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Sponsor/Company:	sanofi-aventis	**Study identifier:**	
Drug substance(s):	rasburicase	**Study Code:**	EFC4983 (SR29142)
		Date:	21 August 2006

Title of the study:	Study of efficacy and safety of rasburicase for the treatment/prevention of hyperuricemia related to tumor lysis syndrome in adult patients with relapsing aggressive non Hodgkin's lymphoma, previously treated or not with urate oxidase and presenting with hyperuricemia and/or bulky disease (GRAAL2)
Investigator:	Pr. Bertrand COIFFIER, Centre Hospitalier Lyon Sud – Service Hématologie, Chemin du Grand Revoyet, 69310 Pierre Bénite, FRANCE
Study centers:	14 centers (7 in France, 1 in Belgium, 4 in Italy, 2 in Germany)
Publications (reference):	None
Study period: **Date first subject enrolled:** 24 July 2002 **Date last subject completed:** 10 January 2005	**Phase of development:** Phase 2
Objectives: *Primary:*	The primary objective of this study was to evaluate the efficacy of rasburicase in terms of treatment/prevention of hyperuricemia related to tumor lysis syndrome (TLS) in 2 populations of adult patients, previously treated or not with urate oxidase, with relapsing aggressive non-Hodgkin's lymphoma (NHL) and at risk of TLS, presenting with hyperuricemia and/or bulky disease at diagnostic of relapse.
Secondary:	The secondary objectives were to: • evaluate the efficacy of rasburicase in terms of renal protection, assessing also the evolution of other biological parameters; • evaluate the safety of rasburicase in the 2 populations of patients; • correlate efficacy and safety results with antibodies generation/ level.
Methodology:	Phase 2, multicentric, open-label study
Number of subjects: **Evaluated:**	Planned: 100 Included: 33 Treated: 33 (23 naïve, 10 pre-treated) Efficacy: 33 Safety: 33 (The study was terminated prematurely due to poor enrollment)
Diagnosis and criteria for inclusion:	Patients with histologically proven aggressive Non Hodgkin's Lymphoma, including diffuse large B cell, peripheral T cell, immunoblastic, Burkitt type, anaplastic large cell lymphomas, lymphoblastic lymphomas, transformation of indolent lymphomas and at their first or subsequent relapse of the lymphoma.

Investigational product: *Dose:* *Administration:*	SR29142 (rasburicase) 0.20 mg/kg/day for 4 to 7 days Intravenous route/30-minute infusion The first intravenous injection of rasburicase was to be started no later than 24 hours before initiation of chemotherapy combined with or not with immunotherapy (rituximab) and continued at least during the first 3 days of chemotherapy (4 days in total).
Duration of treatment:	Not to exceed 7 days **Duration of observation:** Approximately 3 months
Reference therapy:	Not applicable
Criteria for evaluation: *Efficacy:*	A patient was considered to have responded to rasburicase treatment if their uric acid levels obtained during treatment returned to normal range, and were maintained during at least 4 consecutive days or until the end of treatment. A patient was considered a treatment failure if uric acid normalization was not achieved, or if the patient required study medication prolongation or reintroduction. Efficacy was also evaluated by Investigator's Global Response assessment: • response: normalization of uric acid (<8 mg/dL [476 mmol/L]) and maintenance during at least 4 consecutive days; • failure: persistence of hyperuricemia and/or other metabolic abnormality; • evaluation not done.
Safety:	Adverse events (AEs), laboratory evaluations, anti-rasburicase antibodies.
Statistical methods:	No statistical tests were performed on study endpoints because this study was terminated due to poor enrollment. Descriptive statistics are provided on selected endpoints. Rate of uric acid normalization and maintenance summarized by pre-treatment group. Analyses of adverse events consisting of incidence rate summaries presented by pre-treatment cohort. Anti-rasburicase antibody results summarized by pre-treatment cohort.
Bioanalytical methods	Sampling: *Plasma:* Anti-SR29142 antibodies: at baseline, 7 to 14 days and approximately 3 months after the last administration. Assay: *Plasma:* Antibodies were detected using a validated ELISA method.

