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Sponsor/Company: sanofi-aventis **Drug substance**: Elitek/Fasturtec (rasburicase, SR29142)	**Study Identifier**: NCT00230178 **Study code**: EFC4978

Title of the study:
Evaluation of single agent rasburicase for 5 days versus sequential treatment with rasburicase from Day 1 through 3 followed by oral allopurinol from Day 3 through 5 (overlap on Day 3) versus single agent oral allopurinol for 5 days in the management of plasma uric acid in adult patients with leukemia, lymphoma, and solid tumor malignancies at risk for hyperuricemia and tumor lysis syndrome

Study centers: Multicenter

Study period:

Date first patient enrolled: 23-Apr-2004
Date last patient completed: 02-Dec-2007

Phase of development: Phase 3

Objectives:

The primary objective was to compare the adequacy of control of plasma uric acid concentration and the safety profile in 3 arms, A (5 days of rasburicase alone), B (3 days of rasburicase and 3 days of allopurinol with 1 day overlap), and C (5 days of oral allopurinol alone).

The secondary objectives were:

- to collect and evaluate safety data in 3 arms
- to evaluate plasma uric acid area under the plasma concentration time curve (AUC) from baseline (within 4h prior to anti-hyperuricemic treatment) through 48 hours after the last per-protocol planned administration of anti-hyperuricemic treatments. If the chemotherapy extended beyond 5 days and up to 10 days, uric acid samples were collected up to 48 hours after the last dose of chemotherapy. However, if the chemotherapy extended beyond 10 days, then 1 sample was collected midway between Day 10 and planned end of chemotherapy and final sample 48 hours after the final chemotherapy dose.
- to evaluate incidence, duration, and type of immune responses (IgG, IgE, and neutralizing antibody) to rasburicase
- to evaluate efficacy and safety of rasburicase in relation to antibody generation and antibody titer
- to evaluate the pharmacokinetics of rasburicase in adult patients allocated to Arm A (selected centers) to receive rasburicase at 0.20 mg/kg for 5 days.

Methodology:
Randomized, multi-center, open-label, parallel-designed study with 3 arms:

Number of subjects:
Planned: 276 evaluable patients (92 per arm) Randomized: 280 (Arm A: 94; Arm B: 93; Arm C: 93) Treated: 275 (Arm A: 92; Arm B: 92; Arm C: 91)
Efficacy :intent-to-treat (ITT): 280 (Arm A: 94; Arm B: 93; Arm C: 93); modified ITT (mITT): 275 (Arm A: 92; Arm B: 92; Arm C: 91), per protocol (PP): 205 (Arm A: 71; Arm B: 71; Arm C: 63)
Safety: 275 (Arm A: 92; Arm B: 92; Arm C: 91)
Pharmacokinetics: 8 (Arm A: 8; Arm B: 0; Arm C: 0)

Diagnosis and criteria for inclusion:
Patients, age ≥18 years of age, were eligible for the study if they were either at high risk or potential risk for tumor lysis syndrome (TLS)

Investigational product: Rasburicase - Active substance supplied in vials of 1.5 mg each

Dose: 0.20 mg/kg/day, Arm A: Days 1 through 5; Arm B: Days 1 through 3

Administration: 30 minutes intravenous (IV) infusion

Duration of treatment: 5 days
Duration of observation: Observation for adverse events (AEs) continued for an additional 30 days after the last dose of antihyperuricemic treatment was given.

Reference therapy: Allopurinol

Dose: 300 mg tablet - Arm B: Days 3 through 5; Arm C: Days 1 through 5

Administration: Oral

Criteria for evaluation:

Efficacy:
The primary endpoint of this study was the categorical classification of patients as either treatment successes or treatment failures. This determination was made based on the uric acid values beginning 48 hours after the initiation of the antihyperuricemic treatment and ending 48 hours after the last per protocol planned administration of anti-hyperuricemic treatment. Patients were considered a treatment success (responder) if the plasma uric acid level at T3 (Day 3) through T7 (Day 7) was ≤7.5 mg/dL. If, for a particular patient, at least 1 plasma uric acid level at Day 3 through Day 7 was >7.5 mg/dL, the patient was considered a treatment failure.

