*These results are supplied for informational purposes only.*
*Prescribing decisions should be made based on the approved package insert in the country of prescription*

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| **Sponsor/company:** | sanofi-aventis | **ClinialTrials.gov Identifier:** | NCT00651911 |
| | | **Study Code:** | L_8637 |
| **Generic drug name:** | Rasburicase | **Date:** | 31/Mar/2008 |

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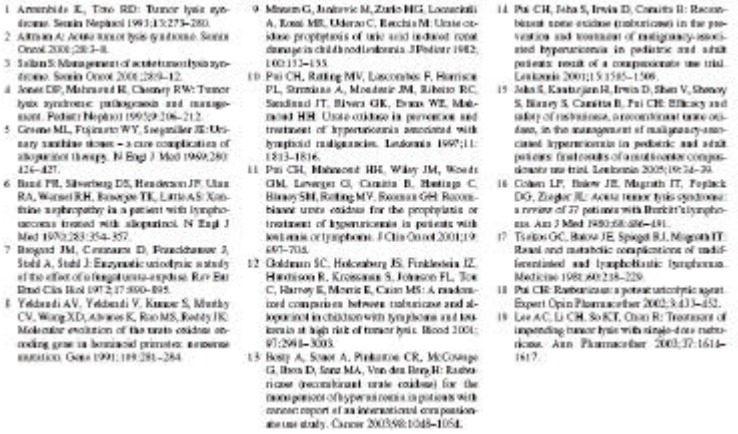
| **Title of the study:** | A clinical trial of Rasburicase to treat patients prophylactically or therapeutically for tumor lysis syndrome (L_8637) |
| **Investigator(s):** | 1) Dr. Der-Cherng Liang<br>Department of Pediatrics, Mackay Memorial Hospital, Taiwan<br>2) Dr. Sheng-Fung Lin<br>Kaohsiung Medical University Hospital, Taiwan<br>3) Kai-Hsin Lin<br>National Taiwan University School of Medicine<br>4) Lee-Yung Shih<br>Chang-Gung Memorial Hospital |
| **Study center(s):** | 1) Mackay Memorial Hospital, Taiwan<br>2) Kaohsiung Medical University Hospital, Taiwan<br>3) National Taiwan University School of Medicine, Taiwan<br>4) Chang-Gung Memorial Hospital, Taiwan |
| **Publications (reference):** |  |

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| **Study period:**<br>Date first **patient/subject** enrolled: 01-JUL-2003 *Date of first signed informed consent*<br>Date last **patient/subject** completed: 24-MAY-2004 *Date of last patient last visit* | **Phase of development:**<br>IV |

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| **Objectives:** | 1. To access the uricolytic response to treatment with Rasburicase<br>2. To evaluate tumor lysis risk factors, treatments for tumor lysis syndrome, and complications of treatment in patients treated prophylactically or therapeutically for tumor lysis syndrome<br>3. To analyze the above data to guide the design of future prospective studies |

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| **Methodology:** | An open-labeled, non-randomized, multicenter study to determine the efficacy and safety of Rasburicase used for the prevention and treatment of tumor lysis syndrome. | | |
| **Number of patients/subjects:** | Planned:<br>45 | Randomized:<br>NA | Treated:<br>45 |
| **Evaluated:** | Efficacy:<br>45 | Safety:<br>45 | Pharmacokinetics:<br>NA |
| **Diagnosis and criteria for inclusion:** | 1) Male or female at any age<br>2) Chemotherapy planned for at least 3 cycles<br>3) Undergoing cytoreductive chemotherapy for ALL, multiple myeloma or Burkitt's lymphoma stage III or IV.<br>4) With a minimum life expectancy of 3 months.<br>5) Uric acid > 8 mg/dL<br>6) Negative pregnancy tests ≤ 2 weeks and efficient contraceptive method.<br>7) Negative HIV serology ≤ 4 weeks.<br>8) Patient or legal guardian has signed a written informed consent. | | |
| **Investigational product:**<br>Dose:<br>Administration: | Rasburicase (Fasturtec®)<br>0.20mg/kg/day<br>IV | | |
| **Duration of treatment:**<br>0.20mg/kg/day for 3 to 7 days, once daily | **Duration of observation:**<br>Follow up of 4 weeks after the last study drug injection | | |
| **Reference therapy:**<br>Dose:<br>Administration: | NA<br>NA<br>NA | | |
| **Criteria for evaluation:** | | | |
| Efficacy:<br>Or<br>Pharmacodynamics: | • The **efficacy of Rasburicase for prevention and treatment of hyperuricemia** was assessed by evaluation of the number of responders after completion of the 3 days of Rasburicase treatment under chemotherapy. [Responder: the patient's blood uric acid value returns to normal range (% of patients with blood uric acid <8mg)]<br>• The **efficacy of Rasburicase in terms of renal protection** was assessed under treatment and after the end of treatment by evaluation of the evolution (improvement, normalization or worsening) of the serum creatinine levels. | | |
| Safety: | The **safety of Rasburicase utilization** was assessed by analysis of all adverse events reported by the patient or noted by the investigator.<br>Standard laboratory data of uric acid (mg/dL), calcium (mg/dL), phosphorus (mg/dL), potassium (meq/L), creatinine (mg/dL), and LDH blood values were assessed.<br>For leukemias, White Blood Cell (WBC) was assessed. | | |
| Pharmacokinetics: | NA | | |
| Pharmacokinetic sampling times and bioanalytical methods: | NA | | |

