SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL NP22002)

COMPANY: NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	NP22002 – An exploratory study to evaluate the biological activity of R1507, a human monoclonal antibody antagonist of the insulin-like growth factor receptor (IGF-1R), in women with operable breast cancer / Report No. [redacted] / January 2011.
INVESTIGATORS / CENTERS AND COUNTRIES	[redacted] United Kingdom.
PUBLICATION (REFERENCE)	Not applicable.

PERIOD OF TRIAL	July 3, 2009 to July 15, 2010	CLINICAL PHASE	1

OBJECTIVES

Primary Objectives

Study part 1:

- To evaluate the effect of R1507 treatment on IGF-1R expression in breast cancer cells.

Study part 2 (not conducted):

- To define and confirm a pharmacokinetic/pharmacodynamics (PK/PD) threshold effect of R1507 by assessing lower dose levels.

Secondary Objectives

Study part 1 and part 2 (part 2 not conducted):

- To evaluate the effect of R1507 treatment in breast cancer cells:
  - on p-AKT level
  - on Ki67 index
  - on apoptotic index
- To correlate R1507 PK parameters in serum with biologic changes in tumor tissue.
- To evaluate the safety and tolerability of R1507 in patients with breast cancer.

	Exploratory Objectives Study part 1 and part 2 (part 2 not conducted): • To evaluate the effect of R1507 treatment in breast cancer cells on changes in broad gene expression. • To evaluate skin and peripheral blood mononuclear cells (PBMCs) as surrogate tissues for breast tumor treated with R1507. • To evaluate the effect of R1507 on insulin-like growth factor binding proteins (IGFBPs) in blood and breast tumor tissue.
STUDY DESIGN	This was an open-label single-arm study, to explore the PD effects of R1507 in women with operable breast cancer.
NUMBER OF SUBJECTS	For study part 1, the planned sample size was a maximum of 40 patients with 15 patients planned for, and up to 25 patients accrued during, the preplanned interim assessment. Study part 2 was not conducted. Details of planned subjects numbers for this part are described in the protocol on page 163.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Female patients ≥ 18 years of age with a histological diagnosis of invasive, operable breast cancer and available liquid nitrogen-stored breast tissue samples from previous standard-of-care breast cancer diagnostic biopsy. Patients were also required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see page 205). See page 169 and page 170 for full inclusion and exclusion criteria.
TRIAL DRUG / STROKE (BATCH) No.	R1507 CHO (formulation RO4858696/F05; [redacted]).
DOSE / ROUTE / REGIMEN / DURATION	In part 1 of the study, a single dose of R1507 16 mg/kg was given intravenously (IV). In part 2 of the study (not conducted), a single dose of R1507 9 mg/kg, 3 mg/kg or 1 mg/kg was to be given IV.
CRITERIA FOR EVALUATION	
PHARMACODYNAMICS:	PD assessments included analysis of serum and tumor biopsy samples for biomarkers potentially related to IGF signaling (see page 178). In addition, PBMC and skin samples were taken before R1507 administration and at the time of breast surgery (the skin sample was optional prior to R1507 administration); these were analyzed for the same biomarkers as the tumor tissues (see page 162).
PHARMACOKINETICS:	
SAFETY:	Safety assessments included adverse events (AEs), clinical laboratory tests (hematology and biochemistry, coagulation, urinalysis, urine/serum pregnancy test), vital signs (temperature, resting blood pressure, pulse and respiratory rate), 12-lead electrocardiograms, chest X-ray, physical examination.

STATISTICAL METHODS	Details of the planned statistical analyses (not conducted) of the primary and secondary variables can be found on page 190. Descriptive statistics were used to analyze all safety data.

METHODOLOGY:

Full details of the study methodology are provided in the study protocol (page 120).

The study consisted of a screening visit (days -14 to -1), a baseline visit (days -7 to -1), a 4-week treatment phase (a single R1507 16 mg/kg IV dose on day 1 and definitive breast surgery 8 days later) and a follow-up visit (up to 30 days after the single dose of R1507).

Prior to dosing (R1507 16 mg/kg) on day 1, a physical examination was performed and blood samples for hematology, biochemistry, coagulation, PK/PD, and PBMC samples were collected. Vital signs were assessed prior to administration of R1507 and every 15 minutes during R1507 infusion. Each patient was maintained in observation for 1 hour after R1507 infusion.

As part of the standard of care, after identification of a suspicious breast lesion, each patient must have undergone a diagnostic biopsy and have 2 samples available for submission, one fresh frozen biopsy specimen and one specimen embedded in paraffin. After confirmation of the diagnosis and provision of informed consent, study specific procedures would be conducted. In patients who consented to this optional procedure, prior to, or on, study day 1, an approximately 2 mm punch biopsy was taken from the affected breast skin of each patient who consented to this optional procedure. Patients were then treated with a single dose of R1507 (16 mg/kg i.v. over 90 minutes). On study day 8 (± 3-days), breast cancer tissue samples were collected from the affected breast during surgery (paraffin embedded and fresh frozen) and a skin biopsy was taken from the skin overlying the operated/affected breast. The breast and skin tissue samples were used for study-specific biomarker analyses.

