*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<br>**Drug substance(s):** XRP9881 (larotaxel) | **Study Identifier:** NCT00386685<br>**Study code:** TCD6595 |
| **Title of the study:** Open label, uncontrolled study of XRP9881 in combination with trastuzumab (Herceptin®) in patients with HER2 positive metastatic breast cancer (MBC) | |
| **Study center(s):** 8 sites in European countries (1 in Belgium, 5 in France, 1 in Sweden and 1 in Switzerland). | |
| **Study period:**<br>Date first patient enrolled: 18 July 2006<br>Study Completion Date (Study cut-off date): 07 October 2008 | |
| **Phase of development:** Phase 2 | |
| **Objectives:**<br>**Primary objective:**<br>To assess the antitumor activity of XRP9881 in combination with trastuzumab as assessed by objective response rate (RR) observed during the study period (lasting up to 6 months after the last patient was enrolled).<br>**Secondary objectives:**<br>• To assess the safety and tolerability of XRP9881 in combination with trastuzumab<br>• To assess any pharmacokinetic (PK) interaction of XRP9881 and trastuzumab when given in combination<br>• To evaluate the progression-free survival (PFS) and overall survival (OS). | |
| **Methodology:** Multicenter, open-label, uncontrolled study of XRP9881 administered at the dose of 90 mg/m² every 3 weeks (q3w) in combination with trastuzumab administered q3w at a loading dose of 8 mg/kg followed by 6 mg/kg/ q3w in patients with HER2 positive MBC. | |
| **Number of patients:** Planned: 49 patients Included: 51 Treated: 49 | |
| **Diagnosis and criteria for inclusion:** Female patients aged at least 18 years, with histologically or cytologically proven diagnosis of breast cancer and HER2 positive status, metastatic or locally recurrent and inoperable with a curative intent, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, and with a measurable disease as defined by response evaluation criteria in solids tumors (RECIST). | |
| **Investigational product:** XRP9881 (larotaxel) 40 mg/mL vial<br>Dose: 90 mg/m². Dose reductions of XRP9881 were planned according to the type, severity of toxicities or non recovery of toxicities to grade ≤1 at D22.<br>Administration: 1-hour intravenous (i.v.) infusion. The i.v. premedication required included dexchlorpheniramine 5 mg, diphenhydramine 25 mg or other antihistamines, dexamethasone 8 mg or equivalent steroid, at least 30 minutes prior to XRP9881 administration. Ranitidine or other histamine H2 antagonist with the exception of cimetidine were recommended.<br>XRP9881 was administered 30 minutes after the end of the combination treatment trastuzumab administration, every 3 weeks (q3w). | |

**Duration of treatment:** Patients were treated until disease progression, unacceptable toxicity or patient/investigator's decision

**Duration of observation:** Patients were followed for safety up to 30 days after last infusion

**Reference therapy:** None

**Criteria for evaluation:**

Efficacy: Tumor assessments were done at baseline and every 2 cycles (at the end of Cycles 2, 4, 6, 8, etc.) using the same method for each assessment; by X-ray, computer tomography (CT) scan, magnetic resonance imaging (MRI) (unless CT contrast is contraindicated) or clinical examination, by the Investigators, based on RECIST criteria; and, in case of treatment discontinuation and no progression, every 6 weeks during the follow-up period until disease progression, start of a new anti-tumor therapy, death or study cut-off date, whichever came first.

Safety: Adverse events (AEs), vital signs, physical examinations, ECOG PS and laboratory safety tests (including complete blood counts and serum chemistry) were recorded prior to drugs administration, at designated interval throughout the study and up to 30 days after the end of study treatment. Adverse events were graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Event classification Version 3.0. Left ventricular ejection fraction was assessed by echocardiography or multiple gated acquisition scan at baseline, every 3 cycles and at the end of treatment.

Pharmacokinetics: PK parameters were assessed for XRP9881 by Bayesian estimation using the Nonmem program and were performed for trastuzumab by a noncompartmental analysis using WinNonlin software, for all patients at Cycle 1 and at Cycle 6 (if applicable at Cycle 6).

**Pharmacokinetic sampling times and bioanalytical methods:**

Venous blood samples were collected at designated time-points at Cycle 1 and at Cycle 6 for XRP9881 and trastuzumab. The plasma concentrations of XRP9881 were determined by a liquid chromatography mass spectrometry technique (LC/MS-MS – LOQ = 1 ng/mL). The serum concentrations of trastuzumab were assayed by a validated immunoassay method (LOQ = 20 µg/mL).

