1. Title page

Diagnostic value of ^{18}F-choline PET/CT for the detection of systemic prostate cancer disease.

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Protocol reference: 2008-CaP-FCH	Clinical study phase: III	
Study period from: to: FPFV: 17 May 2010 LPLV: 30 June 2013	Early termination: Yes: No: X	
Indication: Diagnostic value of ^{18}F-choline PET/CT ([^{18}F]-FCH PET/CT) for the detection of systemic prostate cancer disease.	Archiving: The trial master file is archived at CIS bio international (Saclay, France)	
Generic name: [^{18}F]-FCH, solution for intravenous injection	Formulation number: NA	Substance code number: NA
Earlier reports from the same study: None		

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This study was conducted in compliance with Good Clinical Practice (GCP).

Study objectives

The primary objective of the present study was to assess the sensitivity and specificity of [^{18}F]-FCH PET/CT for systemic disease (i.e., lymph node metastases and/or organ metastases and/or bone metastases) on a body region basis.

The second objectives were to assess the performances of [^{18}F]-FCH PET/CT for LN metastases, bone metastases, organ metastases detection, on a body-region, and on a patient basis. It was aimed to assess the agreement rate between [^{18}F]-FCH PET/CT and MRI for the primary tumor detection. It was also planned to assess the impact of [^{18}F]-FCH PET/CT on tumor primary staging and consequently on therapy choice. Finally, the safety profile of [^{18}F]-FCH PET/CT was checked.

2. Synopsis

Name of Sponsor/Company:	CIS bio international	
Name of finished product:	CHOLICIS	
Name of active ingredient:	^{18}F-choline (^{18}F-Fluoromethylcholine)	
Reference of finished product	[^{18}F]-FCH	
Title of study:	Diagnostic value of 18F-choline PET/CT for the detection of systemic prostate cancer disease	
Publication(s):	N/A	
Coordinating investigators:	**France :** **Spain :**	Dr Henri de CLERMONT-GALLERANDE Dr Gregorio GARMENDIA
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Study period	**Date of first subject, first visit:** 17 May 2010 **Date of last subject, last visit:** 30 June 2013	**Clinical phase:** III
Objectives:	**Primary study objective:** Sensitivity and specificity of [^{18}F]-FCH PET/CT for systemic disease (i.e., lymph node metastases and/or organ metastases and/or bone metastases) on a body region basis. **Secondary objectives** : • Sensitivity and specificity of [^{18}F]-FCH PET/CT for lymph node metastases using histopathology as the SOR and CT as a comparator (per lymph node area; only lymph nodes area with histopathological analysis). Quantification using SUV (quantitative uptake in lymph nodes) will be used. • Agreement rate between [^{18}F]-FCH PET/CT and CT for organ metastases on a region basis. Discrepant cases will be documented by MRI (except for lung metastases). For lung metastases, discrepant results will be documented by a chest CT performed within 6 months after [^{18}F]-FCH PET/CT. • Agreement rate between [^{18}F]-FCH PET/CT and bone scintigraphy with regard to bone metastases (on a body region basis). Discrepant cases will be documented by MRI. • Sensitivity and specificity of [^{18}F]-FCH PET/CT for systemic disease (i.e., lymph node metastases and/or organ metastases and/or bone metastases) on a patient basis. • Agreement rate between [^{18}F]-FCH PET/CT and pelvic MRI (if available) for the primary tumor. • Modification of tumor primary staging and patient management. • Safety of [^{18}F]-FCH	
Study design:	Intra-individual comparison, non-randomized, controlled, prospective, open label, phase 3 with central image evaluation	
Number of patients:	**Planned:** 150 patients overall for 117 evaluable patients (considering 20% drop-out) **Analysed:** 149 patients enrolled and 148 administered	
Diagnosis and main criteria for inclusion:	Male patients after a first diagnosis of prostate cancer based on histo-pathological examination (needle biopsy of the primary tumor) and with high risk disease according to d'Amico criteria: - stages $\geq$ T2c and/or - PSA $\geq$ 20 ng/mL (for patients treated with testosterone 5 alpha-reductase inhibitor PSA level $\geq$ 10 ng/mL) and/or - Gleason score $\geq$ 8 or - Gleason score = 7 with either predominance of grade 4 or percentage of positive biopsy > 50%	

