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Sponsor/Company:	sanofi-aventis	**Study identifier:**	NCT00290992
Drug substance(s):	SR29142 (Rasburicase)	**Study Code:**	ACT5080
		Date:	21 June 2007

Title of the study:	Open-label, multi-center study of SR29142 as uricolytic therapy/prophylaxis for hyperuricemia in pediatric patients with newly diagnosed hematological malignancies at high risk for Tumor Lysis Syndrome
Coordinating Investigator:	**Coordinating Investigator:** Ichiro Tsukimoto, Department of Pediatrics, Toho University Medical Center, Omori Hospital **Medical Officer :** Eiji Uchida, Professor, Second Department of Pharmacology, Showa University School of Medicine
Study centers:	21 centers in Japan
Publications:	None
Study period: Date first patient enrolled: 21 June 2005 Date last patient completed: 19 April 2006	**Phase of development:** Phase II
Objectives:	
Primary:	• The primary objective of this study is to estimate response rate in pediatric patients with newly diagnosed hematological malignancies at high risk of tumor lysis syndrome (TLS) who are treated with SR29142, by evaluation of plasma uric acid concentration.
Secondary:	• The secondary objectives of this study is to investigate the safety in this population, the area under the plasma concentration (AUC) of plasma uric acid, the rate of uric acid reduction at 4 hours after study drug infusion, anti-SR29142 antibody, anti-Saccharomyces cerevisiae protein (SCP) antibody, and pharmacokinetic parameters of SR29142.
Methodology:	A multi-center, repeated dose, open-label, parallel group study
Number of patients:	Planned: 30 patients Randomized: 30 patients Treated: 30 patients 15 patients for 0.15 mg/kg, 15 patients for 0.20 mg/kg

Diagnosis and criteria for inclusion:	• <18 years of age • Patient with newly diagnosed hematological malignancies presenting with hyperuricemia: − Uric acid > 7.5 mg/dL in patients ≥ 13 years old − Uric acid > 6.5 mg/dL in patients < 13 years old OR, patient with newly diagnosed hematological malignancies presenting with high tumor burden defined as: − Non-Hodgkin's lymphoma, Stage IV regardless of uric acid level, − Non-Hodgkin's lymphoma stage III regardless of uric acid level with one of the following: − At least 1 lymph node or mass > 5 cm in diameter − Lactate dehydrogenase (LDH) ≥ 3 x ULN (IU/L) − Acute leukemia with white blood cell count (WBC) ≥ 50,000/mm^3 or LDH ≥ 3 x ULN (IU/L) regardless of uric acid level • Patient received induction chemotherapy (including cytoreductive corticosteroids) no sooner than 4 and no later than 24 hours after SR29142 administration • Patient was expected to have a minimum life expectancy of 45 days and a performance status (PS) ≤ 3 on the East Coast Oncology Group (ECOG) scale or a PS ≥ 30 on the Lansky score as per the Investigator's preference • Written informed consent signed by the patient (if possible) and his/her legally authorized representative	
Investigational product: Dose: Administration:	SR29142: freeze-dried powder, 7.5 mg/vial 0.15 or 0.20 mg/kg/day Drip infusion through intravenous line	
Duration of treatment:	5 days (once daily)	**Duration of observation:** Maximum of 45 days. Screening to treatment : Max 7 days Treatment period: 5 days Follow-up period: 31 ± 2 days (Max 33 days)
Reference therapy:	Not applicable	
Criteria for evaluation: Efficacy:	**Primary efficacy variable** The primary efficacy variable was response rate; the percentage of responder patients. Responders were defined as patients with a plasma uric acid level decreased to the endpoint (uric acid: ≤ 7.5 mg/dL in patients ≥ 13 years old and ≤ 6.5 mg/dL in patients < 13 years old) by 48 hours after the start of first drug infusion and lasting until 24 hours after the start of final (Day 5) drug infusion. **Secondary efficacy variable** • Plasma uric acid concentration and its change from baseline at each time point. • Individual plasma uric acid AUC from Day 1 just before administration up to the last available point until Day 6 was calculated using the trapezoidal rule for each patient. • Individual inhibitory rate of plasma uric acid at 4hr and 48hr after the first administration and 24hr after the last administration (i.e. D1H4, D3H0 and D6H0, respectively) was calculated for each patient. • Renal function: Serum creatinine, potassium, phosphorus, calcium.	

