2 Synopsis

Trial Registration ID-number	**EudraCT number**
NCT00617253	2006-005751-16

Title of Trial

An open-label, dose escalation safety and tolerability trial of the combination of subcutaneous (s.c). recombinant human IL-21 (rIL-21) and sunitinib (phase 1) followed by an open label stratified randomised 2-arm trial of rIL-21 plus sunitinib versus sunitinib alone (phase 2a) in subjects with stage IV renal cell carcinoma (RCC)

This report includes results from the phase 1 part with dose escalation.

Investigator

There was one principal investigator for each of the trial sites in The Netherlands and Germany. [redacted] was appointed as signatory investigator.

Trial Site

Two trial sites were initiated in The Netherlands and were actively recruiting subjects. Three trial sites were initiated in Germany and two of the three sites were actively recruiting subjects, while one trial site, [redacted], never screened any subjects.

Publications

The results from the phase 1 part of the trial have been presented as a poster at the following conference:
EORTC-NCI-AACR, 2008, Abstract No.: 408
Phase 1 study of recombinant human interleukin-21 (rIL-21) in combination with sunitinib in patients with metastatic renal cell carcinoma (RCC)

Trial Period	**Development Phase**
12 July 2007 to 30 June 2008	Phase 1

Objectives

Primary Objective:

- To assess the safety and tolerability of increasing doses of rIL-21, administered s.c. in a thrice weekly regimen, in combination with sunitinib 50 mg once daily (OD) per oral (p.o.) in the approved '4 weeks on 2 weeks off'-schedule; and to determine the maximal tolerated dose (MTD) in subjects with stage IV RCC

Secondary Objectives:

- To describe the pharmacokinetic (PK) responses in subjects treated with this regimen (rIL-21 and sunitinib)
- To assess if antibodies against recombinant interleukin-21 (IL-21) are induced during therapy
- To describe the pharmacodynamic responses in subjects treated with this regimen
- To measure effects of this treatment regimen on tumour size according to Response Evaluation Criteria in Solid Tumours (RECIST) (if applicable)

Methodology

This was a multi-national open-label dose escalation safety and tolerability phase 1 trial evaluating rIL-21 administered s.c. thrice weekly in combination with 50 mg sunitinib administered p.o. once daily for 4 weeks followed by 2-week pause. Treatment with sunitinib was initiated 1 week in advance of rIL-21 treatment. A maximum of 21 weeks of rIL-21 treatment and 22 weeks of sunitinib treatment was to be applied within the trial. Estimated dose levels of rIL-21 were 3, 10, 30, and 100 µg/kg body weight until the MTD was determined. If tumour responses occurred or stable disease (SD) was observed (assessed at the evaluations at Week 10 – main trial) extended treatment with rIL-21 and sunitinib was to be administered for up to 12 weeks (extended trial). The assessment was also done at Week 16.

Safety and tolerability was assessed using the United States (.U.S.) National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. The first 10 weeks of treatment constituted the period for evaluation of dose-limiting toxicities (DLT). Safety was monitored for 3 weeks after last treatment with rIL-21.

Number of Subjects Planned and Analysed

It was planned that around 3-6 subjects will be enrolled at each dose level, dependent on the observed DLTs. The

total number of subjects to be included was estimated to be 15-18. The number of subjects included in the trial is shown below:

Subjects		**Full Analysis Set N (%)**
Screened		11
Included	Eligible	10 (100.0)
	Not Eligible	0 (0.0)
Main Trial	Exposed	9 (90.0)
	Withdrawn	5 (50.0)
	Adverse Event	5 (50.0)
	Non-compliance	0 (0.0)
	Withdrawal Criteria	0 (0.0)
	Other	0 (0.0)
	Completed	4 (40.0)
Extension	Exposed	3 (30.0)
	Completed	3 (30.0)

Diagnosis and Main Criteria for Inclusion

Subjects with histologically verified and surgically incurable stage IV RCC, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and life expectancy of at least 3 months were included in the trial.

Test Product, Dose and Mode of Administration, Batch Number

Subjects were treated with s.c. administrations of rIL-21 thrice weekly (e.g. Monday, Wednesday, and Friday) for 9 weeks (Weeks 2-10). The trial product was rIL-21, 10 mg/mL for injections, 0.8 mL per vial. The dose was given as s.c. injections. A maximum volume of 1.0 mL was given per injection. Recombinant IL-21 treatment was initiated one week after sunitinib treatment. The subjects were hospitalised for 24 hours after the first dose administration of rIL-21 (Day 8) for PK, haematology, and body temperature assessments. At Days 10, 12, and 15 the subjects were observed for 3 hours after administration of rIL-21. At the subsequent dose administrations there was no observation required unless it was judged necessary by the investigator. The first three doses of rIL-21 were administered at the clinical site/hospital. The batch number of rIL-21 injection was PD06014.

