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Sponsor / Company: sanofi-aventis	**Study Identifier:** NCT00230217
Drug substance: Elitek/Fasturtec (rasburicase, SR29142)	**Study code:** EFC5339

Title of the study:

Evaluation of single agent rasburicase in treatment/prevention of hyperuricemia associated with tumor lysis syndrome in adult and pediatric patients with lymphoma/leukemia/solid tumor malignancies at their first relapse or refractory disease (EFC5339)

Study center(s): Multicenter study with 16 active centers in the USA

Study period:

Date first patient enrolled: 01-Mar-2004

Date last patient completed: 25-Jul-2006

Phase of development: Phase 4

Objectives:

The primary objective was to assess the response to rasburicase in 2 populations of patients with lymphoma/leukemia/solid tumor malignancies, those previously treated with a uricolytic agent and those not previously treated with a uricolytic agent at their first relapse or refractory disease.

The secondary objectives were:

- To evaluate safety of rasburicase in the 2 patient populations
- To evaluate plasma uric acid area under the curve from baseline (within 4 hours prior to rasburicase treatment) through study Day 7 (ie, 48 hours after the planned administration of rasburicase). If 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 was collected 48 hours after the final chemotherapy dose (see amendment 03)
- To evaluate incidence, duration, and type of immune responses, immunoglobulin G (IgG) and immunoglobulin E (IgE), and neutralizing antibody)
- To evaluate efficacy and safety of rasburicase in relation to antibody generation and antibody titer.

The protocol-defined objectives and some secondary efficacy objectives were not met because of poor enrollment in the pretreated arm (Arm A) due to lack of availability of relapsed/refractory patients previously treated with a uricolytic agent. Accrual was completed for the naive arm (Arm B). Immunogenicity data are pending.

Methodology:

This was a multicenter, 2 arm, open-label study. Eighty-five (85) patients were enrolled in each arm (a minimum of 35 high risk patients per arm):

- Arm A (pretreated): patients previously treated with a uricolytic agent
- Arm B (naïve): patients not previously treated with a uricolytic agent

Number of patients:

Planned: 170; Enrolled and treated: 94 (9 pretreated and 85 naïve)

Evaluated: Efficacy and safety: 94 (9 pretreated and 85 naïve)

Diagnosis and criteria for inclusion:

Patients were eligible for this study if they were either at high risk or potential risk for tumor lysis syndrome (TLS). A patient was at high risk for TLS if he/she presented with:

- Hyperuricemia of malignancy (plasma uric acid >7.5 mg/dL) or
- He/she had the diagnosis of a very aggressive lymphoma/leukemia based on the Revised European-American Lymphoma (REAL) classification of lymphoma/leukemia in its first relapse or
- acute myelogenous leukemia (AML) or
- chronic myelogenous leukemia (CML) or
- High grade myelodysplastic syndrome (refractory anemia with excess blast, refractory anemia with excess blast in transformation, or chronic myelomonocytic leukemia) only if the patients have ≥10% bone marrow blasts and undergoing aggressive chemotherapy similar to AML
- A patient was at potential risk for TLS if he/she presented with the diagnosis of an aggressive lymphoma/leukemia based on the REAL classification of lymphoma/leukemia plus 1 or more of the following criteria:
  - Lactate dehydrogenase [IU/L) ≥2 x upper limit of normal (ULN)
  - Stage III-IV disease
  - Stage I-II disease with 1 lymph node/tumor >5 cm in diameter
- Patients previously treated with a uricolytic agent or not at their first relapse or refractory disease
- Eastern Cooperative Oncology Group (ECOG) performance status 0-3
- Life expectancy >3 months

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

Dose: 0.20 mg/kg/day for 5 days

Administration: Intravenous

Duration of treatment: 5 days

Duration of observation: Observations for adverse events continued for an additional 30 days after the last rasburicase dose.

Reference therapy: None

Criteria for evaluation:

Efficacy:

Efficacy was based on plasma uric acid levels up to 48 hours after the treatment was stopped. A positive response to treatment was defined as achievement and/or maintenance of plasma uric acid concentration ≤7.5 mg/dL within 48 hours from initiation of rasburicase up to 48 hours after the last planned administration of rasburicase. Another efficacy measure was the assessment of the area under the curve of plasma uric acid, based on plasma uric acid measurements up to 48 hours after treatment was stopped.

Safety:

Safety was based on collection and assessment of all adverse events, coded according to Medical Dictionary for Regulatory Activities (MedDRA Version 10), intensity graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC Version 3.0) and laboratory data including blood cell counts, electrolytes, creatinine, liver function tests, 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.

Statistical methods:

The primary analysis was based on the modified intent-to-treat (mITT) population, defined as all patients who received at least one dose of study drug. The rate of treatment success (defined as response rate) and its 95% binomial confidence limits were calculated for each arm (see Amendment A01).

Secondary analyses such as analyses of uric acid area under the curve, time to first confirmed demonstration of control of uric acid, etc. were not performed due to limited interpretability resulting from the lack of enrollment to the pretreated arm (Arm A).

Safety analyses were carried out using the safety population. The duration, dosage, and cumulative number of doses were summarized separately for the 2 treatment arms. The incidence and frequency of patients experiencing any adverse event, events by body system, and specific events, were summarized for each treatment group using counts and percentages. The incidence of laboratory toxicities as graded by the NCI-CTC (Version 3.0) was summarized for each arm.

Summary:

Efficacy results:

This study was stopped prematurely due to lack of accrual on the pretreated arm (Arm A). The lack of accrual was due to low potential for TLS in the retreatment setting and consequently limited use of rasburicase. The naïve arm (Arm B) completed accrual as planned.

In the mITT population, the overall response rate was 88.9% in pretreated patients and 90.6% in naïve patients. In the mITT population, the response rate for pediatric patients was 83.3% in the pretreated arm and 100% in the naïve arm. For adult patients the response rate was 100% in the pretreated arm and 89.3% in the naïve arm.

Safety results:

Patients were treated from 2 to 6 days with the majority treated for 5 days as specified in the protocol. Overall, all patients experienced an adverse event, 39 patients had an serious adverse event, and 5 patients discontinued due to an adverse event. The majority of adverse events were unrelated to rasburicase and due to underlying hematological malignancy and/or concomitant chemotherapy. Eight adult patients died within 30 days of last dose, 3 due to progressive disease and 5 due to adverse events unrelated to rasburicase treatment (sepsis, neutropenic sepsis, pneumonia/hypoxia, neutropenic infection leading to respiratory failure, and venoocclusive disease). Within each arm and overall, most adverse events were hematologic in nature (thrombocytopenia, anemia, and neutropenia) and due to concomitant chemotherapy. The most common serious adverse events were febrile neutropenia and neutropenic infection. Five patients, all in the naïve arm, discontinued study treatment due to adverse events (aspartate aminotransferase increased, convulsions, panic attack, bradycardia, and bone pain). The aspartate aminotransferase increases, bradycardia, and convulsions were classified as related to rasburicase by the Investigator. In addition, 1 patient interrupted rasburicase treatment due to an adverse event of hemolysis.

In the naïve arm, 1 adult patient experienced grade 3 hemolysis and 2 adult patients experienced grade 2 hypersensitivity. The hypersensitivity cases occurred 7 and 9 days after last rasburicase treatment and these events were assessed as not related to rasburicase administration.

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