**Statistical methods:**

The primary efficacy endpoint was the best overall response (BOR) in the all treated population during the study period. The RR was defined as the proportion of patients with confirmed complete response (CR) or partial response (PR) relative according to the RECIST criteria based on the Investigator's assessment of the disease. The primary analysis showed RR with two-sided 95% confidence interval (CI) calculated using the Clopper-Pearson exact method.

Secondary endpoints included safety profile and secondary efficacy endpoints (PFS, OS) were descriptively analyzed.
Pharmacokinetics: After having checked the equality of variances of XRP9881 plasma clearance (CL), a t-test was performed to compare XRP9881 CL at Cycle 1 and at Cycle 6. Then, XRP9881 plasma CLs when given in combination with trastuzumab (Cycle 1) were compared to those obtained in monotherapy with the same schedule of administration (Pool of Phase I, monotherapy studies) using a t-test.

**Summary:**

A total of 49 female Caucasian patients with HER2 positive metastatic breast cancer were included and received at least 1 cycle of XRP9881.

Efficacy results:

The objective response rate (RR) was 44.9% (95% CI: [30.7%: 59.8%]). The median PFS was 7.13 months (95% CI, [5.68:11.10]). The median OS was not reached at the time of study cut-off.

Safety results:

All patients in the treated population experienced treatment emergent adverse events (TEAEs), graded 3 or 4 for 67.3% of patients.

The most frequent gastrointestinal event was diarrhea (all grades, 77.6%; Grade 3-4, 8.2%). The incidence of all grades for nausea, stomatitis and vomiting were respectively 65.3%, 38.8% and 34.7% but Grade 3 or 4 events were observed in less than 5% of the patients.

The most frequent general disorders and administration site conditions TEAE were asthenia and fatigue (all grades 71.4% and 16.3%), with Grade 3-4 of 18.4% and 4.1% respectively, and pyrexia reported by 28.6% of patients.

Grade 3 musculoskeletal and connective tissue disorders were reported in 4.1% of patients, for myalgia (2.0%, all grades 51.0%) and arthralgia (4.1%, all grades 46.9%).

The incidence of peripheral sensory neuropathy was 28.6% for all grades and 2.0% for Grade 3-4. The incidence of all grades (Grades 3-4) paraesthesia, dyesaesthesia and hypoaesthesia was 24.5% (4.1%), 10.2% (none) and 8.2% (2.0%) respectively.

Alopecia was reported in 73.5% of patients. The incidence of rash, nail disorders, nail toxicity, dry skin disorders and palmar-plantar erythrodysesthesia syndrome was respectively for all grades: 14.3%, 8.2%, 8.2%, 8.2% and 6.1%. No Grade 3-4 skin and subcutaneous tissue disorders were reported.

The incidence of neutropenic infection and febrile neutropenia was 6.1% (4.1%, Grades 3-4) and 6.1% (all Grade 3-4) respectively. Only 1 patient (2.0%) had Grade 3 drug hypersensitivity.

The main hematological toxicity was Grade 3 or 4 neutropenia (75.5%).

Seventeen patients (34.7%) had at least 1 treatment emergent serious adverse event (SAE): Grade 3-4 were reported in 13 patients (26.5%). Two deaths occurred within the 30 days following the last dose of study treatment (related sepsis and atrial fibrillation after Cycle 1, and unrelated suicide concomitant to a depression after Cycle 2).

Pharmacokinetic results:

In this combination study, mean XRP9881 clearance was similar after the administration of a loading dose of 8 mg/kg of trastuzumab (Cycle 1) and after the loading dose of 8 mg/kg of trastuzumab followed by 5 consecutive administrations at 6 mg/kg every 3 weeks (Cycle 6) with mean clearance of 35.4 ± 10.9 L/h/m² in Cycle 1 and 36.3 ± 12.4 L/h/m² in Cycle 6 and with mean steady state volume of distribution of 777 ± 484 L/m² in Cycle 1 and 893 ± 384 L/m² in Cycle 6.

These clearance values were similar to the mean value of 33.1 ± 9.60 L/h/m² obtained from pooled Phase 1 data (monotherapy studies). No significant statistical difference in the PK of XRP9881 could be observed when administered either alone or in combination with trastuzumab (single loading dose or after 6 consecutive administrations every 3 weeks).

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