Summary:

Patient Characteristics at Entry

	Pre-treated N=10		Naive N=23	
Mean Age(years)	62.4		62.0	
Gender (M/F)	4/6		13/10	
Performance status at baseline				
PS 0-1	8	(80.0%)	17	(73.9%)
PS 2-4	2	(20.0%)	6	(26.1%)
Stage at baseline				
Stage I-II	2	(20.0%)	6	(26.1%)
Stage III-IV	8	(80.0%)	17	(73.9%)
Prior uricemic treatment				
Uricozyme only	8	(80.0%)	0	(0%)
Fasturtec only	1	(10.0%)	0	(0%)
Both Fasturtec and Uricozyme	1	(10.0%)	0	(0%)
Type of lymphoma				
Diffuse large B cell	8	(80.0%)	16	(69.6%)
Peripheral T cell	1	(10.0%)	0	(0%)
Immunoblastic	0	(0%)	0	(0%)
Burkitt	0	(0%)	0	(0%)
Anaplastic large cell	0	(0%)	1	(4.3%)
Lymphoblastic lymphoma	0	(0%)	2	(8.7%)
Transformation of indolent Lymphoma	0	(0%)	4	(17.4%)
Other	1	(10.0%)	0	(0%)
IPI index				
At least one criterion met	10	(100%)	23	(100%)
Age > 60	6	(60.0%)	17	(73.9%)
LDH ≥ 1N	7	(70.0%)	19	(82.6%)
Stage III-IV	8	(80.0%)	17	(73.9%)
PS 2-4	2	(20.0%)	6	(26.1%)
Extranodal site involvement	5	(50.0%)	4	(17.4%)
Initial chemotherapy treatment				
CHOP/RITUXIMAB	2	(20.0%)	0	(0%)
DHAP	2	(20.0%)	5	(21.7%)
ESHAP	1	(10.0%)	0	(0%)
Other	5	(50.0%)	18	(78.3%)
Day of first chemotherapy cycle				
1 day after first intake	9	(90.0%)	19	(82.6%)
2 days after first intake	0	(0%)	1	(4.3%)
1 day before first intake	0	(0%)	1	(4.3%)
Day of first intake	1	(10.0%)	2	(8.7%)

CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone and bleomycin ; DHAP = dexamethasone, high-dose cytarabine, cisplatin; ESHAP = etoposide, methylprednisolone, cytarabine and cisplatin; IPI = international prognostic index; LDH = lactate dehydrogenase

Summary (continued):

Efficacy results:

According to the Investigator's global response, all pre-treated patients were responders as were 20 (87.0%) of the naïve patients. Two naïve patients were classified as failures. One patient was a responder according to the uric acid criteria (411 micromol/L to 0) but was classified as a failure due to elevated creatinine. The second patient had a clinically significant decrease in uric acid after 3 doses of rasburicase (375 micromol/L to 12 micromol/L) but was classified as a failure because he was lost to follow-up. One patient was not evaluated for response due to Investigator decision to remove the patient from the study.

Uric acid normalized or was controlled in 100% of patients. Only 2 patients had an elevated uric acid level at screening, the remainder had bulky disease with normal baseline uric acid levels.

Investigator's global response assessment after 4 days of rasburicase treatment

Response	**Pre-treated N=10**	**Naive N=23**	**Total N=33**
Response classification	n/N(%) (95% CI)	n/N(%) (95% CI)	n/N(%) (95% CI)
Response	10 / 10 (100%) (69.1% - 100.0%)	20 / 23 (87.0%) (66.4% - 97.2%)	30 / 33 (90.9%) (75.7% - 98.1%)
Failure	0 / 10 (0%) (0.0% - 30.8%)	2 / 23 (8.7%) (1.1% - 28.0%)	2 / 33 (6.1%) (0.7% - 20.2%)
Evaluation Not Done	0 / 10 (0%) (0.0% - 30.8%)	1 / 23 (4.3%) (0.1% - 21.9%)	1 / 33 (3.0%) (0.1% - 15.8%)

Uric acid response

Response	**Pre-treated N=10**	**Naive N=23**	**Total N=33**
Uric Acid normal (<8.0 mg/dL)			
YES - all patients	10 / 10 (100%)	23 / 23 (100%)	33 / 33 (100%)
YES - patients treated 4 days or more	8 / 10 (80.0%)	20 / 23 (87.0%)	28 / 33 (84.8%)

