Clinical Study Report Synopsis
ANG206

GE Healthcare

Title: Final Clinical Study Report Synopsis of an Open-Label, Multi-Centre, Phase 2a Study to Assess the Feasibility and Safety of Intravenous Bolus Administration of 99mTc-NC100692 Injection in Imaging Metastases in Late Stage Cancer Patients

This is an exact copy of the synopsis from the final clinical study report for the study ANG206. The final clinical study report (document-identifier: CC ANG206 CREP) was authorised for use by the Head of Global Medical on 17 July 2006 (Version 1.0, effective date 18 July 2006).

2 SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
GE Healthcare Ltd. and its Affiliates</td><td rowspan="3">Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:

Volume:

Reference:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Name of Finished Product:
Kit for the preparation of ^{99m}Tc-NC100692 Injection</td></tr>
<tr><td>Name of Active Ingredient:
^{99m}Tc-NC100692</td></tr>
<tr><td colspan="3">Investigators and Study Centres: The study was conducted in 8 study centres in Europe and 4 study centres in USA</td></tr>
<tr><td colspan="3">Investigators and Centres for Independent Evaluation of Images: All images were evaluated at the study centres.</td></tr>
<tr><td colspan="3">Publication (reference): Not applicable.</td></tr>
<tr><td colspan="2">Study Period: 09 March 2005 (first subject first visit) 22 January 2006 (last subject last visit)</td><td>Phase of Development:
Phase 2</td></tr>
<tr><td colspan="3">Objectives
Primary Objectives:
• To determine the feasibility of detecting metastatic lesions located in liver, lung, bone and brain using scintigraphic imaging following the administration of ^{99m}Tc-NC100692 Injection in subjects with primary cancer in the breast, lung (non-small cell), ovary, or prostate or with melanoma, and compare to current anatomical imaging for detection of metastases.
Secondary Objectives:
• To assess the ability of ^{99m}Tc-NC100692 Injection-aided scintigraphic imaging to detect the response of metastases to treatment after approximately 3 weeks of therapy.
• To assess the safety profile of repeat dosing with ^{99m}Tc-NC100692 Injection in subjects with metastatic cancer.</td></tr>
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Study Design:
The study ANG206 was a phase 2a, multi-centre, open-label, non-randomised study and was the first study within the indication of monitoring response of lesions to therapy in late stage cancer patients. The study determined whether ^{99m}Tc-NC100692 Injection can be used for detection of distant metastases in the most common organs for metastatic spread of disease (liver, lung, bone and brain).
26 subjects with late stage cancer were included in 12 centres across Europe and the USA.
All subjects received an administration of ^{99m}Tc-NC100692 Injection. Subjects where metastases were detected on the scintigraphic images and who were referred for a standard treatment regimen received a second administration of ^{99m}Tc-NC100692 Injection after the first cycle of treatment. The subjects who were monitored after the first cycle of treatment were included in the study for a period of approximately 3 weeks after chemotherapy start. For subjects where metastases were not detected on the scintigraphic images or where no treatment was initiated, a second imaging procedure was not performed.
Safety measurements (haematology, serum biochemistry, coagulation, urinalysis, vital signs, pulse oximetry,12-lead ECG assessments, and a physical examination) were performed up to 2 hours 30 minutes after injection. AEs were followed up via telephone 24 hours after injection.

Selection of Subjects:
Subjects who had been diagnosed with primary breast, lung (non-small cell), ovarian or prostate cancer or malignant melanoma and with metastases to liver, lungs, bone or brain were included in this study. Prior to the enrolment of the first subject, the focus of the study was changed to subjects with metastatic breast or metastatic lung cancer. The opportunity to enrol subjects with ovarian or prostate cancer or malignant melanoma was allowed and therefore no formal amendment made. On completion of the study only breast and lung cancer patients had been enrolled. The metastases had to be diagnosed using CT, MRI, or bone scintigraphy (as appropriate). The subjects were also to be evaluated for chemotherapy or radiation therapy.

Number of Subjects (planned and analysed):
Approximately 80 subjects were planned to be recruited; a total of 26 subjects were included in this study.
Efficacy: 25 subjects were evaluable for efficacy after Imaging Session 1, and 18 subjects after Imaging Session 2.
Safety: All 26 subjects dosed with ^{99m}Tc-NC100692 Injection at Imaging Session 1 and all 19 subjects dosed at Imaging Session 2 were included in the safety evaluation.
Non-completers: A total of 6 subjects was recorded as non-completers.

Treatment of Subjects

Investigational Medicinal Product´(IMP): Subjects received ^{99m}Tc-NC100692 Injection as an intravenous bolus injection under direct supervision of study personnel. Subjects received an intravenous injection of 5.5 mL of ^{99m}Tc-NC100692 Injection at a rate of 2-4 mL per second. After administration, the line was to be flushed with 5 mL of Sodium Chloride (0.9% w/v). Each subject was to receive a 75 µg dose of NC100692 and a ^{99m}Tc activity in the range of 800-1100 MBq. Those subjects monitored after the first cycle of treatment were to receive a second administration of ^{99m}Tc-NC100692 Injection of the same volume and activity approximately 3 weeks after the first injection.

Standard of Truth: The ^{99m}Tc-NC100692 Injection-Single Photon Emission Computed Tomography (SPECT) images were compared on-site with the reference standard (the standard diagnostic modality at the study centre). The diagnosis was based on contrast-enhanced (CE) CT, MRI, or bone scintigraphy (as appropriate). The images were compared for correctly identified malignant lesions. Regarding the response to treatment, the diagnostic conclusion regarding response of the lesion to treatment at the clinic was recorded as a reference standard. This reference standard was compared to the changes in the ^{99m}Tc-NC100692 Injection-SPECT images by the on-site investigator. The reference standard for measuring response of the metastases to treatment was available after 6-9 weeks.