The secondary criterion for evaluation of this study was to evaluate uric acid AUC from baseline (within 4 hours prior to first anti-hyperuricemic treatment) through 48 hours after the-anti-hyperuricemic treatment is stopped.

Safety:
Assessment of all AEs (National Cancer Institute – Common Terminology Criteria [NCI-CTC] Version 3.0) and laboratory data, including blood cell counts, electrolytes, and antibody titers (plasma IgE, IgG, and neutralizing antibody). If there was an immune response to rasburicase, its incidence, duration, type, and impact on efficacy/safety of rasburicase was evaluated. Adverse events were coded with Medical Dictionary for Regulatory Activities (MedDRA) Version 10.1.

Pharmacokinetics:
The following rasburicase pharmacokinetic (PK) parameters were determined by non-compartmental analysis: plasma concentration observed before the treatment administration during repeated dosing (C_{min}), plasma concentration observed at the end of IV infusion (C_{eoi}), terminal elimination 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 24 h (AUC_{0-24}), and accumulation ratio (R) for C_{eoi} and AUC_{0-24}.

Pharmacokinetic sampling times and bioanalytical methods:
Pharmacokinetic sampling was done at the following times: Day 1 at predose, 0.5, 4, 8, 24 hours, Day 2 to 4, at predose, Day 5 at predose, 0.5, 4, 8, 24, 72, and 216 hours after the start of the IV infusion of study drug in Arm A (0.20 mg/kg for 5 days).

Bioanalytical methods:
Rasburicase plasma concentrations were determined by a validated enzyme-linked immunosorbant assay (ELISA) with a lower limit of quantification (LLOQ) of 0.7 ng/mL.
Anti-rasburicase antibodies were determined by ELISA for the detection of human immunoglobulins directed against rasburicase.

Statistical methods:

Analysis was performed on the following populations:

mITT Population: The mITT population consisted of all patients who received at least 1 dose of study drug. This population was used for the primary efficacy analysis.

Safety (exposed) Population: The exposed population consisted of all patients who received at least 1 dose of study drug. For this study, the safety population was the same as the mITT population.

ITT Population: The ITT population consisted of all randomized patients.

PP Population: The PP population excluded any patients who had not received study therapy as planned, or who had one or more missing uric acid samples and no other samples showing lack of uric acid control.

All patients given treatment assignment from the randomization system were considered randomized. A patient was considered treated' if the patient received any amount of rasburicase or allopurinol.

The response rate (rate of treatment success) in Arm A was compared to that of Arm C, intending to show superiority of Arm A. If Arm A was shown to be superior to Arm C, then Arm B was compared to Arm C, to show superiority of Arm B over Arm C.

A formal interim analysis was scheduled to be carried out when the response classifications were known for 46 patients in each treatment arm, with an intention of stopping the trial early if there was a significant difference in response rates in Arms A and C.

At the interim analysis, a type 1 error rate of 0.305% was spent according to the O'Brien-Fleming spending approach. Therefore, at the time of interim analysis, Arm A was considered statistically superior to Arm C if the lower one-sided 99.85% confidence limit of the difference in response rates between Arm A and Arm C was greater than 0%. The confidence limits were constructed using Wilson's method.

At the final analysis, a type 1 error rate of 4.695 was spent. Therefore the lower one-sided 97.65% confidence limit of the difference in response rates between Arm A and Arm C was constructed using Wilson's method, and the Arm A was considered statistically superior to Arm C if this lower limit was larger than 0%.

In addition an exploratory sensitivity analysis was performed in which patients with missing uric assessments on both Day 6 and Day 7 were classified as either responders, non-responders or non-evaluable, while patients with only 1 missing assessment on Day 6 or Day 7 and uric acid results consistent with the responder definition (<7.5 mg/dL), were classified as responders.

