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

Sponsor/company:	sanofi-aventis	ClincialTrials.gov Identifier:	NCT00302653
		Study Code:	L_9436
Generic drug name:	Rasburicase	Date:	20/Nov/2009

Title of the study:	Phase IV study of Rasburicase for treatment of hyperuricemia in patients with tumoral lysis syndrome (Code: L_9436)
Investigator(s):	Vicente Odoni Filho (coordinator investigator). Address: Av. Dr. Enéas de Carvalho Aguiar, 255 - Cerqueira César - São Paulo - Brazil Zip Code: 05403-000
Study center(s):	Multicenter study (3 BR sites).
Publications (reference):	Poster in Congress of the SIOP (International Society of Paediatric Oncology) 2008 – "Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia in children with acute leukemia and NHL: a Brazilian multicenter open label study". Author: Vicente Odoni Filho.

Study period:

Date first patient enrolled: 16-Feb-2006*

Date last patient completed: 28-Nov-2006

*Date of the basal visit

Informed consent date was not reported on the CRF, instead of that, there is a field for date and one for signature where the PI assured that the Informed Consent Process was performed before the realization of any procedure related to the study.

Phase of development:

Phase IV

Objectives:	The purpose of this study was to determinate if rasburicase was effective and safe to treat patients with hyperuricemia. Efficacy was analyzed through the number of patients that after rasburicase treatment presented uric acid level considered normal according to each local laboratory reference values. Rasburicase's efficacy was also evaluated by renal protection through the serum creatinin levels comparing to laboratorial reference values after rasburicase´s treatment. Safety was evaluated by frequency and intensity of adverse events presented and laboratorial examinations.	
Design:	Multi-center study, non-comparative and open label.	
Number of patients/subjects:	Planned: 40	Treated: 32
Evaluated:	Efficacy: 21	Safety: 32

Diagnosis and criteria for inclusion:	Patients aged less than 18 years with acute hyperuricemia (uric acid > 8.0 mg/dl) before or during chemotherapy for hematologic malignancies or who had risk factors for development of tumoral lysis (LDH>2 x upper limit of normality and/or serum creatinin>upper limit of normality and/or leukocyte count above 50,000/mm3 in patients with leukemia).
Criteria for evaluation:	
Safety:	Frequency and intensity of Adverse events reported by the patient or noted by the investigator. Efficacy: Percentage of patients with uric acid level considered as normal, according to the reference normal laboratory levels at 24-48 hours and at 28 (± 3) days after the last dose of rasburicase. Percentage of patients with creatinin level considered as normal, according to the reference normal laboratory levels at 24-48 hours and at 28 (± 3) days after the last dose of rasburicase.
Statistical methods:	All patients who received at least one dose of rasburicase have been included in the SAFETY Population. All subjects who received at least one dose of rasburicase and had baseline and at least one uric acid measurement post-treatment available (24-48 hours or 28± 3 days) were included in the ITT Population (Intention-To-Treat Population). All patients who received at least one dose of rasburicase, performed baseline and 24-48 hours uric acid exams and did not fit in any relevant protocol violation criteria were included in PP Population (Per-Protocol Population). It was performed a Macnemars'Test to compare the levels of acid uric and creatinin at baseline with the levels observed at 24-48 hours post-treatment visit, in terms of Normal Reference Laboratory Values (NRV) for both population, ITT and PP. The results were described in five categories: Under, Normal, Upper, undetectable and less than a specific value. In the last case the value stated in the laboratory documents was always less than the Upper NRV. The categories "Under", "Normal", "Undetectable" and "Less than a value" were grouped together in a class named as "Normal" to perform the Macnemars'Test. The safety parameters were analyzed taking in consideration all patients who received the study medication. Only descriptive methods were used to analyze the adverse events occurrence. All tests were performed adopting a significance level of 0,05.

