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Sponsor / Company: sanofi-aventis	Study Identifier: NCT00631579
Drug substance(s): rasburicase	Study code: ARD5290
Title of the study: Open-label, multicenter study of repeated doses of SR29142 (rasburicase) as a uricolytic therapy for hyperuricemia in adult patients with leukemia or lymphoma	
Study center(s): 9 study centers in Japan	
Study period: Date first patient enrolled: 01-Apr-2003 Date last patient completed: 29-Jun-2004	
Phase of development: Phase II	
Objectives: <u>Primary objective:</u> <ul style="list-style-type: none"> ▪ To evaluate the safety in patients with malignant lymphoma or acute leukemia who were repeatedly administered SR29142 for 5 days, in two dosage groups (0.15 mg/kg and 0.20 mg/kg). The safety was evaluated via physical examination and laboratory tests, and Adverse Events (AEs) observed from the first administration to 36 days after the first administration; ▪ To evaluate the efficacy in patients with malignant lymphoma or acute leukemia who were repeatedly administered SR29142 for 5 days, in two dosage groups (0.15 mg/kg and 0.20 mg/kg). The efficacy was evaluated via plasma uric acid levels from the first infusion to 24 hours after the last infusion. <u>Secondary objective:</u> <ul style="list-style-type: none"> ▪ To determine the pharmacokinetic (PK) parameters of SR29142 in patients with malignant lymphoma and acute leukemia; ▪ To assess anti-SR29142 antibody production in patients with malignant lymphoma and acute leukemia; ▪ To estimate the optimal dosage of SR29142 for Japanese patients from the results of efficacy and safety evaluations. 	
Methodology: Multi-center, open-label, randomized repeated dose study	
Number of patients: Planned: 50 Randomized: 50 Treated: 50 Evaluated for safety: 50; efficacy: 50; pharmacokinetics: 21	
Diagnosis and criteria for inclusion: <ul style="list-style-type: none"> ▪ ≥18, <75 years of age, male or female; ▪ Patient suffering from: <ul style="list-style-type: none"> - Acute leukemia with white blood cell (WBC) count ≥ 20,000/mm³ without regard to uric acid level; or - Lymphoma, Stage ≥ III without regard to uric acid level; or - Lymphomas, Stage II with bulky disease (defined as a node or nodal mass ≥ 10 cm, or the maximum width of a mediastinal mass ≥ one-third of the internal transverse diameter of the thorax at the level of T5/6); or - Lymphoma or leukemia, without regard to classification or morphology, with uric acid level ≥ 8.0 mg/dL, and lactate dehydrogenase (LDH) level ≥ twice the upper limit of normal (ULN). 	

Diagnosis and criteria for inclusion (cont'd):

- Patient was scheduled to be treated with approved chemotherapeutic agent(s) as effective treatment for the disease being treated as first induction;
- Patient was expected to have a minimum life expectancy of 40 days and a PS \leq 3 on the Eastern Cooperative Oncology Group (ECOG) scale;
- Patient was able to enter the hospital from 24 hr before first administration to Day 8;
- Written informed consent was signed by the patient and his legally authorized representative if the patient were less than 20 years old.

Investigational product: Rasburicase (SR29142): freeze-dried powder, 7.5 mg/vial, white to off-white pellet

Dose: 0.15, and 0.20 mg/kg daily

Administration: Intravenous infusion over 30 minutes

Duration of treatment: 5 days

Duration of observation: Maximum of 40 days

Criteria for evaluation:

Efficacy:

Primary endpoint: Responder: Patients with a plasma uric acid level decreased to the endpoint (\leq 7.5 mg/dL) by 48 hr after the start of first drug infusion and lasting until 24 hr after the start of final (Day 5) drug infusion.

Secondary endpoints: The following pharmacodynamic parameters were evaluated as secondary efficacy endpoints:

- Inhibitory rate of plasma uric acid at 4hr after first administration on day 1 versus baseline;
- Inhibitory rate of plasma uric acid at 8hr after first administration on day 1 versus baseline;
- Inhibitory rate of plasma uric acid at 48hr after first administration versus baseline;
- Inhibitory rate of plasma uric acid at 24hr after last administration versus baseline;
- Plasma uric acid area under curve (AUC);
- Amount of allantoin in urine and urinary allantoin excretion rate (Allantoin is a product of uric acid metabolism by rasburicase and is a surrogate marker of rasburicase activity);
- Renal function: Serum Creatinine, K, P, Ca and Creatinine clearance.

Safety:

Safety was assessed via clinical observations, laboratory tests, vital signs (blood pressure, pulse rate, and body temperature), and the occurrence of AEs (evaluated according to the JCOG version of National Cancer Institute-Common Toxicity Criteria [NCI-CTC] version 2.0).

