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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00563771
		Study Code:	L_8720
Generic drug name:	Rasburicase	**Date:**	23/Jan/2008

Study title :	Phase IV, compassionate use program of rasburicase for treatment of hyperuricemia in children and adolescent patients with tumor lysis syndrome
Investigators :	Prof. Hyo-Seop Ahn (coordinating investigator), Prof. Hong-Hwai Koo, Prof. Hoon Kook, Prof. Hak-Ki Kim, Prof. Jong-Jin Seo, Associate Prof. Hee-Young Shin, Associate Prof. Chuhl-Joo Lyu, Prof. Kun-Soo Lee, Prof. Kwang-Chul Lee
Study centers :	8 centers in Korea : Catholic University of Korea, St. Mary's Hospital, Kyungpook National University Hospital, Korea University Medical Center Ahnam Hospital, Samsung Medical Center, Seoul National University Hospital, Asan Medical Center, Yonsei University College of Medicine, Severance Hospital, Chonnam National University Hospital
Study period : First patient enrolled : 25-Mar-2003 Last patient completed : 26-Jan- 2004	**Study design :** Open-label, multi-center (8), non-comparative, compassionate, phase IV study
Study objective :	To provide treatment opportunity to children and adolescent patients with hematologic malignancies by supplying the product not marketed yet and to observe the efficacy and safety of rasburicase used in the treatment of hyperuricemia. The investigational drug of this study was already approved by the Korea Food and Drug Administration as an orphan drug in April 2002, but its launch was delayed. So, the drug was provided through the compassionate use program.
Study method :	The baseline assessment was conducted within 48 hours before the administration of the investigational drug in children and adolescent patients with hematologic malignancies suffering from acute hyperuricemia (uric acid > 7.5 mg/dL) before or during chemotherapy. And rasburicase was given 1~2 times a day for 3~5 days. Blood chemistry test was performed and adverse events were evaluated through the follow-up 4 weeks after the administration of the last dose of the investigational drug.

Number of patients :

	Number of patients
Planned	30
Enrolled	38
Treated	38
Off study at F/U of 4 weeks post last dose :	
Completed study	29
Adverse event	0
Death	8
Other(protocol violation)	1
Evaluable for efficacy (modified ITT)	38
Evaluable for safety (ITT)	38

Indication and main criteria for inclusion :

- Age < 18 yrs old
- Acute hyperuricemia patients before / during chemotherapy for hematologic malignancies (uric acid > 7.5 mg/dL)
- With a minimum life expectancy of 3 months
- Having previously signed a written informed consent.

Exclusion criteria :

- Hypersensitivity to uricase or any of the excipients.
- Known history of G6PD deficiency.
- Previous treatment with Rasburicase or Uricozyme®.
- Treatment with any investigational drug within 30 days before planned first Rasburicase administration.

Investigational drug :

- Investigational drug and contents: Rasburicase (Fasturtec®) 1.5 mg/vial
- Dosage and administration:
  - Rasburicase 0.20mg/kg/day was intravenously administered once a day for 3~5 days before or during chemotherapy. Additional doses of rasburicase were permitted q12h during the first 72 hours of chemotherapy in case hyperuricemia persisted or the patient was considered to be at significant risk of tumor lysis complications.
  - If hypouricemic treatment needed to be prolonged over 5 days and uric acid was above the upper limit of normal, allopurinol per os at the dose of 300 mg/day would be started. Then treatment would be adjusted so that the dose might not be over 10 mg/kg/day and continued as needed.

Duration of study per patient : 5 weeks	**Duration of treatment :** planned: 3~5 days, actual: 1~5 days	**Observation period:** follow-up of 4 weeks after the last dose of study drug

Criteria for and method of evaluation :

Efficacy : Primary endpoint :

The efficacy of the study drug was evaluated by measuring blood uric acid and evaluating the number of responders within 24 hours after the completion of Rasburicase treatment. Response was defined as achievement of uric acid level
= 7.0 mg/dL.

Secondary endpoint:

The difference between uric acid levels before treatment and after the administration of the last rasburicase was evaluated.