Summary:	Between 16-Feb-2006 and 30-Oct-2006, thirty three patients were enrolled to the study. From this total, 18 (54,5%) patients were female and 19 patients (57,6%) were black-caucasian biracial, with a median age of 7,0 years (6 months – 16 years). Concerning diagnosis at inclusion, 21 (63,6%) patients presented leukemia, 10 (30,3%) patients presented lymphoma and 2 (6,1%) patients, neuroblastoma. The mean LDH at baseline was 3240,9 (standard deviation=4483,8), a mean about 8.7 times (1,3 to 54,9) greater than the upper limit value of reference. From the total of patients, one patient did not receive any study medication due to death (patient with HIV that developed a sepsis). The other 32 patients were treated for a mean of 5,3 days (standard deviation: 1,7 days; 1 - 7 days) , receiving a mean of 20,4 bottles of rasburicase. The flow chart presented below describes the distribution of patients: 33: enrolled ↓ 1: death due to sepsis 32: treated * ↓ 2:death / 1:transferred to another institution 29: Visit 24/48 hours after treatment done ↓ 3: death 26: Visit 28± 3 days after treatment done * 1: Treated only for two days due to allergy reaction for rasburicase (the patient was not excluded from the PP population) The following flow chart describes the population for analyses: 32: treated - Safety population ↓ 5: without acid uric measurement at 24/48 hours and at 28± 3 days visits 3: uric acid measurement at baseline not done 2: Death 1: Transferred to another institution 21: ITT population ↓ 1: Protocol violation: without inclusion criteria 20: PP population

Efficacy results:

or

Pharmacodynamic results:

Uric Acid Levels

According both ITT and PP population, at 24-48 hours post-treatment visit, uric acid levels decreased from basal day, for all of the patients.

Table 1 – Percentage of patients by class of Uric Acid Level compared to the basal value (ITT Population).

ITT	Decreased		Unchanged		Increased		Not done / Damaged / Cancelled		Total
	N	%	N	%	N	%	N	%	
Day 1	9	42.9%	8	38.1%	4	19.0%	0	0.0%	21
Day 2	17	81.0%	0	0.0%	0	0.0%	4	19.0%	21
Day 3	18	90.0%	0	0.0%	0	0.0%	2	10.0%	20
Day 4	18	94.7%	0	0.0%	0	0.0%	1	5.3%	19
Day 5	13	81.3%	0	0.0%	0	0.0%	3	18.8%	16
Day 6	5	50.0%	0	0.0%	0	0.0%	5	50.0%	10
Day 7	5	71.4%	0	0.0%	0	0.0%	2	28.6%	7
24-48 hours	21	100.0%	0	0.0%	0	0.0%	0	0.0%	21
Day 28	6	31.6%	0	0.0%	3	15.8%	10	52.6%	19

Table 2 – Percentage of patients by class of Uric Acid Level compared to the basal value (PP Population).

PP	Decreased		Unchanged		Increased		Not done / Damaged / Cancelled		Total
	N	%	N	%	N	%	N	%	
Day 1	9	45.0%	8	40.0%	3	15.0%	0	0.0%	20
Day 2	16	80.0%	0	0.0%	0	0.0%	4	20.0%	20
Day 3	17	89.5%	0	0.0%	0	0.0%	2	10.5%	19
Day 4	17	94.4%	0	0.0%	0	0.0%	1	5.6%	18
Day 5	13	86.7%	0	0.0%	0	0.0%	2	13.3%	15
Day 6	5	55.6%	0	0.0%	0	0.0%	4	44.4%	9
Day 7	4	66.7%	0	0.0%	0	0.0%	2	33.3%	6
24-48 hours	20	100.0%	0	0.0%	0	0.0%	0	0.0%	20
Day 28	6	33.3%	0	0.0%	3	16.7%	9	50.0%	18

For ITT and PP analysis, for both post-treatment visits, none of the patients presented acid uric levels upper NRV.

Table 3 – Percentage of patients by class of Uric Acid Levels compared to the NRV (ITT Population).

