SYNOPSIS OF POST-MARKETING CLINICAL STUDY

Sponsor of post-marketing clinical study

Aventis Pharma Ltd. (Currently sanofi-aventis K.K.)

Post-marketing clinical study protocol identification code

XRP4274E/4101

Title

Evaluation of the pharmacokinetics of Riluzole (XRP4274) and RPR112512 following repeated oral administration of a Rilutek® tablet twice daily for 8 days in healthy Japanese and Caucasian adult male subjects

Post-marketing clinical study Investigator, study site

[redacted]

Study duration and dates	Study initiation date: 25 November 2004 Study completion date: 30 March 2005	**Study phase**	Post-marketing clinical study (study as a condition for approval

Objectives

Primary objective

To evaluate and compare the pharmacokinetics of XRP4274 and its metabolite RPR112512 after repeated oral administration of a Rilutek® tablet twice daily for 8 days in healthy Japanese and Caucasian adult male subjects

Secondary objective

To assess the safety and tolerance of XRP4274 after repeated oral administration of a Rilutek® tablet twice daily for 8 days in healthy Japanese and Caucasian adult male subjects

Study design

A single-center, open-label, repeated oral administration study

Target number of subjects

16 healthy Japanese adult male subjects and 16 healthy Caucasian adult male subjects (32 subjects in total)

Inclusion criteria

1. Healthy adult men aged between 20 and 45 years, inclusive.
2. Ethnic origin
   - Caucasian subjects: Caucasians residing in Europe and/or North America.
   - Japanese subjects: Persons with Japanese citizenship whose parents were both Japanese and who had resided in Europe and/or North America for less than 10 years at the time of giving written consent.
3. Body Mass Index (BMI) between 18.5 and 27 kg/m^2, inclusive, and weight between 55 and 90 kg.
4. Subjects who had the ability to read and write, comprehend and complete necessary information.
5. Subjects who were able to understand the study contents and give written consent prior to any examination specified in the post-marketing clinical study protocol.
6. Subjects testing negative in drug screening (barbiturates, benzodiazepines, amphetamines, opiates, cocaine and cannabinoids) at screening.
7. Subjects who agreed not to consume beverages containing alcohol or caffeine (tea, coffee, chocolate or cola) from 24 hours before the first administration until 96 hours after the final administration or grapefruit from 72 before the first administration.
8. Subjects who were able to be hospitalized in the study center during the inpatient period of the study.

Exclusion criteria

1. Subjects considered inappropriate for the study by the post-marketing clinical study investigator or sub-investigator based on the screening results.
2. Smokers or former smokers who had smoked during the 6 months before the initiation of the treatment for the study or who had a smoking history of ≥ 5 pack-year (1 pack-year equals 20 cigarettes per day for 1 year).
3. Habitual consumption of large quantities of coffee or tea (equivalent to ≥ 6 cups/day).
4. Habitual consumption of large amounts of cruciferous vegetables (Brussels sprouts, cabbage, broccoli, turnip or cauliflower), i.e. ≥ 2 times per week.
5. Habitual consumption of large amounts of charbroiled food, i.e. ≥ 2 times per week.
6. Use of acetaminophen within 2 days before the study, or regular user of acetaminophen.
7. Failure in the following tests:
   - Medical history and physical examination

- Laboratory tests (hematology/coagulation, biochemistry and dipstick urinalysis)
- Standard 12-lead electrocardiogram
- Screening for hepatitis and HIV

8. Treatment with any drug known to be toxic to major organs within 3 months before the initiation of the study treatment.
9. Treatment with any other investigational product within 3 months before study entry.
10. Likelihood of receiving treatment with drugs prohibited by the post-marketing clinical study protocol during the study period.
11. History of clinically significant illnesses within 3 months before the initiation of the study treatment.
12. Past or present history of gastrointestinal, liver or kidney disease, or other conditions considered to interfere with the absorption, distribution, metabolism or excretion of the post-marketing clinical study drug.
13. History of hypersensitivity to the study drug or drugs with a similar chemical structure.
14. Drug addiction or alcohol dependence.
15. Consumption of ≥ 20 g of alcohol (0.5 L of beer, 0.25 L of wine or 3 glasses of liquor) per day.
16. Food allergies.
17. Blood collection of ≥ 450 mL during the 3 months before the initiation of the study treatment.
18. Past use of the study drug.
19. Regular use of prescription or OTC medicines.
20. Shift-workers, except those able to comply with the study requirements.
21. Lack of the ability to understand the nature, scope and possible consequences of the study.
22. Poor compliance in the past.
23. Low probability for compliance with the post-marketing clinical study protocol, e.g. uncooperative attitude, inability to return for follow-up visits or unlikelihood of completion of the study.
24. Persons directly involved in the conduct of the post-marketing clinical study, including the investigator, sub-investigator, research assistant, pharmacist, study coordinator, and other staff members.

Post-marketing clinical study drug

Rilutek® tablet: a film-coated tablet containing 50 mg of riluzole.