Antigenicity of SR29142 was evaluated during the treatment. If the result were positive, the patient was to be followed (if possible) until antibody was no longer present.

Pharmacokinetics:

The following SR29142 pharmacokinetic parameters were determined by non-compartmental analysis: plasma concentration observed before treatment administration during repeated dosing (C_{min}), plasma concentration observed at end of an IV infusion (C_{eoi}), terminal half-life associated with the terminal slope ($t_{1/2z}$), area under the plasma concentration versus time curve from time zero to the real time 24h (AUC_{0-24}), and R (accumulation ratio) for AUC_{0-24} .

Statistical methods:**Efficacy:**

Responders were defined as patients with a plasma uric acid level that decreased to the endpoint (≤ 7.5 mg/dL) by 48 hr after the start of first study drug infusion and lasting until 24 hr after the start of final (Day 5) study drug infusion.

For total amount of allantoin in urine, descriptive statistics were calculated by treatment group and treatment groups compared using a t-test, and 95% CIs were calculated. Descriptive statistics at each period were calculated by treatment group, and the time course was presented graphically by treatment group. For allantoin excretion rate, descriptive statistics at each day were calculated by treatment group. For plasma uric acid AUC, descriptive statistics were calculated by treatment group and be compared by treatment group using a t-test, and 95% CI.

Safety:

Number (incidence) of AEs was summarized by dose regimen. Clinical laboratory evaluations, vital signs, and electrocardiogram (ECG) results were summarized using number of observations, mean, standard deviation (SD), minimum and maximum by dose regimen. The changes from baseline were summarized similarly.

For circulating antibody determination, results at each time point were summarized using number and percent of patients by treatment group. Positive rate at each time point and 95% confidence interval (CI) were computed by treatment group.

Pharmacokinetics:

Pharmacokinetic parameters of SR29142 were summarized by mean, SD, coefficient of variation (CV), minimum and maximum for each dose group. Dose proportionality for AUC₀₋₂₄ and C_{eo} were evaluated using the log transformed power model. An estimate and 90% CI for the difference in dose group means (0.20 mg/kg – 0.15 mg/kg) was computed within the mixed model framework (for each day if the dose by day interaction term was retained in the model), and converted to a ratio of adjusted means by the antilog transformation.

Summary:**Study population:**

Overall, the mean age was 52.5 years ranging from 19 to 73 years. Twelve patients (24%) were ≥ 65 years old. An equal proportion of males and females were randomized. The majority of patients (68%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0. Demographic characteristics were similar between the 2 dose groups. Demographic characteristics were similar between the 2 dose groups whether based on hyperuricemic status or risk category.

A total of 5 (10%) patients were hyperuricemic at baseline and approximately half were stage IV lymphoma patients. Diagnosis and baseline disease status were similar between the 2 dose groups whether based on hyperuricemic status or risk category.

Efficacy results:

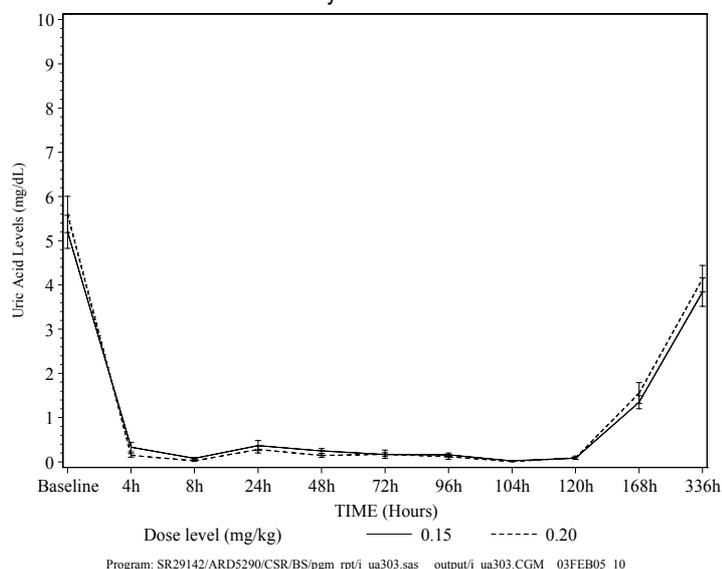
The response rate was 100% in the 0.15 mg/kg group and 96% in the 0.20 mg/kg group. The overall response rate for this study was 98% (95% confidence interval: 89.3-100.0).

Exploratory analysis revealed that the response rate was similar within each dose group when evaluated by hyperuricemic status or risk category.

Mean plasma uric acid concentrations by dose over time are presented in the following figure. Uric acid levels declined rapidly within 4 hours of the first dose and returned to normal at Day 15.

Efficacy results (cont'd):

Mean plasma uric acid concentrations by dose over time are presented in the following figure. Uric acid levels declined rapidly within 4 hours of the first dose and returned to normal at Day 15.