Safety :

Safety was evaluated by analyzing adverse events and laboratory test results.

For adverse events that occurred during the administration of Rasburicase and up to 7 days after the completion of the treatment, toxicity was evaluated according to NCI Common Toxicity Criteria 2.0 grading system, and the relationship to the study drug and outcomes of adverse events shown up to 4 weeks after the last treatment were also evaluated.

Statistical methods :

Efficacy : For the primary efficacy variables, frequency, ratio and 95% lower confidence limit were presented. For the secondary efficacy variables, descriptive statistics were presented and paired t-test and Wilcoxon's signed rank test were performed.

Safety : For the safety evaluation variables, descriptive statistics were presented by each item of the clinical laboratory tests, and for adverse events, frequency, ratio and mean number of adverse events per patient and AE rate of whole patients presented.

Results :

Demographic characteristics :

Summary of baseline demographic characteristics

Parameters		Number(%) of patients
Age	0 – 5	13 (34.2)
	5 – 10	13 (34.2)
	10 - 15	11 (29.0)
	15 - 18	1 (2.6)
Gender	Male	27 (71.0)
	Female	11 (29.0)
ECOG Score	= 1	17 (44.7)
	2, 3, 4	21 (55.3)
Diagnosis	Non Hodgkin's Lymphoma	7 (18.4)
	Leukemia	30 (78.9)
	NA	1 (2.6)

Weight (Kg)	Mean	34.1
	Median	26.5
	Min	5.1
	Max	85.0

Administration of study drug :

Summary of exposure to Rasburicase : Daily dose and total cumulative dose

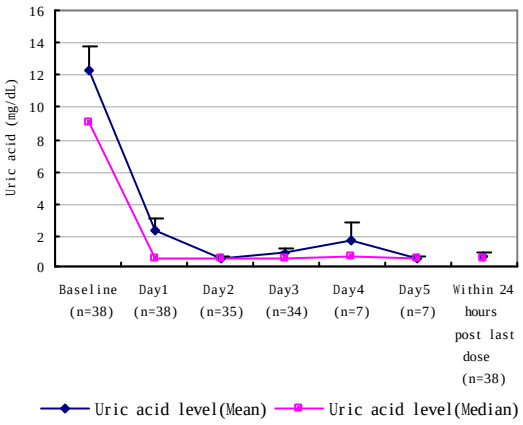
Category	Statistics	
Total number of doses	N	124
Number of doses per patient	Mean	3.26
	Median	3.00
	Min	1
	Max	6
Daily dose per patient (mg)	Mean	6.78
	Median	5.40
	Min	1.02
	Max	16.50
Cumulative dose per patient (mg)	Mean	21.58
	Median	15.90
	Min	2.80
	Max	60.00
Number of days treated per patient	Mean	3.18
	Median	3.00
	Min	1
	Max	5

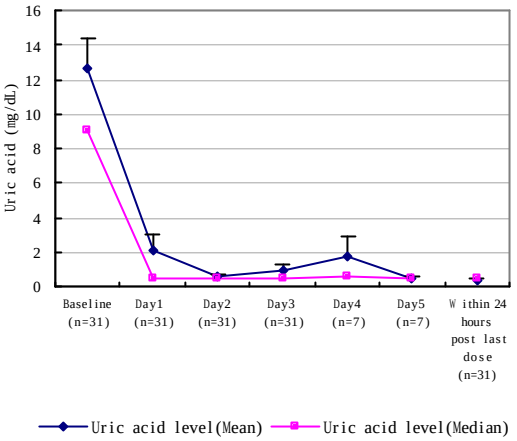
Efficacy : Primary efficacy evaluation

- The uric acid endpoint (= 7.0 mg/dL) was reached in 37 patients among 38 patients of the modified ITT population* with 97.4% (95% exact confidence lower limit: 88.1%) of efficacy rate. And the uric acid endpoint was also reached after the last dose of rasburicase in all 31 patients of the PP1 population** and in all 25 patients of the PP2 population***, so an efficacy rate of 100% (95% exact confidence lower limit: PP1 population – 90.8%, PP2 population – 88.7%) was obtained.