Criteria for evaluation:	
Safety:	• Safety was assessed on clinical observations, laboratory tests, vital signs (blood pressure, pulse rate, body temperature, and body weight), and the occurrence of adverse events. • Anti-SR29142 antibody and anti-SCP antibody.
Pharmacokinetics:	PK Parameters. AUC_{0-24}: Day 1 and Day 5, C_{min}: Day 1 and Day 5, C_{eoi}: Day 1 and Day 5, $t_{1/2z}$: Day 5.
Pharmacokinetic sampling times and bioanalytical methods:	***Sampling times:*** Pharmacokinetic plasma samplings were performed for each dose on 10 evaluable patients (who weighed 10 kg and over at the registration) at Day 1(before administration, end of infusion, 4 hours and 8 hours after starting administration), Day 2 (before administration), Day 5 (before administration, end of infusion, 4 hours and 8 hours after starting administration) and Day 6 (24 hours after starting administration at Day 5). ***Bioanalytical methods***: *Uric acid levels* • Uric acid determination was made at each medical institution, in principle, within 4 hours of blood collection, otherwise the plasma was immediately frozen. *Anti-SR29142 antibody* • Samples tested positive by enzyme-linked immunosorbent assay (ELISA) were analyzed for inhibition of uricolytic activity of SR29142. *Anti-SCP antibody* • Samples were determined by ELISAs. *SR29142 plasma concentration* • Samples were determined by ELISA with a low limit of quantification (LLOQ) of 1.4 ng/mL.
Statistical methods:	Primary objective was the evaluation of efficacy in terms of estimated response rate and associated 95% confidence intervals (CI) in patients enrolled who received at least 1 dose of study drug. Secondary objectives included estimates of AUC of plasma uric acid, the inhibitory rate of plasma uric acid at 4 hours after study drug infusion, and proportion of patients who develop positive IgG and neutralizing antibodies. The incidence of adverse events was summarized by type of event and toxicity grade. Toxicities were graded according to the Japanese version JCOG/JSCO of CTCAE v3.0. Pharmacokinetic parameters of SR29142 (C_{min} , C_{eoi} , AUC_{0-24} and $t_{1/2}$ [Day 5 only]), were calculated and summarized by mean, standard deviation (SD), coefficient of variation (CV), minimum and maximum for each dose group. Dose proportionality for AUC_{0-24} and C_{eoi}, and within-patient, between-patient, and total variances for log of AUC_{0-24} were evaluated.

Summary:

Overall, the mean age was 8.8 years ranging from 0 (2 months old) to 17 years old in enrolled patients. The majority of patients (53.3%) were 6 to 12 years old. The mean weight was 32.25 kg and one patient was under 10 kg. The majority of patients had ECOG performance status of 0 (40%) or 1 (40%). There were no notable differences between dose groups for demographic and baseline characteristics.

Efficacy results:

Fifteen patients were evaluable for response for the 0.15 mg/kg group and 15 for the 0.20 mg/kg group. One patient in the 0.20mg/kg group was classified as non-evaluable patient for response rate calculation. The overall response rate was 96.6% (28/29). The response rate in the 0.15 mg/kg group was 93.3% (14/15) and in the 0.20 mg/kg group was 100% (14/14) respectively. One patient in the 0.15 mg/kg group was considered as a non-responder. Response rates in patients who had hyperuricemia at baseline were 87.5% (7/8) in the 0.15 mg/kg group and 100.0% (5/5) in the 0.20 mg/kg group. Response rates were high and similar in both dose groups.

Safety results:

The overall safety data regarding AEs was similar between the two dose groups from the point of view of AEs occurrence and type of AEs by preferred term. The majority of AEs reported during the study period judged by investigator are attributed to the underlying cancer and/or the chemotherapy. Only one patient had SAEs (multiple cerebral haemorrhage, brain oedema, brain herniation) after SR29142 administration in the 0.15 mg/kg group, these events were judged by the investigator not to be related to SR29142.
AEs expected from SR29142, were based on its protein nature (hypersensitivity) as well as its mechanism of action (production of H_2O_2 as by-product resulting in hemolysis and methemoglobinemia). Hypersensitivity-associated reactions, regardless of relationship to study medication, occurred in 20 patients (66.7%). Most hypersensitivity-associated reactions were pyrexia (40.0%), all of which were grade 1 or 2 and mild. Hypersensitivity and hemolysis occurred in 2 patients (6.7%) and 1 patient (3.3%) respectively, but there were no serious AEs.
Anti-SCP antibody was detected before SR29142 administration in one patient. Another patient had anti-SR29142 antibody on Day 29, however, the result was negative after 6 months of the initial administration. These patients did not have an AE of hypersensitivity-associated reactions.

Pharmacokinetic results:

After 5 days of administration of SR29142 as a 30-min intravenous infusion to Japanese pediatric patients at the doses of 0.15 and 0.20 mg/kg /day, SR29142 exposure appeared to be dose proportional. SR29142 exhibited slight accumulation on Day 5 as measured by AUC_{0-24} and C_{eoi}. $t_{1/2z}$ was comparable for both groups and variability in AUC_{0-24} and C_{eoi} values were small.

Mean (SD) SR29142 PK Parameters

	Day 1		Day 5			
Dose Group (mg/kg)	**C_{eoi} (ng/mL)**	**AUC_{0-24} (ng •h/mL)**	**C_{min} (ng/mL)**	**C_{eoi} (ng/mL)**	**AUC_{0-24} (ng*h /mL)**	**$t_{1.2z}$ (h)**
0.15 (n=10)	2160 (512)	28200 (7270)	536 (218)	2490 (373)	29700 (6460)	11.6 (4.96)
0.20 (n=9)	2580* (432)	31500 (4540)	780 (335)	3050 (383)	38100 (5640)	11.2 (3.06)

* n=10

Date of full report: 18 May 2007