An interim analysis was planned after 15 patients had been enrolled [redacted]. Breast tissue samples were evaluated for IGF-1R levels before and after one R1507 dose by immunohistochemistry. If sufficient biologic effect of R1507 (down-regulation) had been demonstrated in study part 1, three additional treatments would have been dosed in part 2.

All patients were followed for 30 days after the single R1507 16 mg/kg dose for safety monitoring and blood sampling.

REASONS FOR STUDY TERMINATION:

[redacted] The study was discontinued before completion of enrollment into part 1 or initiation of part 2. This synopsis report presents an overview of the biomarker data collected and all safety data collected during the study (cut-off, July 15 2010, corresponding to follow-up visit for SAE).

STUDY POPULATION:

Disposition of Patients:

Eight patients were enrolled into part 1 of the study at a single center ([redacted], United Kingdom).

Premature Withdrawal:

No patients withdrew prematurely from the study (page 10).

Overview of Analysis Populations:

All 8 patients enrolled were included in the safety population. [redacted], only limited PD and PK analyses were performed.

Demographic Data:

All 8 women included in the trial were white, with ages ranging from 46 to 70 years (see page 11). All patients had a stage IIA ductal tumor (see page 14).

PHARMACODYNAMIC RESULTS:

Three biomarkers, IGF1R, pAKT and Ki-67, defined in the primary and part of secondary objectives of the study were assessed by immunohistochemistry on the diagnostic and surgery samples. All 8 patients expressed high to very high levels of IGF1R on the cell membrane (H score between 105 to 290) and in cytoplasma (H score 70-205). On day 6, after one dose of R1507 (16 mg/kg IV), 6 out of 8 patients showed a slight numerical down-regulation of the membrane IGF1R level and up-regulation of the cytoplasmic IGF1R level. Although these dynamic changes are consistent with the expected directions, the magnitude is insignificant and within the error of semi-quantitative measurement of the immunohistochemistry assay. Six out of 8 patients showed very high nuclear pAKT levels (H score 230-300) and essentially no difference between pre- and post treatment measurements. Only one patient [redacted] with more moderate pre-dosing nuclear pAKT level showed a drastic decrease (by 2.5 fold). Relatively large decrease in Ki-67 expression was observed only in patient number [redacted] (~30%) and large increase in patient number [redacted] (~80%). All other patients showed smaller changes in either direction.

SAFETY RESULTS:

Extent of Exposure to Study Treatment:

Eight patients received a single dose of RO4858696 of 16 mg/kg corresponding to absolute doses of between 850 mg and 1338 mg (page 15).

Adverse Events:

All AEs reported during the study are listed on page 16 . (See page 21 for a glossary of AE preferred terms).

Thirty-five AEs were reported by the 8 patients included in the study (page 23). Procedural complications, of which most were incision site pain were the most commonly reported events (13 events, of which 7 were incision site pain). Reproductive system and breast disorders (6 events, of which 2 were amenorrhea), were the next most commonly reported. Less than 5 AEs were reported in each of the other body systems. All AEs were classified as mild or moderate in intensity. The relationship was considered as probable for 1 event (vessel puncture site hematoma) and possible for 5 events in 4 patients (all reproductive system and breast disorders) (page 25).

Deaths and Serious Adverse Events:

There were no deaths and 2 SAEs in patient [redacted] (sensory disturbance and peripheral coldness) (page 28). The causal relationship was considered to be remote for both events, which presented after surgery. The events were unresolved at the unscheduled last study visit (July 15 2010).

Laboratory Safety Parameters:

A listing of laboratory test results is presented on page 29 . These results are summarized by NCI-CTC on page 49 and the corresponding shift tables are presented on page 59 . Three shifts were reported-two from grade 0 to grade 1 (lymphocytes and ALAT) and one from grade 0 to grade 3 (INR) in patient [redacted] at the follow-up visit. The grade 3 INR was not associated with any other issues and was not reported as an adverse event (page 16).

Vital Signs:

Instances of high and low diastolic BP, high systolic BP and high and low heart rate were reported in all patients throughout the study (page 68). Some of the patients had abnormalities at screening and there was no clear temporal relationship with administration of study drug.

Electrocardiogram:

There were no reports of abnormal ECGs (after screening, ECGs were only performed if clinically indicated).

CONCLUSIONS:

- The two SAEs (sensory disturbance and peripheral coldness) were reported in 1 patient; both were considered remotely related to the study drug.
- Of the 35 AEs reported, 1 was considered as probably related (vessel puncture site hematoma) and 5 as possibly related (all reproductive system and breast disorders).
- Apart from an isolated grade 3 elevation in INR at the follow-up visit, there were no noteworthy findings for laboratory tests or vital signs.
- Membrane IGF1R level decreased only marginally in some of the patients after receiving one dose of R1507.
- pAKT and Ki-67 level reduction, which would reveal the effect of anti-IGF1R in the receptor's signal transduction and cell proliferation, was not observed after a single dose of administration of the drug.