Summary (continued):

Safety results:

Summary of Treatment Exposure

	Pre-treated N=10	Naive N=23
Total Number of Doses		
N	10	23
Median	4	4
Mean (SD)	3.9 (0.6)	4.2 (0.8)
Range [min - max]	3 - 5	3 - 7
Total Cumulative Dose		
N	10	23
Median	51.0	52.0
Mean (SD)	56.55 (23.13)	56.74 (16.47)
Range [min - max]	36.0 - 114.5	36.0 - 100.0
Number of Days Treated		
N	10	23
Median	4	4
Mean (SD)	3.9 (0.6)	4.1 (0.8)
Range [min - max]	3 - 5	3 - 7
Number of Days Treated		
3 days	2 (20.0%)	3 (13.0%)
4 days	7 (70.0%)	16 (69.6%)
5-7 days	1 (10.0%)	4 (17.4%)

Note: the difference between summary statistics of number of doses and days treated is due to subject 25034127 who was dosed twice on Day 3

All pre-treated patients had at least 1 AE, as did 20 (87.0%) of naïve patients. Two (8.7%) naïve patients had treatment-related AEs. Four pre-treated patients (40.0%) and 8 naïve patients (34.8%) had SAEs. One pre-treated patient withdrew from the study due to a rasburicase overdose. One patient in each cohort died during the follow-up period due to progressive disease. Five naïve patients died after follow-up.

Summary (continued):

Safety results (continued):

Safety Summary

Parameter	Pre-treated N=10	Naive N=23
Patients with any AE	10 (100%)	20 (87.0%)
Patients with any treatment-related AE	0 (0%)	2 (8.7%)
Patients with any SAE	4 (40.0%)	8 (34.8%)
Patients permanently withdrawn from the study due to AE[a]	1 (10.0%)	0 (0%)
Deaths during treatment period	0 (0%)	0 (0%)
Deaths during follow-up[b]	1 (10.0%)	1 (4.3%)
Deaths after follow-up	0 (0%)	5 (21.7%)

[a] Due to overdose

[b] Both deaths were attributable to progressive disease

Number of Patients with AEs ≥20% (worse grade by patient)

System Organ Class	Adverse Event	Pre-treated N=10		Naive N=23	
		All Grades	Grade 3,4	All Grades	Grade 3,4
Any class	Any event	10 (100%)	8 (80.0%)	20 (87.0%)	18 (78.3%)
Body as a whole - general disorders	Any event	4 (40.0%)	0 (0%)	4 (17.4%)	1 (4.3%)
	Asthenia	2 (20.0%)	0 (0%)	3 (13.0%)	1 (4.3%)
Cardiovascular disorders, general	Any event	3 (30.0%)	2 (20.0%)	3 (13.0%)	2 (8.7%)
Gastro-intestinal system disorders	Any event	5 (50.0%)	2 (20.0%)	8 (34.8%)	5 (21.7%)
	Constipation	2 (20.0%)	0 (0%)	2 (8.7%)	1 (4.3%)
	Mucositis NOS	2 (20.0%)	2 (20.0%)	0 (0%)	0 (0%)
Liver and biliary system disorders	Any event	3 (30.0%)	1 (10.0%)	8 (34.8%)	1 (4.3%)
	SGOT increased	2 (20.0%)	0 (0%)	3 (13.0%)	0 (0%)
Metabolic and nutritional disorders	Any event	9 (90.0%)	3 (30.0%)	18 (78.3%)	8 (34.8%)
	Hyperglycaemia	3 (30.0%)	0 (0%)	2 (8.7%)	1 (4.3%)
	Hyperphosphataemia	3 (30.0%)	0 (0%)	8 (34.8%)	1 (4.3%)
	Hyperuricaemia	2 (20.0%)	0 (0%)	5 (21.7%)	0 (0%)
	Hypocalcaemia	4 (40.0%)	0 (0%)	3 (13.0%)	0 (0%)
	Hypokalaemia	2 (20.0%)	2 (20.0%)	3 (13.0%)	0 (0%)
	Hyponatraemia	2 (20.0%)	1 (10.0%)	4 (17.4%)	2 (8.7%)
	Hypoproteinaemia	2 (20.0%)	0 (0%)	1 (4.3%)	0 (0%)
	LDH increased	1 (10.0%)	1 (10.0%)	7 (30.4%)	3 (13.0%)
	NPN increased	2 (20.0%)	0 (0%)	1 (4.3%)	0 (0%)
	Phosphatase alkaline increased	0 (0%)	0 (0%)	5 (21.7%)	0 (0%)
	Serum iron increased	2 (20.0%)	0 (0%)	0 (0%)	0 (0%)
Platelet, bleeding & clotting disorders	Any event	6 (60.0%)	5 (50.0%)	9 (39.1%)	8 (34.8%)
	Thrombocytopenia	4 (40.0%)	4 (40.0%)	9 (39.1%)	8 (34.8%)
Red blood cell disorders	Any event	7 (70.0%)	6 (60.0%)	8 (34.8%)	5 (21.7%)
	Anaemia	7 (70.0%)	6 (60.0%)	7 (30.4%)	4 (17.4%)
Respiratory system disorders	Any event	3 (30.0%)	1 (10.0%)	3 (13.0%)	2 (8.7%)
	Dyspnoea	2 (20.0%)	1 (10.0%)	1 (4.3%)	1 (4.3%)
Urinary system disorders	Any event	2 (20.0%)	0 (0%)	1 (4.3%)	0 (0%)
White cell and res disorders	Any event	5 (50.0%)	4 (40.0%)	8 (34.8%)	8 (34.8%)
	Febrile neutropenia	2 (20.0%)	2 (20.0%)	3 (13.0%)	3 (13.0%)
	Leucopenia	2 (20.0%)	1 (10.0%)	5 (21.7%)	5 (21.7%)