Study products	
Test product:	[^{18}F]-FCH, 225 ± 10 % MBq/mL at calibration
Dose:	4 MBq /kg of body mass
Route of administration:	Intravenous administration
Batch numbers:	Refer to Appendix 16.1.6
Duration of treatment:	Single injection
Reference product:	NA
Dose:	
Route of administration:	
Batch numbers:	
Duration of treatment:	
Criteria for evaluation:	
Efficacy:	Primary efficacy analysis: A z-test on the basis of generalized estimation equations will be used to test on the diagnostic value of [^{18}F]-FCH PET/CT in terms of sensitivity and specificity. Secondary efficacy analysis: Descriptive statistics will be provided for the secondary efficacy variables.
Safety:	The safety variables will be analysed descriptively.
Statistical methods:	Data Analysis set: The primary statistical analyses of the efficacy were conducted on the per-protocol (PP) population, which consists of all patients who received the required dose of [^{18}F]-FCH and who did not have any major protocol deviations. In addition, an intent-to-treat (ITT) analysis will be carried out on the full analysis set (FAS) for the primary efficacy endpoint. The FAS will include all patients regardless of any protocol deviations. The safety analysis will be performed on the FAS. Statistical analysis of efficacy Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) were calculated for quantitative variables; frequency counts by category will be given for qualitative variables. Confidence intervals were given where appropriate. If not else wise stated, these intervals were two-sided and provided 95% confidence. Primary efficacy analysis: A z-test on the basis of generalized estimation equations (GEEs) at a one-sided level of significance of 2.5% were used to test on the diagnostic value of [^{18}F]-FCH PET/CT in terms of sensitivity and specificity. Secondary efficacy analysis: Descriptive statistics based on the PP population were provided for the secondary efficacy variables. For the estimation of sensitivity and specificity and agreement rates and the comparison of these parameters between

different modalities, z tests on the basis of GEEs were used analogous to the primary analysis.

Statistical analysis of safety

The safety variables were analysed descriptively.

Study population:

A total of 149 patients were enrolled in the clinical study. One of them did not receive the investigational product due to manufacturing failure and no possibility to postpone the exam. One other patient signed an informed consent form but finally decided to not participate in the study before any study drug administration and before any screening examination.

The mean age of the study population was 67.15 years (range 49 – 84)

From May 2010 to January 2013, 148 patients with newly diagnosed prostate cancer at high risk disease (stages ≥ T2c and/or PSA ≥ 20 ng/mL (for patients treated with testosterone 5 alpha-reductase inhibitor PSA level ≥ 10 ng/mL) and/or Gleason score ≥ 8, or Gleason score = 7 with either predominance of grade 4 or percentage of positive biopsy > 50%) received the investigational product.

The Full Analysis Set for primary efficacy endpoint consisted of the 148 patients who received a dose of [^{18}F]-FCH.

Efficacy results:

The Per-protocol population (PP) for efficacy consists of 141 patients who received a dose of [^{18}F]-FCH and who did not have major protocol deviations affecting the validity of the analysis of the primary objective.

Region-based analysis

The primary efficacy variables were the sensitivity and the specificity of [^{18}F]-FCH PET/CT for the systemic disease **on a per region basis** (LN metastases and/or metastases in distant organs and/or bone metastases). The average across readers sensitivity and specificity were 0.44 and 0.99 respectively.

One additional variable was the region-based sensitivity/specificity of [^{18}F]-FCH PET/CT in comparison to that of CT for LN metastases detection (anatomopathology as SOT). Among the 56 patients of the PP population who underwent a PLND, 7 patients had a total of 13 regions with LN metastases. The across reader region-based sensitivity and specificity for LN detection were 10% (95%CI 3-28%) and 96% (95%CI 91-98%) respectively.

The secondary variables included the region-basis agreement rates between [^{18}F]-FCH PET/CT and CT for organ metastases, and between [^{18}F]-FCH PET/CT and BS for bone metastases. Eight patients presented with bone metastases. The sensitivity and specificity of [^{18}F]-FCH PET/CT for bone metastases on a per-region basis were 70% (95%CI 31-92%) and 99% (95%CI 98-99%) respectively. Twelve patients presented with organ metastases. The sensitivity and specificity of [^{18}F]-FCH PET/CT for organ metastases on a per-region basis were 38% (95%CI 17-64%) and 100% (95%CI 99-100%) respectively.

