim analysis were documented prior to unblinding. No adjustments for the interim analysis were made in the final reporting of the study.

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 day using summary statistics.
- Since only an improvement in scores for R317573 compared with 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%.
- The following data were analyzed by analysis of covariance (ANCOVA), with pairwise comparisons of each dose level against placebo for PSS, VAS anxiety and Stanford sleepiness scale:
  - Change from challenge (post CCK-4 challenge - pre CCK-4 challenge) data for Day 8. The Day -1 data were included as a covariate in the model.
  - Change from baseline (post CCK-4 challenge on Day 8 - post CCK-4 challenge on Day -1). The post CCK-4 data on Day -1 were included as a covariate in the model.
- The SSAI was analyzed by ANOVA for change from prechallenge on Day -1 to prechallenge on Day 8. The prechallenge data on Day -1 were included as a covariate in the model.
- ANCOVA was used to compare cortisol, ACTH, insulin and glucose concentrations on Day 8 for each dose versus placebo by deriving AUCs and using Day -1 as a covariate.
- For continuous blood pressure, pulse rate and respiratory rate, the change from challenge data were analyzed using the same model as for the change from challenge psychometric assessment data, by deriving the average pre-challenge and the maximum post-challenge values, investigating changes from each R317573 group versus placebo for Day 8 with Day -1 as covariate.
- Additionally, all pharmacodynamic measurements on Day 8 were compared with Day -1 matched time points by use of 2-sided paired T-tests.

Pharmacokinetic/Pharmacodynamic Analyses

- The influence of plasma concentrations of R317573 (and its acid metabolite) on the dynamic responses (ACTH, cortisol and psychometric tests) subsequent to CCK-4 administration were analyzed graphically.
- Only if deemed useful after graphical analysis, a suitable pharmacokinetic/pharmacodynamic (PK/PD) model would be applied to describe the exposure-effect relationship.

Safety Analyses

- The safety analyses were performed using descriptive statistics only. All subjects receiving at least one dose of study drug were included in the safety analysis.

SUMMARY - CONCLUSIONS

PHARMACOKINETICS:

- After 1 week at 100 mg b.i.d., trough plasma concentrations of R317573 were in line with previous steady-state data obtained after 2 weeks of dosing. For the metabolite R337676, trough plasma concentrations

SYNOPSIS (CONTINUED)

were similar to values observed in previous studies after 1 week of dosing but lower than after 2 weeks of dosing (steady state).

- For a total daily dose of 200 mg, the once daily regimen resulted in more fluctuation compared with the b.i.d. regimen: trough plasma concentrations were about half the values observed with b.i.d. dosing; C_{2h} concentrations were about twice the values observed with b.i.d. dosing.
- The mean R317573 plasma concentrations immediately before CCK-4 injection for the 100 mg b.i.d., 200 mg o.d. and 40 mg o.d. treatment groups were 121 ± 26.8, 44.5 ± 9.83 and 14.4 ± 5.06 ng/mL, respectively.
- Very low amounts of parent drug and metabolite were present in urine, mainly as glucuronides (well below 1% of the total dose).
- Mean (median for t_{max}) pharmacokinetic parameters for R317573 and its acid metabolite are presented in the tables below:

R317573 Mean Pharmacokinetic Parameters

Parameter	40 mg o.d.[a] (n=12)	200 mg o.d.[a] (n=12)	100 mg b.i.d.[a] (n=12)
$C_{predose}$ (ng/mL)	8.71 ± 3.31	27.9 ± 7.64	48.5 ± 17.5
C_{2h} (ng/mL)	63.2 ± 22.2	234 ± 61.5	121 ± 26.8
C_{max} (ng/mL)	NA	NA	158 ± 40.9
C_{14h} (ng/mL)	14.4 ± 5.06	44.5 ± 9.83	NA
t_{max} (h)[b]	NA	NA	2.05
AUC_{3h} (ng.h/mL)	NA	NA	324 ± 78.4
Ae_{12h} (%)[c]	NA	NA	0.0009 ± 0.0004
Ae_{12h} (%)[d]	NA	NA	0.61 ± 0.30

[a] CCK-4 injection took place at approximately 2 hours after the Day 8 (morning) dose for Cohort 1 (100 mg b.i.d.) and at approximately 14 hours after the Day 7 (evening) dose for Cohort 5 (200 mg o.d.) and Cohort 3 (40 mg o.d.). R317573 plasma concentrations observed before CCK-4 injection are shaded in grey.
[b] Median values are presented.
[c] Amount R317573 excreted in urine during the 0 to 12 hour interval after dosing and before deglucuronidation.
[d] Amount R317573 excreted in urine during the 0 to 12 hour interval after dosing and after deglucuronidation.
NA = not applicable.

