Science and Medical Affairs **Global Medical Affairs**	
Abbreviated Clinical Study Report	

Study Code: XALIP_C_02090 **Document Status: Final** **Date: 05-Mar-2010**

SYNOPSIS

Title of the study:	A multi-center, randomized, double blind, placebo controlled Phase III study to assess the efficacy of xaliproden in patients with oxaliplatin-induced peripheral sensory neuropathy (PSN) following adjuvant chemotherapy for colon cancer Study Code: XALIP_C_02090 Study Name: XENON	
Coordinating Investigator:	[redacted]	
Study centers:	A total of 34 active centers participated in the study: 7 centers in Germany, 7 centers in France, 6 centers in the UK, 4 centers in Canada, 4 centers in Spain, 3 centers in Italy, and 3 centers in the US.	
Publications (reference):	None	
Study period: Date first patient enrolled: 23-Jan-2008 Date last patient completed: 27-Nov-2009		**Phase of development:** Phase III
Objectives:	Primary objective: To assess the effect of xaliproden hydrochloride (xaliproden) 1 mg per oral daily on the rate of complete resolution of PSN at 6 months, following randomization, after the completion of oxaliplatin-based adjuvant chemotherapy for colon cancer. Secondary objectives: • To assess the effect of xaliproden on patient-reported outcomes using the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group 12-item neurotoxicity subscale (FACT/GOG NTX-12). • To assess the effect of xaliproden on the rate of at least partial recovery of Grade ≥2 PSN at 6 months. • To assess the effect of xaliproden on the time to complete recovery from PSN. • To evaluate the safety profile of xaliproden.	
Methodology:	This was an international, multi-center, Phase III, randomized, two arm, double blind, placebo controlled study. The study was terminated early as a result of lack of efficacy in another Phase III study and the discontinuation of development of xaliproden by sanofi-aventis.	

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Number of patients:	

	Planned	Randomized (ITT population)	Treated (safety population)
Placebo	122	51	51
Xaliproden	122	51	50[a]
Total	244	102	101

ITT: intent-to-treat.
[a] One patient who was randomized to receive xaliproden withdrew consent before taking the first dose of study treatment.

Main diagnosis and criteria for inclusion:	Patients aged ≥18 years who had received an oxaliplatin-containing chemotherapy regimen post complete surgical removal of primary colon tumor (with the last infusion of oxaliplatin ≤6 weeks before randomization). Patients had to have Grade ≥1 PSN as defined by the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) (Version 3.0), and an Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2.
Investigational product:	Xaliproden hydrochloride
Dose:	1.0 mg capsule
Administration:	Oral
Batch numbers:	[redacted]
Duration of treatment: Up to 6 months or complete neurological recovery (PSN Grade 0), whichever came first.	**Duration of observation:** Up to 6 months of study treatment, then follow-up at 9 and 12 months after randomization.
Reference therapy:	Placebo
Dose:	Not applicable (placebo capsule to match 1.0 mg xaliproden hydrochloride capsule)
Administration:	Oral
Batch numbers:	[redacted]
Criteria for evaluation:	The current report is an abbreviated report, and as such, only the safety results are presented in full. The following safety criteria were evaluated: adverse events (AEs)/serious AEs (SAEs), hematology and biochemistry, monitoring for potential deep venous thrombo-embolism/pulmonary embolism (including D-dimer assay), monitoring for potential diabetes (glycated hemoglobin [HbA1c]), vital signs, monitoring for potential cardiomyopathy by electrocardiogram (ECG), physical examination, and ECOG Performance Status. Because of the early termination of the study, only the primary efficacy variable, complete PSN resolution at 6 months, was evaluated. Neurological sensory toxicity was graded by the investigator according to the NCI-CTCAE (Version 3.0) criteria for neuropathy (sensory).