Summary (continued):

Safety results (continued):

Two naïve patients had treatment-related AEs. These were Grade 3 hypophosphatemia and Grade 1 micturition frequency abnormal.

Two pre-treated patients and 3 naïve patients had hypersensitivity-related reactions. None of these events was related to study treatment.

Hypersensitivity Events

SOC/Adverse Event	Pre-treated N=10		Naive N=23	
	All Grades	Grade 3,4	All Grades	Grade 3,4
Any event	2 (20.0%)	1 (10.0%)	3 (13.0%)	2 (8.7%)
Body as a whole - general disorders				
Any event	0 (0%)	0 (0%)	1 (4.3%)	0 (0%)
Allergic reaction	0 (0%)	0 (0%)	1 (4.3%)	0 (0%)
Cardiovascular disorders, general				
Any event	2 (20.0%)	1 (10.0%)	2 (8.7%)	1 (4.3%)
Hypotension	1 (10.0%)	1 (10.0%)	1 (4.3%)	0 (0%)
Oedema	1 (10.0%)	0 (0%)	0 (0%)	0 (0%)
Oedema generalised	0 (0%)	0 (0%)	1 (4.3%)	1 (4.3%)
Respiratory system disorders				
Any event	2 (20.0%)	1 (10.0%)	1 (4.3%)	1 (4.3%)
Bronchospasm	1 (10.0%)	1 (10.0%)	0 (0%)	0 (0%)
Dyspnoea	2 (20.0%)	1 (10.0%)	1 (4.3%)	1 (4.3%)

One pre-treated patient and 6 naïve patients died during the study. None of these deaths was related to study treatment.

Four pre-treated patients (40.0%) and 8 naïve patients (34.8%) experienced SAEs. Grade 3 or 4 SAEs were reported in 3 pre-treated patients and 8 naïve patients.

Number of Deaths

	Pre-treated N=10	Naive N=23
Total Number of Deaths	1 (10.0%)	6 (26.1%)
Deaths during treatment period	0 (0%)	0 (0%)
Deaths during follow-up	1 (10.0%)	1 (4.3%)
Deaths after follow-up	0 (0%)	5 (21.7%)

Anti-SR29142 antibodies:

Twenty-three patients (9 pre-treated, 14 naïve) provided samples for antibody assessment. No antibodies were detectable in the 23 patients at any time before and after treatment.

Date of report: 28 November 2005