Patient-based analysis

Agreement rate between [^{18}F]-FCH PET/CT and MRI for detection of primary tumour local extension was assessed in 101 patients (with SOR) and was 94% (95%CI 87-97%).

Across reader agreement rate between [^{18}F]-FCH PET/CT and CT for LN metastases on a patient basis was 68% (95%CI 56-78%).

Sensitivity and specificity for bone metastases on a patient basis using truth panel final assessment as SOR were 67% and 91% respectively (57% and 93% for BS).

Sensitivity for organ metastases was 42% (95%CI 19-69%) and specificity was 99% (95%CI 97-100%).

Based on truth panel assessment of TNM staging ("correct TNM staging") the impact of [^{18}F]-FCH PET/CT on TNM staging was assessed for each T, N or M classification. A positive impact on diagnostic understanding was defined as modification of TNM classification between pre- and post imaging towards the "correct TNM classification" assessed by the Truth Panel (improved diagnostic understanding). The correctness of T-staging was improved in 56 patients (39.7%), falsely modified in 19 patients (13.5%) and unchanged in 66 patients (46.8%); the correctness of [^{18}F]-FCH PET/CT on N-staging was improved in 23 patients (16.3%), falsely modified in 7 patients (5.0%) and unchanged in 111 patients (78.7%); the correctness of [^{18}F]-FCH PET/CT on M-staging was improved in 30 patients (21.3%), falsely modified in 13 patients (9.2%) and unchanged in 98 patients (69.5%). In addition, the impact of [^{18}F]-FCH PET/CT across therapy options led to a positive change in 27 patients (19.1%), negative change in 5 patients (3.5%) and did not lead to any change in 109 patients (77.3%). The change from before to after [^{18}F]-FCH PET/CT was then correct in 27/32 patients with change (82%).

The three readers demonstrated a substantial agreement (inter-reader reproducibility) in sensitivity assessment and a fair agreement in specificity assessment. During the blind read session, the intra-reader reproducibility was also tested in 30 patients (read twice) and the reproducibility was in the range of 96.7% – 100 % depending on the reader.

Safety results:

Among the 148 patients who received the study drug, five (5) of them reported at least one adverse event (AE): two patients had abdominal pain associated with diarrhoea for one of them, one patient had diarrhoea, another one had headache and the last experienced acute urinary retention.

Some of them were assessed by the investigator as possibly related to the study drug (abdominal pain with diarrhoea, abdominal pain, and headache).

All adverse events were rated as non-serious except the micturition disorder (acute urinary retention) which was reported as serious. The patient was referred to the emergency room for urological examination and treatment. However, the investigator considered this serious adverse event as related to the underlying prostate cancer lesion involving urethral and bladder problems.

Conclusions:

The primary efficacy was based on the technical efficacy in terms of diagnostic performance of [^{18}F]-FCH PET/CT with regard to the SOR all assessed in a blinded read. The specificity was found to be 99% (95% CI 98%; 99%) across readers in the complete case analysis. This was much higher than the prespecified limit of acceptance of 85%. The sensitivity was found to be 42% (95% CI 20%; 66%) across readers in the complete case analysis. The sensitivity was therefore found to be lower than the prespecified limit of acceptance of 70%.

The performances of [^{18}F]-FCH PET/CT were poor for LN detection and organ metastases. However [^{18}F]-FCH PET/CT performed well in bone metastases detection.

The inter-reader agreement and intra-reader reproducibility were good.

Despite a moderate sensitivity, the impact of [^{18}F]-FCH PET/CT on the T, N, and M correct staging in the truth panel assessment was positive in more patients than it was negative (T stage: 40% with positive impact, 14% with negative impact; N stage: 16% with positive impact, 5% with negative impact; M stage: 21% with positive impact, 9% with negative impact). Also the impact of [^{18}F]-FCH PET/CT on the change in treatment from before PET/CT according to the truth panel was positive with a change towards a correct treatment after PET/CT in 27 of 33 patients with a change overall (82%)**.**

Safety results confirm the good safety profile of [^{18}F]-FCH.

Date of the report: 16 May 2014.