Continuous variables were summarized using tables of descriptive statistics: number of patients with recorded observations, arithmetic mean, standard deviation, median, minimum, and maximum. Categorical variables were summarized using counts and percentages.

Safety analyses were carried out using the safety population. The duration, dosage, and cumulative number of doses were summarized separately for the 3 treatment arms. The incidence and frequency of patients experiencing any AE, events by body system, and specific events, were summarized for each treatment arm using counts and percentages. The incidence of laboratory toxicities as graded by the NCI-CTC Version 3.0 was summarized for each arm.

The following PK parameters were summarized using descriptive statistics: C_{eoi}, C_{min}, AUC_{0-24} on Days 1 and 5, and $t_{1/2z}$ on Day 5. In addition, R and variability estimates for C_{eoi} and AUC_{0-24} were calculated.

Summary:

Efficacy results:

In the mITT population, the response rate was 87.0% on the rasburicase arm, 78.3% on the rasburicase/allopurinol arm, and 65.9% on the allopurinol arm. The response rate was statistically superior on the rasburicase arm compared to the allopurinol arm (p=0.0009). There was a trend for a difference in response rates between the rasburicase/allopurinol arm and the allopurinol arm; however, this difference did not reach statistical significance (p=0.0632).

Response rates in the rasburicase arm were significantly better than those in the allopurinol arm for high risk patients (89.0% vs 68.2%; p=0.0012) and for patients with baseline hyperuricemia (89.5% vs 52.9%; p=0.0151). The comparison of rasburicase/allopurinol vs allopurinol did not reach statistical significance for high risk patients (79.1% vs 68.2%) or for patients with baseline hyperuricemia (76.9% vs 52.9%). In the rasburicase containing arms, no patients failed and exceeded the uric acid plasma control levels <7.5 mg/dL.

In the PP population, the response rate was 100% for the rasburicase arm, 94.4% for the rasburicase/allopurinol arm, and 79.4% for the allopurinol arm. These results were consistent with the primary analysis using the mITT population and demonstrated superiority of both rasburicase containing arms vs allopurinol (p=0.0002 rasburicase vs allopurinol; p=0.0112 rasburicase/allopurinol vs allopurinol). The results in the ITT population also were consistent with those in the mITT population.

The time to control uric acid in hyperuricemic patients was 4.1 hours for the 2 rasburicase-containing arms and 27 hours for the allopurinol arm. The mean plasma uric acid AUC results indicated that there was an 8.4-fold increase in uric acid exposure on the allopurinol arm compared to the rasburicase arm. The differences in the average of plasma uric acid AUC between the rasburicase arm and the allopurinol arm and between the rasburicase/allopurinol arm and the allopurinol arm are statistically significant by one-way ANOVA model.

The results of the exploratory sensitivity analysis showed an improved response rate in both rasburicase arms compared with the allopurinol arm and reached statistical significance.

Safety results:

Patients were treated with rasburicase, rasburicase/allopurinol or allopurinol for between 1 and 15 days with over 90% treated as specified in the protocol. There were no differences between treatment arms in the incidence of AEs, serious AEs or potential hypersensitivity events.

The most frequently occurring AEs across all arms regardless of causality were in the blood and lymphatic system disorders (thrombocytopenia, neutropenia, anemia), the general disorders and administration site conditions (pyrexia, edema peripheral), and the gastrointestinal disorders (nausea, vomiting, diarrhea), which reflect mainly the known toxicities of concomitant chemotherapy administered. The most common serious AEs across all arms were neutropenic infection (4.3 to 8.8%), febrile neutropenia (3.3 to 5.5%), and neutropenic sepsis (1.1 to 5.4%).

Adverse events that were considered related to study drug by the Investigator were low in frequency (approximately 4%, 5%, and 1% in the rasburicase, rasburicase/allopurinol, and allopurinol arms, respectively) with no severe or life threatening events. Most of the AEs were assessed as not related to study drug and were due to chemotherapy and/or underlying hematological malignancies.