Pharmacokinetics

Plasma concentrations of XRP4274 and its metabolite RPR112512 were determined from Day 1 to Day 12 at the following sampling time points:

Day 1 to Day 7: Before AM administration only (5 mL x 7 times)

Day 8: Before and 0.5, 1, 1.5, 2, 4, 6, 8, 12 and 16 hours after the final administration (5 mL x 10 times)

Day 9: 24 and 36 hours after the final administration (5 mL x 2 times)

Day 10: 48 hours after the final administration (5 mL x 1 time)

Day 11: 72 hours after the final administration (5 mL x 1 time)

Day 12: 96 hours after the final administration (5 mL x 1 time)

Plasma concentrations of XRP4274 and RPR112512 were measured using a validated LC/MS/MS method with a lower limit of quantification of 0.5 ng/mL for each compound.

Pharmacodynamics

Not applicable to this study.

Safety

Physical examination

Laboratory tests: hematology/coagulation, blood biochemistry, urinalysis

Blood pressure, pulse rate and body temperature

Standard 12-lead Electrocardiogram (ECG)

Adverse events reported by the subject or observed by the post-marketing clinical study investigator.

Statistical analysis

Pharmacokinetic data

Pharmacokinetic parameters were calculated based on a non-compartmental model.

For XRP4274 and RPR112512, descriptive statistics of the plasma concentration at each measurement and pharmacokinetic parameters, including two-sided 90% Confidence Interval (CI), were obtained for each group.

Comparison of pharmacokinetic parameters between the Japanese and Caucasian groups

Pharmacokinetic parameters (e.g. CL, C_{max} and AUC) for XRP4274 and RPR112512 were compared using the two-sided 90% CI of the difference between the groups.

Safety data

Adverse events were summarized for each subject in a listing. They were classified and presented using the MedDRA system organ class and preferred term code.

Blood pressure, pulse rate, body temperature, laboratory test results and standard 12-lead ECG were presented as descriptive statistics.

All measurements of safety parameters were summarized by race and measurement time point.

Interim analysis

Interim analysis was not planned or performed.

Results - Conditions of the conduct of study and disposition of subjects

The number of enrolled subjects: 16 Japanese subjects and 17 Caucasian subjects (33 in total)
The number of subjects who received treatment: 16 Japanese subjects and 17 Caucasian subjects (33 in total)
Discontinuation of treatment: None
The number of subjects who completed the study: 16 Japanese subjects and 17 Caucasian subjects (33 in total)
The number of subjects included in pharmacokinetic analysis: 16 Japanese subjects and 16 Caucasian subjects (32 in total)
The number of subjects included in safety analysis: 16 Japanese subjects and 17 Caucasian subjects (33 in total)
Demographics: the ranges (minimum value to maximum value) were as follows:

	Japanese subjects	Caucasian subjects
Age (year)	23-39	23-41
Weight (kg)	55.0-76.0	67.0-83.0
Height (cm)	165-183	171-191
BMI（kg/m^2）	18.8-26.3	20.2-26.7

Results - Pharmacokinetics

Pharmacokinetic parameters of XRP4274 (after the final administration)

XRP4274		C max ng/mL	AUC (0-∞) hr･ng/mL	CL L/hr	AUC (0-12) hr･ng/mL
Japanese	Mean	179.24	1346.49	75.4899	733.14
	SD	71.51	515.50	22.6663	272.98
	CV	39.9	38.3	30.0	37.2
	Median	162.00	1276.70	72.6855	688.10
Caucasian	Mean	207.86	1607.87	71.3376	833.76
	SD	78.28	844.51	29.9413	381.76
	CV	37.7	52.5	42.0	45.8
	Median	194.50	1340.95	68.5550	730.85
90% C.I. for difference of two group		-73.6081, 16.3706	-681.2038, 158.4413	-11.7820, 20.0868	-299.7659, 98.5159
p value of one-sided t-test		0.8556	0.8505	0.6693	--------

Pharmacokinetic parameters of RPR112512 (after the final administration)

RPR112512		C max ng/mL	AUC (0-∞) hr･ng/mL	AUC (0-12) hr･ng/mL
Japanese	Mean	68.15	263.8	205.04
	SD	29.85	62.08	48.97
	CV	43.8	23.5	23.9
	Median	61.25	242.30	195.75
Caucasian	Mean	64.01	255.43	189.33
	SD	20.70	69.32	43.62
	CV	32.3	27.1	23.0
	Median	64.45	269.00	198.25
90% C.I. for difference of two group		-11.2760, 19.5510	-31.0914, 47.8789	-12.1123, 43.5373
p value of one-sided t-test		0.3260	0.3604	--------

PK analysis was performed on 32 evaluable subjects.

XRP4274 and RPR112512 were rapidly absorbed in both races, achieving the maximum plasma concentration in 30 minutes to 2 hours after administration.

The plasma concentrations of XRP4274 and RPR112512 after the final administration changed similarly between the Japanese and Caucasian groups, and comparison between races by analysis of variance showed no differences.

Results - Pharmacodynamics

Not applicable to this study.

Results – Safety

No serious adverse events were observed. Except for one case of moderate constipation, which was found not related to the study drug, all adverse events were mild in severity. The main adverse events considered related to the study medication were fatigue, somnolence and headache. Concerning laboratory test values, an increase in ALT above the upper limit of normal was observed in 4 Japanese subjects and in 2 Caucasian subjects. Only one of them exceeded 3 XULN and was reported as adverse event.
Other safety parameters showed no abnormal changes that were clinically significant.
Based on the above, the repeated administration of a Rilutek® tablet was well tolerated generally by both Japanese and Caucasian subjects.

Conclusion

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