Secondary efficacy evaluation

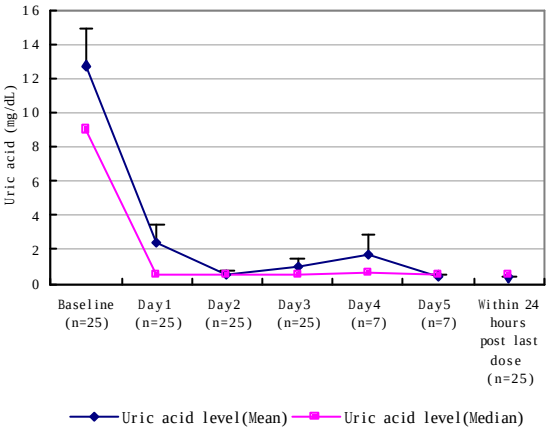
- In the Modified ITT population,* uric acid levels were 12.29 ± 9.14 mg/dL before the treatment and 0.64 ± 1.66 mg/dL after the completion of the treatment, so a significant decrease of uric acid levels by 11.65 ± 9.20 mg/dL was found compared to pre-treatment (Wilcoxon's signed rank test, p-value<0.0001).
- In the PP1 population,** uric acid levels were 12.64 ± 10.03 mg/dL before the treatment and 0.38 ± 0.27 mg/dL after the completion of the treatment, so a significant decrease by 12.26 ± 10.03 mg/dL was found compared to pre-treatment (Wilcoxon's signed rank test, p-value<0.0001).
- In the PP2 population***, uric acid levels were 12.74 ± 10.89mg/dL before the treatment and 0.35 ± 0.26mg/dL after the completion of the treatment, so a significant decrease by 12.39 ± 10.09 mg/dL was found compared to pre-treatment (Wilcoxon's signed rank test, p-value<0.0001).





Mean(±SE) uric acid levels over the treatment period -Modified ITT population*

Mean(±SE) uric acid levels over the treatment period – PP1 population**



Mean(±SE) uric acid levels over the treatment period– PP2 population***

Note : n= number of patients treated with Rasburicase

*Modified ITT population (Modified Intention-to-treat population) :
The patients who received at least one dose of Rasburicase and in who post-treatment uric acid level has been measured

**PP1 population (Per Protocol population based on efficacy analysis) :
The patients who completed a minimal treatment period(3 days) without any major protocol violations from Modified ITT population

***PP2 population (Per Protocol population based on study duration) :
The patients who completed a study period(5weeks including F/U period of 4weeks post last dose) without any major protocol violations from Modified ITT population

Safety :

- During the administration of the study drug, 31 patients (81.6%) received concomitant anti-cancer therapy.

- A total of 115 AEs occurred in 32 patients (84.2%) with on average of 3.0 cases shown per patient.

- The results of analysis of adverse events classified by MedDRA 6.1 System Organ Class showed that the most frequent AEs were gastrointestinal disorders (37 cases - 32.2%) and blood and lymphatic system disorders (14 cases – 12.2%) which were SOCs usually associated with concomitant chemotherapy and the progression of underlying diseases.

- The most frequently reported AEs were headache (11 cases - 9.6%) followed by vomiting (9 cases - 7.8%) and abdominal pain (9 cases - 7.8%). But, if 4 cases of upper abdominal pain were included, AEs related with abdominal pain would total 13 (11.3%) and become the most frequently reported AE.

- Serious adverse event (SAE) and relationship to the study drug :
  5 patients experienced SAEs, among whom 3 patients (13.2%) died. However, no SAEs occurred that were judged to be related to the study drug.