There were no cases of anaphylaxis reported. There were 2 patients with hypersensitivity or drug hypersensitivity reported as related to rasburicase, 7 additional patients were reported with events that were coded as drug hypersensitivity or hypersensitivity. In these 7 patients, the events were classified by the Investigator as not related the study drugs. On further review of the 7 patients with drug hypersensitivity, all but 1 were due to drugs other than rasburicase or allopurinol.

There were no methemoglobinemia or hemolysis events reported.

The incidence of tumor lysis syndrome was low but was more common in the allopurinol arm than in the rasburicase-containing arms (5.5% allopurinol vs 1.1% in each of the rasburicase-containing arms). Renal failure/renal impairment/renal injury was reported in 4 patients in the rasburicase arm (4.3%), 8 patients in the rasburicase/allopurinol arm (8.7%), and 2 patients in the allopurinol arm (2.2%). All cases were considered by the Investigator to be unrelated to study drug. Five cases were considered serious. In the rasburicase-containing arms, most renal failure events occurred more than 2 weeks after the start of rasburicase or rasburicase/allopurinol treatment. The 2 events in the allopurinol arm occurred within the first week of treatment (on Day 2) as a consequence of tumor lysis syndrome.

All deaths during the study were well balanced between arms. None of the deaths were considered to be related to study drug. A greater number of deaths within 30 days of last dose were reported on the rasburicase arm; however, this difference was not statistically significant. A stepwise procedure was conducted to identify the baseline factors that were statistically significant factors for the deaths within 30 days of last dose (rasburicase only vs allopurinol only). It was found that age ≥ 65 years, and grade 3,4 hypophosphatemia, thrombocytopenia, and leukopenia at baseline had a statistically significant impact on the deaths within 30 days of the last dose.

Overall, treatment with rasburicase alone or sequentially given with allopurinol in combination with chemotherapy, has shown an expected safety profile that is consistent with previous studies conducted in pediatric and adult population with rasburicase. No major safety differences were noted.

Pharmacokinetic results:

After 5 days of administration of rasburicase as a 30-minute intravenous infusion to adult patients at the dose of 0.20 mg/kg/day, no accumulation was observed following daily intravenous infusion of SR29142 as assessed by C_{eoi} and AUC_{0-24}. $t_{1/2z}$ was approximately 15.7 hours and total patient variability in C_{eoi} and AUC_{0-24} was 21.8 and 42.6%, respectively.

Pharmacokinetic parameters following once daily 30-min intravenous infusion of rasburicase (5-day treatment) at the dose of 0.20 mg/kg/day in the rasburicase arm (Arm A) is shown in the table below.

Dose (mg/kg/day)	Statistic	Day 1			Day 5			
		C_{eoi} (ng/mL)	C_{min} (ng/mL)	AUC_{0-24} (ng.h/mL)	C_{eoi} (ng/mL)	C_{min} (ng/mL)	AUC_{0-24} (ng.h/mL)	C_{eoi} (ng/mL)
0.20	N	5	7	3	6	7	6	5
	Mean	2710	<LLOQ	32000	2750	573	34800	15.7
	SD	535	NC	8900	687	340	13500	5.72

C_{eoi} = end of infusion concentration, C_{min} = concentration before drug administration, NC = not possible to calculate, LLOQ = lower limit of quantitation (0.7 ng/mL)

Immunogenicity results:

Based on interim results, in this pivotal study, no patients were quantitatively positive for anti−rasburicase IgE antibodies. There were no quantitatively positive IgG antibody results in the rasburicase arm, while a similar number and percentage of patients in the rasburicase/allopurinol and allopurinol arms had quantitatively positive IgG antibodies. The incidence of quantitatively positive neutralizing IgG (NIgG) was low and the presence of NIgG did not affect the antihyperuricemic response to rasburicase or the

occurrence of TLS or renal failure. Overall, there was no correlation between antibody positivity and potential hypersensitivity reactions

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