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| **Statistical methods:** | **1) Primary objectives**<br><br>• The **efficacy of Rasburicase for treatment of hyperuricemia** was assessed by evaluation of the number of responders after completion of the 3 days of Rasburicase treatment under chemotherapy. [Responder: the patient's blood uric acid value returns to normal range (% of patients with blood uric acid <8mg)]<br><br>• The **efficacy of Rasburicase in terms of renal protection** was assessed under treatment and after the end of treatment by evaluation of the evolution (improvement, normalization or worsening) of the serum creatinine levels.<br><br>**2) Secondary objectives**<br><br>• Descriptive statistical analysis has been performed to assess the **optimal duration of Rasburicase treatment**.<br><br>• Descriptive statistical analysis has been performed to assess the establishment of the **optimal sequential use of Rasburicase and allopurinol** when hyporicemic treatment is required after 7 days of Rasburicase treatment.<br><br>• The **safety of Rasburicase utilization** was assessed by analysis of all adverse events. |

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| **Summary:** | The response rate to rasburicase was 100% for lowering the uric acid to normal levels.<br>None of the patients required dialysis for renal failure, including the 7 with pretreatment renal insufficiency.<br>Serum phosphorus levels also remained normal during the patients' chemotherapy, even for patients with impaired renal function before treatment were able to maintain stable phosphorous concentrations and did not require dialysis. Excretion of phosphorous may also have been improved because precipitation of uric acids or its precursor xanthine was diminished after the treatment.<br>Treatment with Rasburicase was well tolerated. A total of 163 doses were administered, and the only adverse effect was a grade 1 vomiting in one adult patient.<br>Results of this open pilot study support the efficacy and safety of rasburicase to treat hyperucimia and help preventing the complications of tumor lysis syndrome in patients with hematologic malignancies. |
| Efficacy results:<br>or<br>Pharmacodynamic results: | Forty-five patients (age range 3-98 years: 18 children and 27 adults) at risk of TLS were enrolled. Of the 18 children (14 males and 4 females), 10 had ALL, 6 had high grade lymphoma and 2 had ALL. Of the 27 adults (18 males and 9 females), 8 had ALL, 4 had high-grade lymphoma, 9 had multiples-myeloma, and 6 had AML. Most patients had a large tumor burden as indicated by high LDH levels and white cell counts. After 2-6 days of treatment (Rasburicase 0.2 mg/kg, IV, once a day, for a median of 3 days in children, and of 4 days in adults), the median uric acid levels in the 18 children decreased from 10.5 mg/dl (range 8-18.6) to 0.5 mg/dl (range 0.0-1.7). Similarly, in the 27 adults, the median levels decreased from 10.8 mg/dl (range 8-24.4) to 0.5 mg/dl (range 0.0-1.6). Thus the response rate to rasburicase was thus 100% for lowering the uric acid to normal levels. |

**Table 2.** Effects of rasburicase on uric acid in pediatric and adult patients

| | Pediatric (n = 18) | Adult (n = 27) |
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| Baseline uric acid, mg/dl | | |
| Median | 10.5 | 10.8 |
| Range | 8.0–18.6 | 8.0–24.4 |
| Uric acid 3 days after treatment began, mg/dl | | |
| Median | 0.5 | 0.5 |
| Range | 0.0–1.7 | 0.0–1.6 |
| Days rasburicase was given | | |
| Median | 3 | 4 |
| Range | 3–6 | 2–6 |

Renal dysfunction was present in 7 patients before chemotherapy was begun (creatinine 1.6-70 mg/dl). However, neither these nor any other patients required dialysis for hyperphosphatemia or renal failure during chemotherapy. Serum phosphorus, calcium and potassium concentrations were maintained within normal limits during the first 3 days of treatment.

**Table 3.** Pre- and posttreatment (3 days after rasburicase treatment began) biochemical changes in patients presenting with renal dysfunction

| | Uric acid mg/dl | Creatinine mg/dl | Phosphorus mg/dl | Potassium mEq/l | Calcium mg/dl |
|---|---|---|---|---|---|
| Pretreatment | | | | | |
| Median | 13.4 | 3.1 | 4.4 | 4.3 | 9.4 |
| Range | 9.5–24.4 | 1.9–7.0 | 3.6–5.3 | 3.4–5.5 | 7.7–15.8 |
| Posttreatment | | | | | |
| Median | 0.5 | 2.7 | 4.2 | 3.9 | 8.8 |
| Range | 0.0–1.3 | 1.2–6.6 | 3.0–5.6 | 3.6–4.6 | 7.3–13.9 |

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| Safety results: | Rasburicase was very well tolerated, with only one adult having grade 1 vomiting of unknown etiology and another patient had grade 1 fever with likely relationship to study drug.<br>None of the death was observed during or attribute to the study treatment. Two patients died during the follow-up period. One was due to disease relapse and the other was metabolic acidosis. |
| Pharmacokinetic results: | NA |
| **Date of report:** | 23-Feb-2005 |