ITT	Under NRV		Normal		Upper NRV		Undefined / Undetectable		Not done / Damaged / Cancelled		Total
	N	%	N	%	N	%	N	%	N	%	
Baseline	2	9,5%	6	28,6%	13	61,9%	0	0,0%	0	0,0%	21
Day 1	5	23,8%	4	19,0%	11	52,4%	1	4,8%	0	0,0%	21
Day 2	13	61,9%	1	4,8%	1	4,8%	2	9,5%	4	19,1%	21
Day 3	16	80,0%	0	0,0%	1	5,0%	1	5,0%	2	10,0%	20
Day 4	16	84,2%	2	10,5%	0	0,0%	0	0,0%	1	5,3%	19
Day 5	12	75,0%	1	6,3%	0	0,0%	0	0,0%	3	18,8%	16
Day 6	4	40,0%	0	0,0%	1	10,0%	0	0,0%	5	50,0%	10
Day 7	4	57,1%	1	14,3%	0	0,0%	0	0,0%	2	28,6%	7
24-48 hours	19	90,5%	1	4,8%	0	0,0%	1	4,8%	0	0,0%	21
Day 28	2	10,5%	7	36,8%	0	0,0%	0	0,0%	10	52,6%	19

	and 24-48 hours after the end of rasburicase treatment. This result was statistically significant (day1, 35,7% of the patients had acid uric levels above the basal limit , and this numbers increase to 84% in the 24-48 hours after treatment. (McNemar test : p<0,001) The same was shown in the PP population. According to ITT and PP analysis, uric acid levels decreased significantly between the basal day and 24-48 hours after the end of rasburicase treatment. This result was statistically significant (day1, 35,7% of the patients had acid uric levels above the basal limit , and this numbers increase to 84% in the 24-48 hours after treatment. (McNemar test : p<0,001) The same was shown in the PP population. Analysing renal function, in ITT population, there was a trend to show that creatinin levels decreased in 24-48 hours post-treatment. However, in PP population, it was observed a statistically significant decrease of creatitnin levels (p=0,0245), In the analysis of potassium, phosphorus, calcium serum levels before and after rasburicase treatment, there wasn't any difference between this two moments.

Efficacy results (cont.):

Table 4 – Percentage of patients by class of Uric Acid Levels compared to the NRV (PP Population).

PP	Under NRV		Normal		Upper NRV		Undefined / Undetectable		Not done / Damaged / Cancelled		Total
	N	%	N	%	N	%	N	%	N	%	
Baseline	1	5.0%	6	30.0%	13	65.0%	0	0.0%	0	0.0%	20
Day 1	4	20.0%	4	20.0%	11	55.0%	1	5.0%	0	0.0%	20
Day 2	12	60.0%	1	5.0%	1	5.0%	2	10.0%	4	20.0%	20
Day 3	15	78.9%	0	0.0%	1	5.3%	1	5.3%	2	10.5%	19
Day 4	15	83.3%	2	11.1%	0	0.0%	0	0.0%	1	5.6%	18
Day 5	12	80.0%	1	6.7%	0	0.0%	0	0.0%	2	13.3%	15
Day 6	4	44.4%	0	0.0%	1	11.1%	0	0.0%	4	44.4%	9
Day 7	3	50.0%	1	16.7%	0	0.0%	0	0.0%	2	33.3%	6
24-48 hours	18	90.0%	1	5.0%	0	0.0%	1	5.0%	0	0.0%	20
Day 28	2	11.1%	7	38.9%	0	0.0%	0	0.0%	9	50.0%	18

For both population, at 24-48hours Post-treatment Visit, it was possible to observe a statistical significant difference between the values of uric acid before (baseline) and after the treatment with rasburicase ($p<0.001$), taking in consideration the Normal Reference Laboratory Values.

Table 5 – Comparison of uric acid levels from Baseline visit to 24-48 visit.

Baseline	*ITT Population (N = 21)* 24-48 hours Visit				*PP Population (N = 20)* 24-48 hours Visit			
	Under NRV / Normal / Undefined / Undetectable		Upper NRV		Under NRV / Normal / Undefined / Undetectable		Upper NRV	
Under NRV / Normal / Undefined / Undetectable	8	38.1%	0	0.0%	7	35.0%	0	0.0%
Upper NRV	13	61.9%	0	0.0%	13	65.0%	0	0.0%
McNemar test	$\chi^2_1 = 11.08$ – $p<0.001$				$\chi^2_1 = 11.08$ – $p<0.001$			

<u>Creatinin levels</u>

To evaluate the renal protection, the creatinin levels were also analyzed.

