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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi **Drug substance(s):** rasburicase (Fasturtec®)	**Study Identifiers:** NCT00607152 **Study code:** RASBU_L_00351
Title of the study: A multi-center, randomized, open-label, active-controlled clinical trial to evaluate the efficacy and safety of Rasburicase (Fasturtec®) in the prevention and treatment of hyperuricemia in patients with hematological malignancies	
Study center(s): 5 study centers in China	
Study period: Date first patient enrolled: 17/Oct/2007 Date last patient completed: 23/Jan/2009	
Phase of development: III	
Objectives: To compare the efficacy and safety of rasburicase and allupurinol in the treatment and prevention of hyperuricemia in patients with non-Hodgkin's lymphoma and acute leukemia.	
Methodology: Multi-center, randomized, controlled, open-label, 1:1 parallel study.	
Number of patients**:**	Planned: 72 Enrolled: 10 (6 in rasburicase group and 4 in allopurinol group)
Evaluated:	Full analysis set: 8 Per protocol: 6 Safety set: 8
Diagnosis and criteria for inclusion: **Main inclusion criteria:** Men and women aged 18 to 65; baseline plasma uric acid ≥7.0 mg/dL (420 µmol/L); expected survival at least 4 weeks; Karnofsky performance status score ≥30%. **Main exclusion criteria:** Acute promyelocytic leukemia; previous use of urate oxidases or rasburicase; hyperleukocythemia patients who required leukocyte removal; use of drugs containing allopurinol within 7 days before enrollment; asparaginase therapy was planned within 24 hours after discontinuation of rasburicase; patients with abnormal liver or renal function; documented history of hereditary allergy or asthma; a history of serious reaction to allopurinol; patients with known deficiency of glucose-6-phosphate dehydrogenase or a history of hemolytic diseases; patients with severe infection or active bleeding etc.	

Study treatments

Investigational medicinal product(s): rasburicase

Formulation: 1.5 mg/vial

Route(s) of administration: intravenous infusion

Dose regimen: Dose in calculated based on 0.20 mg/kg body weight, and used immediately after preparation. Once daily.

Control drug: allopurinol

Formulation: 100 mg/tablet

Route(s) of administration: oral

Dose regimen: three times a day

Duration of treatment: 5 to 7 days for rasburicase group and 7 days for allopurinol group. Follow up after discontinuation until 14 days after first dosing.

Duration of observation: 14 days (maximum of 16 days) from informed consent to last follow-up.

Criteria for evaluation:

Efficacy:

Primary efficacy variables: To compare maximal % reduction in plasma uric acid concentration and area under the curve (AUC) within 7 days after dosing between two groups.

Secondary efficacy variables: To compare the changes in plasma uric acid concentration at each time point after dosing compared to pre-treatment in both groups.

Safety: Vital sign, ECG, laboratory tests, adverse events and serious adverse events.

Statistical methods:

A two-sided test was used for all statistical tests, with P-value ≤0.05 considered as statistically significant for the differences. Efficacy analysis used both full analysis set (FAS) and per protocol set (PPS), and results were predominantly based on FAS analysis.

In analysis of primary efficacy variables (maximal percentage reduction in plasma uric acid concentration and AUC within 7 days after dosing between two groups), maximal % reduction in plasma uric acid concentration and AUC in two groups were described, mean, standard deviation, median, minimum and maximum were calculated. Wilcoxon rank sum test was to be carried out for intergroup comparison according to the protocol. However, as the sample size was too small, it was unreasonable to use Wilcoxon rank sum test for approximate normal distribution to calculate statistic values and p value. For test robustness, group t test and permutation test were used for intergroup comparisons.

In analysis of secondary efficacy variables (changes in plasma uric acid concentration at each time point after dosing compared to pre-treatment in both groups), plasma uric acid concentration at each timepoint and changes from baseline were described, mean, standard deviation, median, maximum and minimum were calculated. Line chart was plotted for median uric acid concentration at each timepoint. Intragroup changes before and after treatment used paired t test. Considering the sample size was too small, it was unreasonable to use Wilcoxon rank sum test for approximate normal distribution to calculate statistic values and p value. For test robustness, group t test and permutation test were used for intergroup comparisons.

Adverse events/reactions were described in safety analysis. For changes in vital signs, paired t test was performed for intragroup comparison before and after treatment and group t test was carried out for intergroup comparisons.