Statistical methods and analysis populations:	All tests were performed with a 5% 2-sided significance level. The primary efficacy variable was complete PSN resolution at 6 months. 'Success' was defined as PSN Grade 0 at the Month 6 visit and 'failure' was defined as a PSN grade greater than 0 at the Month 6 visit. Last observation carried forward (LOCF) was used to impute any missing PSN grades at 6 months. The primary efficacy analysis was based on the ITT population. Complete PSN resolution at 6 months was compared between the placebo and xaliproden groups using Chi-square and Cochran-Mantel-Haenszel tests, stratifying for PSN grade at randomization (PSN Grade = 1, PSN Grade ≥2). As a sensitivity analysis, the Chi-square test was repeated with the LOCF technique applied only to complete resolution cases (Grade = 0). Because of the early termination of the study, no statistical analyses were performed on the secondary efficacy variables. The rate of at least partial recovery of Grade ≥2 PSN at 6 months, and the time to complete recovery from PSN, were not derived. Patient responses to the modified FACT/GOG NTX-12 subscale questionnaire were listed only. No derivations of subscale scores with respect to the FACT/GOG NTX scoring guidelines were made. Safety data were analyzed based on the safety population using descriptive statistics. The ITT population was defined as all randomized patients, regardless of whether they received sthe tudy treatment. Patients were analyzed in the treatment groups to which they were randomly assigned. The safety population was defined as all randomized patients who received at least one dose of study treatment. Patients were analyzed according to the study treatment received.
Summary:	**Efficacy** There was no clinically relevant difference between the 2 treatment groups in the proportion of successes (ie, patients with PSN complete resolution [Grade 0] at the end of treatment [Month 6]): 4 (7.8%) patients in the placebo group and 5 (9.8%) patients in the xaliproden group. The statistical analysis showed that the null hypothesis of equal proportions of successes could not be rejected (Chi-square test: p=0.73). The statistical analysis stratifying by PSN grade at randomization showed no difference in the proportion of successes between the 2 treatment groups (Cochran-Mantel-Haenszel test: p=0.70). The results of the sensitivity analysis were consistent with the primary analysis (Chi-square test: p=0.53). Due to recruitment stopping prematurely, with less than half of the planned number of patients being recruited, the statistical analysis was underpowered and the results should be interpreted with caution. **Safety** There was no notable difference between the 2 treatment groups in the number of patients with any treatment-emergent AE (TEAE) (28 [54.9%] patients in the placebo group and 27 [54.0%] patients in the xaliproden group), related TEAE (4 [7.8%] patients in the placebo group and 5 [10.0%] patients in the xaliproden group), or TEAE leading to discontinuation (3 [5.9%] patients in the placebo group and 5 [10.0%] patients in the xaliproden group). Two (4.0%) patients in the xaliproden group discontinued the study due to TEAEs considered related to the study treatment (atrioventricular block complete in one

	[2.0%] patient, and cerebellar syndrome and dizziness in one [2.0%] patient). The number of patients with treatment-emergent SAEs and related SAEs was slightly higher in the xaliproden group than in the placebo group. Treatment-emergent SAEs were reported for 3 (5.9%) patients in the placebo group (none of which was considered related to the study treatment), and for 7 (14.0%) patients in the xaliproden group (considered related to the study treatment for 3 [6.0%] of the patients: atrioventricular block complete, blood alkaline phosphatase increased, and cerebellar syndrome in one [2.0%] patient each). One (2.0%) patient in the xaliproden group died during the study. The cause of death was reported as colon cancer disease progression. There were no deaths in the placebo group. The most commonly reported TEAEs in the placebo group were asthenia (5 [9.8%] patients) and fatigue (3 [5.9%] patients). The most commonly reported TEAEs in the xaliproden group were diarrhoea (5 [10.0%] patients) and asthenia (4 [8.0%] patients). In both treatment groups, the majority of TEAEs were graded by the investigator as mild (Grade 1) or moderate (Grade 2) in intensity. One significant TEAE (ie, Grade 3 or 4 venous thrombosis, pulmonary embolism, or cardiac or metabolic disorders) was reported during the study: a Grade 3 TEAE of atrioventricular block complete, considered related to the study treatment, in one (2.0%) patient in the xaliproden group. There were no notable mean increases from baseline in HbA1c in either treatment group, and there was no evidence of a xaliproden-related increase in the incidence of positive D-dimer results (in both treatment groups, the proportion of patients with a positive D-dimer result was lower at the Month 3 visit and Month 6 visits than at baseline). There were no potentially clinically significant abnormalities in hematology values. The following potentially clinically significant biochemistry abnormalities were each reported for one patient in the xaliproden group: Grade 3 bilirubin (ie, a value between 3.0 and 10.0 times the upper normal limit), Grade 3 low serum potassium (ie, a value between 2.5 mmol/L and 3.0 mmol/L), and a blood urea nitrogen value between 1.5 and 3.0 times the upper normal limit. There were no notable mean changes from baseline in systolic or diastolic blood pressure, heart rate, or body weight, and no notable increase in the proportion of patients with an abnormal ECG, in either treatment group. In both treatment groups, the most common ECOG Performance Status grade at all visits was 0 ('normal activity'). The worst Performance Status grade during the study was 3 ('in bed >50% of time'), reported for one (2.0%) patient in the placebo group at the Month 6 visit.
Conclusions:	[redacted]

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