Additionally, the ability of rasburicase to prevent hyperuricemia was further supported for both doses by the appearance of large amounts of urinary allantoin, the end point of uric acid metabolism by rasburicase and a marker of SR29142 activity. Excretion of allantoin was graphically similar in both groups. Mean production of allantoin was 100-fold greater than baseline levels following rasburicase administration.

Mean (SD) allantoin excretion rate in urine (mg/h)

Day	0.15 mg/kg	0.20 mg/kg
Pre-dose	1 (2)	1 (2)
1	55 (54)	51 (30)
2	37 (22)	44 (25)
3	47 (21)	40 (21)
4	39 (15)	43 (24)
5	37 (13)	38 (22)
6	23 (9)	25 (13)
7	14 (6)	17 (8)

Pharmacokinetic results:

Increase in exposure of SR29142, as measured by AUC₀₋₂₄ and C_{eoI}, between 0.15 and 0.20 mg/kg was dose-proportional. The steady state was reached rapidly (Day 2 or Day 3).

t_{1/2z} was comparable for both groups. SR29142 exhibited a very slight accumulation on Day 5 as measured by C_{eoI}. Variability on AUC₀₋₂₄ and C_{eoI} was moderate.

Mean (CV%) SR29142 PK Parameters

Dose Group (mg/kg)	Day 1		Day 5			
	AUC ₀₋₂₄ (ng.h/mL)	C _{eoI} (ng/mL)	AUC ₀₋₂₄ (ng.h/mL)	t _{1/2z} (h)	C _{eoI} (ng/mL)	C _{min} (ng/mL)
0.15 (n = 11)	45653 (17)	3734 (29)	48210 (20)	22.5 (26)	3948 (18)	852 (32)
0.20 (n = 10)	59333 (27)	4239 (37)	65154 (35)	16.1 (35)	5126 (29)	1033 (48)

Summary (cont'd):**Safety results:**

Forty-nine patients (98%) completed 5 days of treatment. One patient who was administered 0.20 mg/kg did not complete 5 days of treatment due to a Serious Adverse Event (SAE) leading to withdrawal.

All patients had at least one AE regardless of relationship to study medication. The majority of these AEs were attributed to either chemotherapy and/or hematological malignancies.

All grade drug related AEs occurred in 23 patients (46.0%) overall; 10 patients (40.0%) were in the 0.15 mg/kg treatment group and 13 patients (52.0%) were in the 0.20 mg/kg treatment group. Grade 3-4 drug related AEs occurred in 6 patients (12%) overall; 2 patients (8%) were in 0.15 mg/kg treatment group and 4 patients (16%) were in the 0.20 mg/kg treatment group. The most frequently occurring drug-related AEs were in the Investigations system (6 patients [24.0%] in each treatment group), predominantly liver enzyme elevations. No patients experienced hemolysis or methemoglobinemia during the study.

Hypersensitivity-associated reactions (regardless of causal relationship) occurred in 35 patients overall (70.0%). Grade 3 or 4 hypersensitivity-associated reactions including pyrexia, rash, and hypoxia, regardless of causality were reported in 8 patients (16%). These events were all manageable and resolved with no sequelae.

Eleven patients (22.0% all grades; 5 in the 0.15 mg group and 6 in the 0.20 mg group) had hypersensitivity events that were classified as being related to study treatment. Drug-related Grade 3 and 4 hypersensitivity reactions were reported in 2 patients (4.0%), both of whom were in the 0.2 mg/kg group.

Hypersensitivity AEs included any of the following: anaphylactic shock, bronchospasm, dermatitis, dermatitis exfoliative, dyspnea, hypotension, hypoxia, rash, rash erythematous, rash maculo-papular, urticaria, pyrexia, edema, chest pain, chest discomfort, hypersensitivity, pharynx discomfort, hoarseness, pharyngeal erythema, pruritus, erythema, localized exfoliation, rash papular, swelling face, toxic skin eruption, hot flush, flushing.

No deaths occurred during the study.

One patient in the 0.20 mg/kg treatment group was removed from treatment by the Investigator due to an SAE (elevated hepatic enzymes). Although the uric acid was 5.5 mg/dL at baseline it decreased to <0.1 mg/dL for the 3 days on study drug. The final uric acid level was not obtained and therefore the patient was classified as a non-responder per-protocol.

There were no clinically significant changes in renal function parameters during the study.

None of the patients had anti-SR29142 antibodies on Day 8. Five patients (10%) had anti-SR29142 antibodies on Day 29: 2 from the 0.15 mg/kg dosage group and 3 from 0.20 mg/kg dosage group. For 2 patients in the 0.20 mg/kg dosage group, the presence of antibodies was still detectable at 6 months. One patient had no antibodies at 1 year; the other patient was lost to follow-up.

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