Summary:

Efficacy results:

Primary efficacy variables:

Maximal % reduction in plasma uric acid concentration within 7 days after dosing

FAS results: Mean maximal % reduction in plasma uric acid concentration within 7 days after dosing was 95.10% (standard deviation [SD]8.38%) in rasburicase group and 54.38% (SD 1.40%) in allopurinol group; median of maximal % reduction was 99.17% (interquartle range 6.49%) in rasburicase group and 54.38% (interquartle range 1.98%) in allopurinol group; Difference in maximal % reduction in two groups was statistically significant (p=0.0006), indicating rasburicase was superior to allopurinol in reducing uric acid concentration in hemologically malignant patients with hyperuricemia. PPS results were similar.

AUC of plasma uric acid concentration within 7 days after dosing

FAS results: Median AUC of plasma uric acid concentration within 7 days after dosing was 4655.00 (interquartle range 9098.00) µmol×h/L in rasburicase group and 52 970.7 (interquartle range 23 423.4) µmol×h/L in allopurinol group; intergroup comparison p=0.0037.

PPS results: Median AUC of plasma uric acid concentration within 7 days after dosing was 8375.00 (interquartle range 8845.00)µmol×h/L in rasburicase group and 41 259.0 (interquartle range 0.00) µmol×h/L in allopurinol group; intergroup comparison p=0.0624.

Considering small sample size, robust statistical analysis was additionally performed for primary efficacy variables, and similar results were obtained.

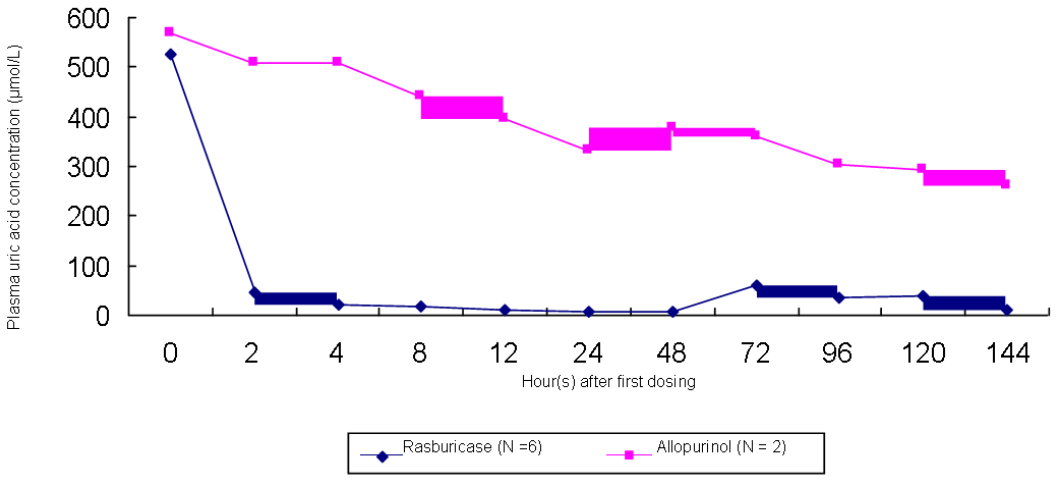
Secondary efficacy variables:

Changes in plasma uric acid concentration after treatment

Changes in plasma uric acid concentration at each timepoint:

FAS results: Plasma uric acid concentration began to decrease markedly 2 hours after first dosing to a median value of 47.00 (interquartile range 225.00) µmol/L in rasburicase group. Median plasma uric acid concentration 2 hours after first dosing in allopurinol group was 509.50 (interquartile range 219.00) µmol/L. Intergroup difference was statistically significant (P=0.0500). Median plasma uric acid concentration at 4 hours after first dosing was 22.50 (interquartile rage 64.00) µmol/L in rasburicase group and 508.00 (interquartile rage 196.00) µmol/L in allopurinol group. Intergroup difference was statistically significant (P = 0.0119). Intergroup differences for 8 hours (P= 0.0097), 12 hours (P=0.0108), 48 hours (P= 0.0077), 72 hours (P=0.0022), 96 hours (P=0.0104) and 120 hours (P=0.0090) were all statistically significant. PPS results were similar.