For both ITT and PP populations, more than 61% of the patients showed decrease in creatinin levels in 24-48 hours visit comparing to baseline levels, for both study population.

Table 6 – Percentage of patients by class of Creatinin Level compared to the basal value (ITT Population).

ITT	Decreased		Unchanged		Increased		Not done		Total
	N	%	N	%	N	%	N	%	
Day 1	4	19.0%	10	47.6%	7	33.3%	0	0.0%	21
Day 2	6	28.6%	8	38.1%	7	33.3%	0	0.0%	21
Day 3	9	45.0%	3	15.0%	7	35.0%	1	5.0%	20
Day 4	11	57.9%	2	10.5%	6	31.6%	0	0.0%	19
Day 5	8	50.0%	2	12.5%	4	25.0%	2	12.5%	16
Day 6	3	30.0%	3	30.0%	2	20.0%	2	20.0%	10
Day 7	6	85.7%	0	0.0%	0	0.0%	1	14.3%	7
24-48 hours	13	61.9%	2	9.5%	3	14.3%	3	14.3%	21
Day 28	11	57.9%	2	10.5%	1	5.3%	5	26.3%	19

Efficacy results (cont.):

Table 7 – Percentage of patients by class of Creatinin Level compared to the basal value (PP Population).

PP	Decreased		Unchanged		Increased		Not done		Total
	N	%	N	%	N	%	N	%	
Day 1	4	20.0%	10	50.0%	6	30.0%	0	0.0%	20
Day 2	6	30.0%	8	40.0%	6	30.0%	0	0.0%	20
Day 3	9	47.4%	3	15.8%	6	31.6%	1	5.3%	19
Day 4	10	55.6%	2	11.1%	6	33.3%	0	0.0%	18
Day 5	8	53.3%	2	13.3%	4	26.7%	1	6.7%	15
Day 6	3	33.3%	3	33.3%	2	22.2%	1	11.1%	9
Day 7	5	83.3%	0	0.0%	0	0.0%	1	16.7%	6
24-48 hours	13	65.0%	1	5.0%	3	15.0%	3	15.0%	20
Day 28	10	55.6%	2	11.1%	1	5.6%	5	27.8%	18

Creatinin baseline levels were considered as normal in 15 (71.4%) patients and in 9 (42.9%) patients in 24-48 hours visit for ITT population.

PP population presented 14 (70.0%) and 8 (40%) patients with normal creatinin levels in baseline and 24-48 hours visits, respectively.

Table 8 – Percentage of patients by class of Creatinin Levels compared to the NRV (ITT Population).

ITT	Under NRV		Normal		Upper NRV		Not done		Total
	N	%	N	%	N	%	N	%	
Baseline	1	4.8%	15	71.4%	5	23.8%	0	0.0%	21
Day 1	2	9.5%	12	57.1%	7	33.3%	0	0.0%	21
Day 2	2	9.5%	11	52.4%	8	38.1%	0	0.0%	21
Day 3	1	5.0%	10	50.0%	8	40.0%	1	5.0%	20
Day 4	2	10.5%	11	57.9%	6	31.6%	0	0.0%	19
Day 5	2	12.5%	8	50.0%	4	25.0%	2	12.5%	16
Day 6	0	0.0%	5	50.0%	3	30.0%	2	20.0%	10
Day 7	0	0.0%	5	71.4%	1	14.3%	1	14.3%	7
24-48 hours	5	23.8%	9	42.9%	4	19.0%	3	14.3%	21
Day 28	4	21.1%	9	47.4%	1	5.3%	5	26.3%	19

Table 9 – Percentage of patients by class of Creatinin Levels compared to the NRV (PP Population).