Duration of Treatment

A maximum of 21 weeks of rIL-21 treatment and 22 weeks of sunitinib treatment was to be applied within the trial.

Reference Therapy, Dose and Mode of Administration, Batch Number

Sunitinib was administered according to manufacturer's instructions (50 mg OD p.o. in the approved '4 weeks on 2 weeks off'-schedule). Sutent® (sunitinib, Pfizer) was supplied in hard gelatine capsules of 12.5 mg. The batch number of Sutent Capsules was E575D.

Criteria for Evaluation – Efficacy

- PK of IL-21 and sunitinib
- Soluble CD25 and genotyping of the IL-21 receptor, perforin 1 and granzyme B genes
- Tumour response
- Anti-rIL-21 antibodies

Criteria for Evaluation – Safety

- Adverse events
- Physical examination
- Vital signs
- Electrocardiogram (ECG) monitoring
- Clinical laboratory tests (haematology, biochemistry and urinalysis)

Statistical Methods

Primary endpoint:

The primary endpoint in the phase 1 part of the trial was toxicity to the combination of rIL-21 and sunitinib, assessed

using the US NCI CTCAE version 3.0. Based on observed DLTs to the combination of rIL-21 and sunitinib, the MTD was estimated.

Secondary endpoints

- Safety: effect of rIL-21 on vital signs (BP, temperature and heart rate), ECG, Electrocardiography / Multiple Gated Acquisition (MUGA) scan, body temperature, haematology, biochemistry and urine analysis, body weight and physical examination.
- PK profiles of rIL-21 and sunitinib in combination with rIL-21: AUC, AUC_{0-24}, $t_{½}$, C_{max},t_{max}, Vz//f and CL/f.
- Biomarkers: effect of rIL-21on sCD25 and genotyping of the IL-21 receptor, perforin 1 and granzyme B genes
- Efficacy: effect of rIL-21 on tumour size, determined as Complete Response (CR), Partial Response (PR), Stable Disease (SD) or Progressive Disease (PD) according to the RECIST criteria.
- Changes in anti-rIL-21 antibody serum concentration

Statistical analyses of the primary endpoint:

No formal statistical analysis was performed. The primary endpoint is presented by summary tables and listings.

Statistical analyses of the secondary endpoint:

All PK parameters for rIL-21 and sunitinib were planned to be derived using non-compartmental methods. The PK endpoints for rIL-21 and sunitinib in combination with rIL-21 were summarised and listed by dose level. The individual time profiles for plasma concentrations of rIL-21 and sunitinib were presented graphically. All secondary safety endpoints were summarised by dose level and visit and listed by dose level.

A statistical analysis of sCD25 was performed using a linear normal model including day, dose level and the interaction day*dose level as fixed effects and subject as a random effect. The sCD25 values, anti-rIL-21 antibodies and SLD for target lesion and the percent change from baseline were summarised by dose level visit and listed by dose level.

Demography of Trial Population

All 9 subjects were White (4 from Netherlands and 5 from Germany) and were diagnosed with Stage IV RCC. There were 3 females and 6 males in the trial. Subjects were between 48 and 71 years of age (median was 55 years) and body weight ranged from 51.4 to 95.1 kg. All 9 subjects were diagnosed with Stage IV RCC. Of the 9 subjects, 6 had clear cell RCC.

Efficacy Results

Pharmacokinetics

- The PK parameters were not estimated for rIL-21 because all serum rIL-21 concentrations were below LLoQ at 3 µg/kg rIL-21 and most rIL-21 concentrations were also below LLoQ at 10 µg/kg rIL-21. Therefore, it was agreed that it served no purpose to estimate the PK parameters for rIL-21
- Given the high variability associated with the PK endpoints for sunitinib assessed, there was no apparent influence on the plasma sunitinib concentration-time profile observed when administered in combination with rIL-21 at doses of up to 10 µg/kg