R337676 Mean Pharmacokinetic Parameters

Parameter	40 mg o.d. (n=12)	200 mg o.d. (n=12)	100 mg b.i.d. (n=12)
$C_{predose}$ (ng/mL)	1,358 ± 541	5,023 ± 2,668	6,198 ± 1,871
C_{2h} (ng/mL)	1,885 ± 536	6,727 ± 3,192	7,203 ± 1,744
C_{14h} (ng/mL)	1,518 ± 511	6,136 ± 3,239	NA
AUC_{3h} (ng.h/mL)	NA	NA	20,464 ± 5,308
Ae_{12h} (%)[a]	NA	NA	0.052 ± 0.022
Ae_{12h} (%)[b]	NA	NA	0.72 ± 0.39

[a] Amount R317573 excreted in urine during the 0 to 12 hour interval after dosing and before deglucuronidation.
[b] Amount R317573 excreted in urine during the 0 to 12 hour interval after dosing and after deglucuronidation.
NA = not applicable.

PHARMACODYNAMICS:

- Administration of R317573 100 mg b.i.d. for 1 week was associated with significant effects on 3 independent anxiety measures (based on data not corrected for pre-CCK-4 values):
  - A reduction in anticipatory anxiety.
  - A reduction in the number of panic symptoms, and significantly lower scores for the symptoms unsteadiness, faintness, paresthesia, and fear of loss of control.
  - Treatment effects on VAS following CCK-4 challenge: fearful (less), happy (more), relaxed (more) and sad (less).
- Administration of R317573 200 mg o.d. showed behavioral effects of comparable magnitude and same direction as those observed in the 100 mg b.i.d. cohort, although the variance was greater due to cohort differences. Noteworthy effects (based on data not corrected for pre-CCK 4 values) were:
  - The number of panic symptoms tended to decrease (not statistically significant).
  - Treatment effects on VAS following CCK-4 challenge: sad (less).
- In the 100 mg b.i.d. cohort, the cortisol response to the CCK-4 challenge was significantly reduced. A similar

SYNOPSIS (CONTINUED)

tendency was observed in the 200 mg o.d. cohort, but this decreased response was not statistically significant.

- The maximal pulse rate, relative to baseline, following the CCK 4 challenge was significantly reduced compared with placebo after 1 week at R317573 100 mg b.i.d. (uncorrected data only). The systolic blood pressure also tended to be lower in the 100 mg b.i.d. group, but without reaching statistical significance.
- R317573 dosing for 1 week at 100 mg b.i.d., 200 mg o.d., or 40 mg o.d. had no sedative effects, as measured with the Stanford Sleepiness Scale.
- Compared with placebo, the R317573 40 mg o.d. dosage regimen had no significant effects on key anxiety measures. Cortisol responses to CCK-4 were also not affected in this dose group.

SAFETY RESULTS:

- There were no deaths, and none of the subjects reported serious or severe treatment-emergent adverse events.
- One subject participating in the placebo group of Cohort 1 was withdrawn from the study on Day 6 (before administration of the morning dose) because of increasing liver function tests, which were reported as a moderate adverse event that was possibly related to the study medication. The adverse event started on Day 5 and lasted for 11 days. Both aspartate (AST) and alanine (ALT) aminotransferase levels started to increase on Day 5 and reached clinically significant levels on Day 6 (AST: 1.5 × the upper normal limit [ULN], ALT: 2.7 × ULN), after which levels gradually decreased again. At Follow-Up (Day 15) both AST and ALT levels had normalized.
- Only 1 additional subject displayed clinically significant increased liver enzymes. This subject, who participated in the R317573 100 mg b.i.d. group, had increased ALT levels (2.4 × ULN) on Day 8. Also this subject's AST levels were increased on Day 8 and at Follow Up (1.3 × ULN), but these were considered not clinically significant by the investigator. These increases in ALT and AST were reported as a moderate treatment emergent adverse event that was probably related to the study medication.
- Mean ALT levels tended to increase between Day -1 and Follow-Up (i.e., Day 13 to Day 17) in the R317573 100 mg b.i.d. and 200 mg o.d. treated groups, although the values remained within normal limits. No other time- or dose-dependent changes were observed in mean laboratory parameters.
- Forty (63%) subjects reported at least 1 treatment-emergent adverse event, 15 (56%) during placebo treatment and 25 (69%) during R317573 treatment. The most common adverse events after intake of R317573 were headache (30.6%, placebo 18.5%), rhinitis (11.1%, placebo 11.1%), dizziness (8.3%, placebo 3.7%), and nausea (8.3%, placebo 0%). Overall, the incidence of adverse events was similar between the R317573 and the placebo treated groups, except for headache, which seemed to occur more frequently at the 2 highest doses (placebo: 18.5%; 40 mg o.d.: 16.7%; 100 mg b.i.d.: 33.3%; 200 mg o.d.: 41.7%).
- One subject in the 200 mg o.d.-treated group reported erythematous rash on the soles that lasted for 2 days and was considered mild and doubtfully related to the study medication.
- There were no clear, consistent treatment- or time-related changes in vitals signs and all ECGs were considered clinically normal. No subjects had QTc intervals of more than 450 milliseconds during the study.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

- For endocrine responses, PSS, SSAI and VAS scales, there were no apparent concentration-response trends on top of the dose-response analysis.
- Given there was no clearcut PK/PD-signal in the data, further PK/PD modeling was not deemed useful at this stage.

CONCLUSION:

- Healthy male volunteers given 100 mg R317573 b.i.d. showed reduction in three independent measures of anxiety associated with the CCK-4 challenge, with no sedation after 1 week of treatment. The results obtained in the 200 mg o.d. cohort supported this conclusion, although they were less consistent when compared to the results obtained in the 100 mg b.i.d. cohort.
- While isolated behavioral ratings (VAS scales for anxious, fearful and tense, Day 8 versus Day -1 post CCK-4) suggested a treatment effect of 40 mg R317573 o.d., the absence of any of the effects on neuroendocrine and cardiovascular responses, the panic symptom inventory, and anticipatory anxiety (SSAI) observed with the higher doses, led to the judgement that 40 mg was substantially less effective in reducing anxiogenic effects of CCK-4. Following consultation between the sponsor and the principal investigator, it was anticipated that lower doses of R317573 would be ineffective and the protocol was declared to be complete.

SYNOPSIS (CONTINUED)

- The modest reduction in behavioral response to the CCK-4 challenge observed with the higher doses of R317573, along with the blunting of neuroendocrine and cardiovascular effects of the challenge, suggest that the selective CRF1 receptor antagonist R317573 may have anxiolytic effects in patients. Moreover, the differences between the cohorts suggest that this effect is dose dependent, with greater anxiolytic potential being associated with the higher doses.
- The less consistent effects at 200 mg o.d. and the absence of effect on the CCK-4 responses at 40 mg o.d., compared with the effects seen in the 100 mg b.i.d. group, can possibly be explained by the fact that the pharmacodynamic assessments were performed at observed mean R317573 plasma levels that were 36.8% and 11.9%, respectively, of the R317573 plasma levels at the time of the pharmacodynamic assessments in Cohort 1. The 200 mg o.d. group differed in baseline responses compared with the 100 mg b.i.d. group precluding the planned pooling of the placebo subjects from the two cohorts although the direction of effect was of a similar direction and magnitude as the 100 mg b.i.d. group.
- R317573 administered orally as 40 mg o.d. or 200 mg o.d. for 7 consecutive days, or 100 mg b.i.d. for 7 consecutive days and a single morning dose on Day 8, was well tolerated by healthy male subjects in this study. Effects on liver transaminases (increases in ALT and/or AST) were observed in some subjects in the 100 mg b.i.d. and 200 mg o.d. dose groups; results from studies with longer periods of exposure suggest that the mild increases observed are consistent with dose and time dependent hepatocellular injury with these higher doses. These effects were not associated with any other clinical signs or symptoms; were easily monitorable, mild, and fully reversible with cessation of treatment. No other significant safety issues were identified in this study.

Issue Date of the Clinical Study Report: 13 September 2007

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed Product. Some information in this posting may differ from the approved labeling for the Product. Please refer to the full prescribing information for indications and proper use of the product.