PP	Under NRV		Normal		Upper NRV		Not done		Total
	N	%	N	%	N	%	N	%	
Baseline	1	5.0%	14	70.0%	5	25.0%	0	0.0%	20
Day 1	2	10.0%	11	55.0%	7	35.0%	0	0.0%	20
Day 2	2	10.0%	10	50.0%	8	40.0%	0	0.0%	20
Day 3	1	5.3%	9	47.4%	8	42.1%	1	5.3%	19
Day 4	2	11.1%	10	55.6%	6	33.3%	0	0.0%	18
Day 5	2	13.3%	8	53.3%	4	26.7%	1	6.7%	15
Day 6	0	0.0%	5	55.6%	3	33.3%	1	11.1%	9
Day 7	0	0.0%	4	66.7%	1	16.7%	1	16.7%	6
24-48 hours	5	25.0%	8	40.0%	4	20.0%	3	15.0%	20
Day 28	4	22.2%	8	44.4%	1	5.6%	5	27.8%	18

For both population, at 24-48hours Post-treatment Visit it was not possible to observe a statistical significant difference between the values of uric acid before (baseline) and after the treatment with rasburicase (p=0.4497), taking in consideration the Normal Reference Laboratory Values.

Efficacy results (cont.):

Table 10 – Comparison of creatinin levels from Baseline visit to 24-48 visit.

Baseline	ITT Population 24-48 hours Visit *				PP Population 24-48 hours Visit *			
	Normal		Abnormal		Normal		Abnormal	
Normal	7	38,9%	5	27,8%	6	35,3%	5	29,4%
Abnormal	2	11,1%	4	22,2%	2	11,8%	4	23,5%
McNemar test	$\chi^2_1 =$ 0.57 – p=0.4497-ns				$\chi^2_1 =$ 0.57 – p=0.4497-ns			

Safety results:

From the total number of patients included in the safety analysis, 30 (93.7%) have reported 135 AEs and only 2 (6.3%) patients have presented 3 events considered as related to the rasburicase intake: allergic reaction. Grade 2.

Nineteen patients (59.4%) have reported 25 serious AEs, although none of them has been considered as related to the study medication.

Five (15.6%) patients died due to AEs: sepsis, renal failure and bleeding, and oliguria+ hypovolemia+ acute lung edema+cardiac congestive failure, central nervous system bleeding and sepsis.

One (3.1%) patient withdrawn from the treatment due to allergic reaction.

Table 11 – Patients reporting any adverse event.

Adverse event descriptions	Patients N=32	Number of events
Any	30 (93.7%)	135
Related to rasburicase	2 (6.3%)	3
Serious	19 (59.4%)	25
Serious and related to rasburicase	-	-
Causing death	5 (15.6%)	6
Related to rasburicase and causing death	-	-
Leading to treatment withdrawal	1 (5.1%)	1
Related to rasburicase and leading to treatment withdrawal	-	-

Table 12 – Serious Adverse Events.

Adverse event	Intensity	Rasburicase related ?
Diarrhea + Swelling / Sepsis *	Not Available	No
Sepsis + Pancytopenia *	Not Available	No
Pneumonia + SARA *	Not Available	No
Sepsis *	Not Available	No
Cardiac congestive insufficiency *	Not Available	No
Renal failure / Bleeding *	Not Available	No
Febrile neutropenia	Grade 4	No
Oliguria + Hypovolemia + Cardiac congestive insufficiency + Acute lung edema	Grade 4	No
Febrile neutropenia	Grade 1	No
Febrile granulocytopenia / Diarrhea / Fever	Grade 4 / Grade 3 / Grade 1	No
Febrile granulocytopenia	Grade 4	No
Seizure with transitory heparesis	Grade 2	No
Seizure	Grade 3	No
Epigastric pain	Grade 4	No
Central Nervous System Bleeding	Grade 4	No
Fever	Grade 1	No
Febrile neutropenia / Perianal hyperemia / Creatinin level increase	Grade 3 / Grade 3 / Grade 2	No
Febrile neutropenia	Grade 3	No
Sepsis *	Not Available	No

The most frequently reported kind of adverse event was vomiting, 16 events, presented by 11 patients (34.4%), followed by febrile neutropenia, 6 events, presented by 6 patients (18.8%), and fever, 5 patients (15.6%) who presented 8 events.