Tumour Response

- Best overall tumour response was PR in 1 subject, SD in 1 subject and PD in 1 subject of the 3 subjects evaluable for tumour response
- At Week 10, 2 subjects were evaluated as SD and 1 subject as PD. At Week 16, 2 subjects were evaluated as PR and at Week 22, 1 subject was evaluated as PR and 1 subject was evaluated as SD out of 2 evaluable subjects. The subject with PR at Week [redacted] had PD [redacted] later corresponding to duration of response of [redacted]

Biomarkers

- Increased levels of sCD25 following treatment with rIL-21 were observed for both 3 and 10 µg/kg rIL-21 dose regimens
- A total of 10 SNPs and 9 haplotypes were observed in the IL-21R gene, 8 SNPs and 5 haplotypes in the granzyme B gene and 13 SNPs and 8 haplotypes in the PRF1 gene

Anti-rIL-21 Antibodies

- Anti-rIL-21 antibodies were reported in a total of 4 subjects; 3 subjects were dosed with 3 µg/kg and 1 subject was dosed with 10 µg/kg rIL 21. Neutralising anti-rIL-21 antibodies were demonstrated in 2 out of the 4 subjects being tested positive for the presence of anti-rIL-21 antibodies

Safety Results

- Overall, rIL-21 doses of 3 µg/kg administered s.c. thrice weekly in combination with 50 mg sunitinib administered p.o. once daily for 4 weeks followed by 2 weeks off was tolerated and manageable in subjects with stage IV RCC, while rIL-21 doses of 10 µg/kg administered similarly was not tolerated
- No DLTs were observed at the 3 µg/kg rIL-21 dose level, while 2 DLTs were observed at the 10 µg/kg rIL-21 dose level. The DLTs were neutropenia and thrombocytopenia evaluated to be definitely related to both rIL-21 and sunitinib
- The MTD was not determined per protocol as the SDEG decided not to include more subjects in the 3 µg/kg rIL-21 dose group, as this dose was considered too low for further clinical development
- A total of 160 AEs were reported in 9 subjects during the trial. Approximately half of the AEs (79 of 160 [49%] AEs) reported were due to sunitinib. Of the 9 subjects, 6 experienced an AE of grade 3 severity and 1 subject reported AE of grade 4 severity. The most commonly reported AEs related to rIL-21 and sunitinib were injection site reaction and stomatitis, respectively
- All AEs of grade 3 or 4 severity in both the 3 and 10 µg/kg rIL-21 dose groups were due to sunitinib
- A total of [redacted] SAEs were reported in 1 subject in the 3 µg/kg rIL-21 dose group; [redacted] of the [redacted] SAEs were nontreatment-emergent (as reported [redacted] to rIL-21 dosing) and the remaining [redacted] were treatment-emergent (as reported [redacted] rIL-21 dosing). All [redacted] SAEs were according to the investigator evaluated as definitely related to sunitinib, while the [redacted] serious treatment-emergent AEs were evaluated as unrelated to rIL-21
- No deaths were reported in the trial
- No clinically relevant changes in vital signs, physical finding and ECG were observed during the trial

Conclusions

- Overall, rIL-21 doses of 3 µg/kg administered s.c. thrice weekly in combination with 50 mg sunitinib administered p.o. once daily for 4 weeks followed by 2 weeks off were tolerable and manageable in subjects with stage IV RCC, while rIL-21 doses of 10 µg/kg administered similarly were not tolerable
- No DLTs were observed at the 3 µg/kg rIL-21 dose level, while 2 DLTs were observed at the 10 µg/kg rIL-21 dose level. The DLTs were neutropenia and thrombocytopenia
- The MTD was not determined per protocol as the SDEG decided not to include more subjects in the 3 µg/kg rIL-21 dose group, as this dose was considered too low for further clinical development
- Given the high variability associated with the PK endpoints for sunitinib assessed, there was no apparent influence on the plasma sunitinib concentration-time profile observed when administered in combination with rIL-21 at doses of up to 10 µg/kg
- Anti-rIL-21 antibodies were reported in a total of 4 subjects; 3 subjects were dosed with 3 µg/kg and 1 subject was dosed with 10 µg/kg rIL-21. Neutralising anti-rIL-21 antibodies were demonstrated in 2 out of the 4 subjects being tested positive for the presence of anti-rIL-21 antibodies
- Increased levels of sCD25 following treatment with rIL-21 were observed for both 3 and 10 µg/kg rIL-21 dose regimens
- Best overall tumour response was PR in 1 subject, SD in 1 subject and PD in 1 subject of the 3 subjects evaluable for tumour response

The trial was conducted in accordance with the Declaration of Helsinki (amended 2004) and ICH Good Clinical Practice (May 1996).