Figure 1. Changes in median plasma uric acid concentration within 7 days after treatment (FAS)

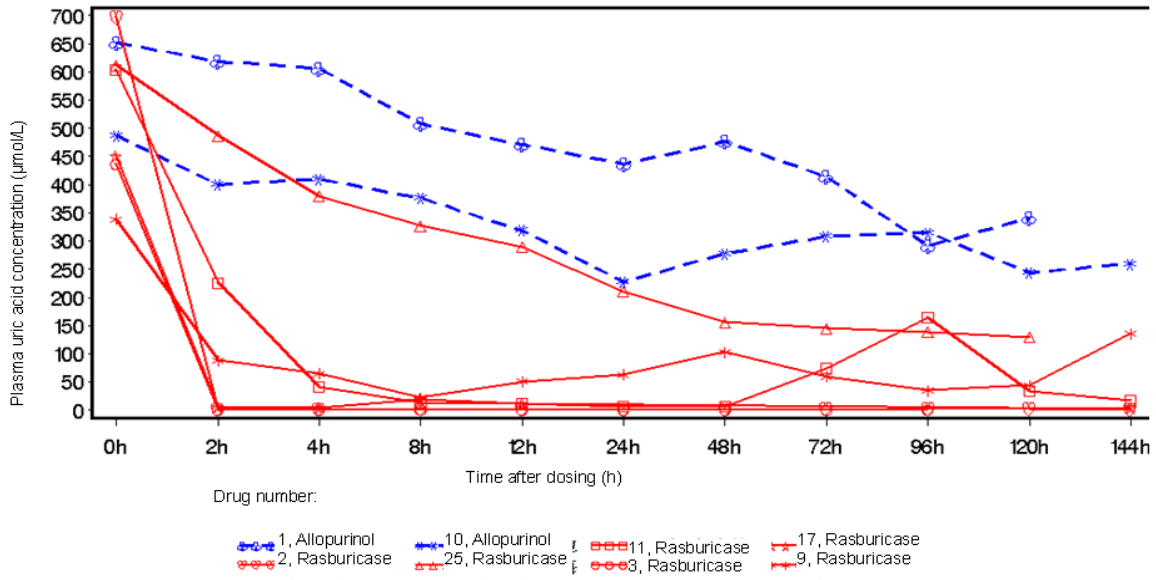


Reduction in plasma uric acid:

FAS results: Reduction in plasma uric acid concentration began to decrease markedly 2 hours after first dosing to a median value of -407.00 (interquartile range 193.00) µmol/L in rasburicase group, which was statistically significant compared to baseline (P = 0.0045). Plasma uric acid concentration continued to decrease 4 hours after first dosing, and the reduction in median from baseline was -441.00 (interquartile range 289.00) µmol/L with statistical significance (P=0.0016). Median values for 8 hours, 12 hours, 48 hours, 72 hours, 96 hours, 120 hours and 144 hours after first dosing all indicated rasburicase markedly reduced plasma uric acid (P values in paired t test with baseline were all lower than 0.05). Reduction from baseline at each timepoint in both groups showed that at 4 hours (P=0.0265), 8 hours (P=0.0309) and 12 hours (P=0.0490) after first dosing, reduction in rasburicase group was superior to that in allopurinol group. PPS results were similar.

The following figure showed individual uric acid concentration change during the study, which was similar to the above mentioned tendency.

Figure 3. Individual uric acid concentration change during the study (FAS)



Considering small sample size, robust statistical analysis was additionally performed for secondary efficacy variables, and similar results were obtained.

Safety results:

Incidence of adverse events in the two treatment groups:

The incidence of adverse events in rasburicase group was 6/6 (100%) of which the incidence of treatment-related adverse events was 1/6 (16.67 %). No serious adverse event was observed in rasburicase group. The incidence of adverse events in allopurinol group was 2/2, and incidence of serious adverse event (led to death) was 1/2 (50.00%). No treatment-related adverse events were observed in allopurinol group.

Only one treatment-related adverse event was observed during this study. This patient in rasburicase group experienced hypokalemia, which was judged to be mild by the investigator. The patient entered the study group (rasburicase) on 27 December 2007 and received rasburicase for 5 days from 28 December 2007 to 01 January 2008. Hypokalemia was observed during blood chemistry examination on 02 January 2008 and 10% KCL and potassium chloride sustained-release tablets (Bu Da Xiu) were given. Before entering the study, the patient's potassium level was 3.42 mmol/L, which was abnormal but not clinically meaningful. Blood potassium after completion of study was 2.97 mmol/L. No other drugs were used during the study and the patient did not report a history of relevant diseases or concomitant diseases. No measures were taken for study drug upon occurrence of above mentioned conditions. The investigator considered that adverse event (hypokalemia) may be related to study drug.

One serious adverse event occurred during this study. This patient in allopurinol group died of sudden cardiac death (lung infection, acute granulocytic leukemia) 5 days after study completion, which was considered not related to study drug by the investigator.

No obvious abnormality was observed in vital signs during study therapy. No significant clinical laboratory test abnormalities were observed.

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