Table 13 – Adverse Events - number of patients and events.

Adverse event	Number of Patients		Number of AE	AE Related to Rasburicase
Vomiting	11	34,4%	16	-
Febrile neutropenia	6	18,8%	6	-
Fever	5	15,6%	8	-
Diarrhea	4	12,5%	5	-
Epigastric pain	4	12,5%	5	-
Náusea	4	12,5%	5	-
Petechiae	4	12,5%	4	-
Headache	3	9,4%	4	-
Lack of appetite	3	9,4%	3	-
Allergic reaction	2	6,3%	3	3
Ankle pain	2	6,3%	2	-
Backacke	2	6,3%	2	-
Bleeding	2	6,3%	2	-
Dry cough	2	6,3%	2	-
Emesis	2	6,3%	2	-
Febrile granulocytopenia	2	6,3%	2	-
Hepatic enzymes increase	2	6,3%	2	-
Sepsis	2	6,3%	3	-
Abdominal pain	1	3,1%	1	-
Anal pain	1	3,1%	1	-
Ankle edema	1	3,1%	1	-
Apnea	1	3,1%	1	-
Asthenia	1	3,1%	1	-
Behaviour change	1	3,1%	1	-
Central nervous system bleeding	1	3,1%	1	-
Cervical echimosis	1	3,1%	1	-
Congestive cardiac insufficiency	1	3,1%	1	-
Constipation	1	3,1%	1	-
Creatinin level increase	1	3,1%	1	-
LDH increase	1	3,1%	1	-
Diarrhea + Swelling	1	3,1%	1	-
Dysphonia	1	3,1%	1	-
Dyspnea	1	3,1%	1	-
Epistaxis	1	3,1%	1	-
Fatigue	1	3,1%	1	-
Febrile peak	1	3,1%	2	-
Gengival bleeding	1	3,1%	1	-
Glycemia level increase	1	3,1%	1	-
Hands edema	1	3,1%	1	-
Hemoglibin level decrease	1	3,1%	1	-
Hemorragic vomiting	1	3,1%	1	-
Hyaline coryza	1	3,1%	1	-

Table 13 – Adverse Events - number of patients and events (Cont.).

Adverse event	Number of Patients		Number of AE	AE Related to Rasburicase
Hypocalcemia	1	3,1%	1	-
Hypokalemia	1	3,1%	1	-
Hypopotassemia	1	3,1%	1	-
Infection	1	3,1%	1	-
Inferior member pain	1	3,1%	1	-
Inferior member edema	1	3,1%	1	-
Leg pain	1	3,1%	1	-
Mandibular pain	1	3,1%	1	-
Mental confusion	1	3,1%	1	-
Mucositis	1	3,1%	1	-
Nervousness	1	3,1%	1	-
Neutropenia	1	3,1%	1	-
Oliguria + Hypovolemia +	1	3,1%	1	-
Oral cavity pain	1	3,1%	1	-
Oropharingeal pain	1	3,1%	1	-
Palpebral edema	1	3,1%	1	-
Perianal hyperemia	1	3,1%	1	-
Pericardium effision	1	3,1%	1	-
Periorbitale echimosis	1	3,1%	1	-
Periorbitale edema	1	3,1%	1	-
Pneumonia	1	3,1%	1	-
Pneumonia + Sara	1	3,1%	1	-
Renal failure	1	3,1%	1	-
Seizure	1	3,1%	1	-
Seizure with transitory	1	3,1%	1	-
Sepsis + Pancytopenia	1	3,1%	1	-
Serum phosphorus level increase	1	3,1%	1	-
Sonolence	1	3,1%	1	-
Sorethroat	1	3,1%	1	-
Sudoresis	1	3,1%	1	-
Swelling	1	3,1%	1	-
Tachypnea	1	3,1%	1	-
Tongue lesions	1	3,1%	1	-
Transaminasis level increase	1	3,1%	1	-

The following table shows the number of non-serious adverse events by grade.