Duration of Imaging: The subjects were included in the study on the day of the first ^{99m}Tc-NC100692 Injection. Dynamic planar imaging of the liver was performed for those subjects who had hepatic metastases. This was a 15-minute duration imaging session beginning immediately at the time of injection of ^{99m}Tc-NC100692 Injection and consisting of 45 sequentially-acquired frames each of 20-second duration. The dynamic imaging was followed by a conjugate-view whole body scan beginning at 45 minutes post-injection (approximately 10-20 minutes duration). A SPECT acquisition was performed nominally at 1 hour 15 minutes post-injection (approximately 30 minutes duration), focusing on 1 anatomical region of metastases (e.g., abdomen, thorax, brain). A second SPECT sequence was obtained 2 hours after injection, if there was a second anatomical region of metastases. On each imaging day, all imaging was to be completed within 2 hours 30 minutes post-injection. The subjects were followed up 24 hours after each imaging day.

Endpoints

Efficacy:

The primary efficacy endpoint in this study was the match (number of correctly identified lesions) between lesions detected from the scintigraphic images compared to those detected by the reference standard.

The secondary efficacy endpoint in this study was the evaluation of the scintigraphic images before and after treatment by the on-site investigators for a qualitative change in lesion appearance (number and size). These results were compared to the standard evaluation of response of metastases to treatment at the site.

Safety:

Safety endpoints included monitoring the occurrence of 1 or more treatment-emergent adverse events (Aes), and changes in a limited physical examination, ECG recordings, serum biochemistry, haematology and coagulation, vital signs and urine analysis from administration of ^{99m}Tc-NC100692 Injection. For subjects who were also being evaluated after the first cycle of treatment, these safety parameters were assessed at both ^{99m}Tc-NC100692 Injection administrations.

Statistical Analyses

Statistical analyses, summaries, listings, and graphical presentations were performed using SAS software. All individual subject data were presented in separate data listings. The primary efficacy endpoint was summarised using descriptive statistics.

Summary of Results

Efficacy:

- The detection rates for metastases associated with primary breast cancer were 1 of 7 lesions (14%) for liver, 4 of 5 (80%) for lung, 8 of 17 (47%) for bone and 1 of 1 (100%) for brain metastases. The detection rates for metastases associated with primary lung cancer was 0 of 2 lesions (0%) for liver, 17 of 18 (94%) for lung, 2 of 2 (100%) for bone and 7 of 9 (78%) for brain metastases. These numbers are based on excluding lesions <1 cm as seen on the reference standard from the analysis.
- Metastases from both primary breast and lung cancer can be visualised with SPECT imaging using ^{99m}Tc-NC100692 Injection. However, the detection rate for liver lesions is poor and most likely related to high background uptake of the agent in the liver.
- Visual assessment of NC100692-SPECT images for qualitative changes after 1 cycle of treatment does not allow a prediction of the outcome of therapy response as judged by CE-CT.

Safety:

Among the 26 subjects evaluated for safety there was overall stability through the follow-up period after the first and second dosing with ^{99m}Tc-NC100692 Injection for all parameters, including clinical laboratory, vital signs, ECG, and physical examination. No clinically important safety signals or trends over time were noted.

Seven subjects (26.9 %) reported a total of 13 AEs not related to cancer therapy. For 2 of these AEs the investigators suspected a relationship to ^{99m}Tc-NC100692 Injection. The majority of AEs (10 AEs) were mild in intensity, 2 AEs were reported as moderate and only 1 as severe. There was 1 SAE reported in this study which was not related to ^{99m}Tc-NC100692 Injection.

A total of 7 AEs related to cancer therapy were reported for 3 subjects (11.5 %). All of these AEs were deemed to be not related to ^{99m}Tc-NC100692 Injection by the investigators and were graded as toxicity grade 1 according to the common toxicity criteria. No SAEs were reported in relation to cancer therapy. In total, no subject had to be withdrawn from the study due to an AE and no subjects died during their participation in the study.

Conclusions:

This phase 2 study was performed in order to answer the key question: "Does the agent detect metastatic lesions located in liver, lung, bone and brain using scintigraphic imaging compared to current anatomical imaging for detection of metastases?". The results demonstrate that metastases in soft tissue such as lung and brain from both primary lung and breast cancer can be visualised with SPECT imaging using ^{99m}Tc-NC100692 Injection. The detection of liver lesions is poor, most likely related to the high background uptake of the agent in the liver. The detection of bone metastases varies; in some subjects few lesions were detected, in other subjects focal uptake was seen on the SPECT images that was not confirmed on the reference standard.

The qualitative assessment of response to chemotherapy after the first cycle of treatment (approximately 23 days after start of treatment) based on on-site evaluations of all detected lesions on SPECT, gives no clear indication that changes in lesion number and size predict the final outcome of chemotherapy.

All of the 26 safetys subjects enrolled into the study were dosed with ^{99m}Tc-NC100692 Injection at the first imaging session; 19 subjects were dosed with ^{99m}Tc-NC100692 Injection at the second imaging session. There was overall stability through the follow-up period after the first and second dosing with ^{99m}Tc-NC100692 Injection for all parameters, including clinical laboratory, vital signs, ECG and physical examination. No clinically important safety signals or trends over time were noted. The use of ^{99m}Tc-NC100692 Injection in subjects with primary breast cancer and primary non-small cell lung cancer is safe and well tolerated.