Summary of Serious adverse events – Number of patients (%)

MedDRA System Organ Class	MedDRA Preferred Term	N (%) (n=38)
Blood and lymphatic system disorders	Disseminated intravascular coagulation	1 (2.6)
	Neutropenia	1 (2.6)
Metabolism and nutrition disorders	Hyperkalaemia	1 (2.6)
Respiratory, thoracic and mediastinal disorders	Pulmonary haemorrhage	1 (2.6)
Vascular disorders	Haemorrhage intracranial	1 (2.6)
Total		5 (13.2)

• 42 cases (36.5%) of moderate to severe adverse events of Grade 3 or 4 were noted.

All grade 3 or 4 adverse events

MedDRA System Organ Class	MedDRA Preferred Term	N (%) (n=115)
Blood and lymphatic system disorders	Disseminated intravascular coagulation	2 (1.7)
	Febrile neutropenia	8 (7.0)
	Neutropenia	3 (2.6)
Endocrine disorders	Hyperglycaemia	1 (0.9)
Gastrointestinal disorders	Abdominal pain upper	1 (0.9)
	Loose stools	1 (0.9)
	Melaena	1 (0.9)
	Nausea	2 (1.7)
	Reflux oesophagitis	1 (0.9)
	Vomiting	1 (0.9)
General disorders and administration site conditions	Catheter site haemorrhage	1 (0.9)
	Catheter site infection	1 (0.9)
Hepatobiliary disorders	Cholecystitis	1 (0.9)
	Hepatic function abnormal	4 (3.5)
Infections and infestations	Febrile infection	1 (0.9)
	Genitourinary tract infection	1 (0.9)
	Pyelonephritis acute	1 (0.9)
Metabolism and nutrition disorders	Hyperglycaemia	1 (0.9)
	Hyperkalaemia	1 (0.9)
	Hypokalaemia	2 (1.7)
	Hyponatraemia	1 (0.9)
	Tetany	1 (0.9)
Neoplasms benign, malignant and unspecified (included cysts and polyps)	Cancer pain	1 (0.9)
Respiratory, thoracic and mediastinal disorders	Pleural effusion	1 (0.9)
	Pulmonary haemorrhage	1 (0.9)
Vascular disorders	Haemorrhage intracranial	1 (0.9)
	Hypertension	1 (0.9)
Total		42 (36.5)

• AEs of likely or unknown relationship to study drug *(Definitely/Probably/Possibly/ Undetermined)* :
9 patients reported 19 AEs (16.5%) of likely or unknown relationship to study drug.

Adverse events of likely or unknown relationship to study drug

MedDRA System Organ Class	MedDRA Preferred Term	N (%) (n=115)	Patient ID	Toxicity Grade	Serious	Relationship	Discontinued
Gastrointestinal disorders	Nausea	4 (3.5)	AMC01	1	No	Probably	No
			AMC03	2	No	Probably	No
			AMC10	1	No	Possibly	No
			CMC01	1	No	Possibly	No
	Vomiting	3 (2.6)	AMC01	2	No	Probably	No
			AMC03	2	No	Probably	No
			AMC10	1	No	Possibly	No
Hepatobiliary disorders	Hepatic function abnormal	4 (3.5)	AMC10	2	No	Probably	No
			AMC01	3	No	Probably	No
			AMC02	3	No	Probably	No
			AMC07	3	No	Probably	No
	Hyperbilirubinaemia	1 (0.9)	AMC09	2	No	Possibly	No
Metabolism and nutrition disorders	Hypokalaemia	1 (0.9)	SMC01	3	No	Possibly	No
Investigations	Weight decreased	1 (0.9)	AMC03	1	No	Possibly	No
Nervous system disorders	Headache	5 (4.3)	AMC01	2	No	Possibly	No
			AMC01	2	No	Possibly	No
			AMC02	2	No	Probably	No
			AMC07	1	No	Possibly	No
			AMC12	1	No	Possibly	No

• Clinical laboratory findings*:*
In the clinical laboratory tests, the test results at baseline and during the treatment were compared. Rapid decrease in WBC and neutrophil counts was observed after the first administration of the study drug, but it was difficult to judge the changes due to the study drug in the clinical laboratory findings because the study drug and anti-cancer drug were concomitantly administered.

Date of the report : 15-Nov-2004