Table 14 – Number of Non-serious Adverse Events by Grade.

Non-Serious Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Vomiting	10 (31.3%)	6 (18.8%)	-	-
Fever	4 (12.5%)	1 (3.1%)	1 (3.1%)	-
Nausea	4 (12.5%)	1 (3.1%)	-	-
Diarrhea	1 (3.1%)	2 (6.3%)	1 (3.1%)	-
Epigastric pain	3 (9.4%)	1 (3.1%)	-	-
Headache	1 (3.1%)	3 (9.4%)	-	-
Petechiae	4 (12.5%)	-	-	-
Allergic reaction	-	3 (9.4%)	-	-
Lack of appetite	3 (9.4%)	-	-	-
Ankle pain	1 (3.1%)	-	1 (3.1%)	-
Backache	2 (6.3%)	-	-	-
Dry cough	2 (6.3%)	-	-	-
Emesis	1 (3.1%)	1 (3.1%)	-	-
Febrile neutropenia	-	-	2 (6.3%)	-
Febrile peak	2 (6.3%)	-	-	-
Hepatic enzymes increase	-	-	1 (3.1%)	1 (3.1%)
Abdominal pain	1 (3.1%)	-	-	-
Anal pain	-	1 (3.1%)	-	-
Ankle edema	-	-	1 (3.1%)	-
Apnea	-	-	1 (3.1%)	-
Asthenia	1 (3.1%)	-	-	-
Behaviour change	1 (3.1%)	-	-	-
Bleeding	1 (3.1%)	-	-	-
Cervical echimosis	1 (3.1%)	-	-	-
Constipation	-	1 (3.1%)	-	-
Dysphonia	1 (3.1%)	-	-	-
Dyspnea	1 (3.1%)	-	-	-
Epistaxis	1 (3.1%)	-	-	-
Fadigue	1 (3.1%)	-	-	-
Gengival bleeding	1 (3.1%)	-	-	-
Glycemia level increase	-	1 (3.1%)	-	-
Hands edema	1 (3.1%)	-	-	-
Hemoglobin level decrease	-	-	1 (3.1%)	-
Hemorrhagic vomiting	1 (3.1%)	-	-	-
Hypokalcemia	1 (3.1%)	-	-	-
Hypocalemia	1 (3.1%)	-	-	-
Hyaline coryza	1 (3.1%)	-	-	-
Hypopotassemia	1 (3.1%)	-	-	-
Infection	-	-	1 (3.1%)	-
Inferior member edema	-	1 (3.1%)	-	-
Inferior member pain	-	1 (3.1%)	-	-
LDH level increase	-	1 (3.1%)	-	-
Leg pain	-	1 (3.1%)	-	-

Table 14 – Number of Non-serious Adverse Events by Grade (Cont.).

Non-Serious Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Mandibular pain	1 (3.1%)	-	-	-
Mental confusion	1 (3.1%)	-	-	-
Mucositis	1 (3.1%)	-	-	-
Nervousless	1 (3.1%)	-	-	-
Neutropenia	-	-	1 (3.1%)	-
Oral cavity pain		1 (3.1%)		
Oropharyngeal pain	1 (3.1%)	-	-	-
Palpebral edema	1 (3.1%)	-	-	-
Pericardium effusion	-	-	1 (3.1%)	-
Periorbitale echimosis	1 (3.1%)	-	-	-
Periorbitale edema	1 (3.1%)	-	-	-
Phosphorus serum level increase	-	1 (3.1%)	-	-
Pneumonia	-	1 (3.1%)	-	-
Sonolence	1 (3.1%)	-	-	-
Sorethroat	1 (3.1%)	-	-	-
Sudoresis	1 (3.1%)	-	-	-
Swelling	1 (3.1%)	-	-	-
Tachypnea	1 (3.1%)	-	-	-
Tongue lesions	1 (3.1%)	-	-	-
Transaminasis increase	1 (3.1%)	-	-	-
Total (% of total adverse event)	69 (62.7%)	28 (25.5%)	12 (10.9%)	1 (0.9%)

Date of report: 20-Nov-2009