Imperial College
London

Evaluation of [^{18}F]fluoroethyl triazole labelled [Tyr^3]Octreotate analogues for the imaging of Neuroendocrine tumours

Protocol Number: FETONET

EudraCT Number: 2013-003152-20

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Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct.
- I agree to personally conduct or supervise the described clinical study in accordance with Good Clinical Practice requirements.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations.

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1. SYNOPSIS

Name of Sponsor/Company: Imperial College.
Name of Finished Product:[^{18}F]fluoroethyltriazole[Tyr^3]Octreotate ([^{18}F]-FET-βAG-TOCA) Injection
Name of Active Ingredient: [^{18}F]-FET-βAG-TOCA
Title of Study: Evaluation of [^{18}F]fluoroethyltriazole[Tyr^3]Octreotate analogues for the imaging of neuroendocrine tumours.
Investigators and Study Centre(s): Imanova.
Phase of Development: Phase 1
Primary Objective: To evaluate the utility of the [^{18}F]fluoroethyl triazole labelled [Tyr^3]Octreotate analogue, [^{18}F]-FET-βAG-TOCA, in the accurate localisation of tumours in patients with a histologic diagnosis of NETs of any site.
Study Design: **Primary Endpoint:** To determine the biodistribution of [^{18}F] following single i.v. administration of [^{18}F]-FET-βAG-TOCA injection To assess tumoural uptake of [^{18}F]-FET-βAG-TOCA **Safety Endpoint:** The occurrence of one or more treatment-emergent adverse events (AEs) from administration of [^{18}F]-FET-βAG-TOCA Injection throughout the study period, and changes in serum biochemistry, haematology, coagulation, immunology, urinalysis, vital signs, ECG, injection site, and physical examination findings.
Selection of Subjects: **Main Inclusion Criteria:** 1. Written informed consent 2. Age ≥ 18 years 3. Histological diagnosis of NET of any site, except where ENETS criteria does not mandate histology for confirmation of diagnosis or patients who have a positive ^{68}Gallium-peptide scan in whom NET diagnosis is pre-operatively definitive. 4. Locally advanced or metastatic disease 5. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 (appendix A) 6. Life expectancy > 3 months 7. Measurable disease defined as a lesion that can be accurately measured in at least one dimension with the longest diameter ≥10mm using conventional techniques 8. Somatostatin receptor imaging within 6 months. (if patient does not have somatostatin receptor imaging they may also be included provided they have measurable disease (≥10mm) on conventional imaging. 9. Adequate organ system function as defined in Table 1 **Main Exclusion Criteria:** • Patients received chemotherapy within 3 weeks of study or radiotherapy within 4 weeks of study • Active uncontrolled infections, gastrointestinal disease, haemolysis or any serious co-existing medical illness • Psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule • Pregnant or lactating women • Females of childbearing potential who are unwilling to avoid pregnancy, for the duration of the study • Presence of any underlying medical conditions which in the investigators opinion would make the patients unsuitable for treatment • Satisfactory baseline haematologic and organ function Patient not expected to be able to tolerate the scanning sessions
Number of Patients Planned: 56 patients with diagnosis of neuroendocrine tumours of any site

Treatment of Subjects:

Investigational Tracer: Subjects will receive a single i.v. bolus injection of 1-10 mL of [^{18}F]-FET-βAG-TOCA injection over a period of at least 30 seconds. The tracer injection will be followed by a saline flush. Patients will receive a maximum ^{18}F activity of 165 MBq.

Statistical Methods and Planned Analysis:

Using results of dynamic scanning and metabolite analysis an appropriate protocol will be designed to analyse the diagnostic static scans. The internal radiation dosimetry as well as biodistribution of the tracer will be calculated. Comparison between FET-βAG-TOCA PET and standard of care somatostatin receptor imaging will be made based on
both a per-patient and per-lesion based analysis. Non-parametric McNemar test with Bonferroni correction for multiple comparison will be used. The association between SSTR1-5 expression and imaging parameters obtained will be assessed. Data will be analysed using SPSS 16.0 for Windows.

Bio-distribution and Radiation Dosimetry

Bio-distribution data in patients will consist of ^{18}F activity content in organs and tissues of interest, ^{18}F activity
concentrations in whole blood and plasma and of ^{18}F activity excreted in the urine. Descriptive statistics will be generated for bio-distribution data at each time point for each organ and tissue of interest. The amount of ^{18}F activity excreted in urine in patients will be calculated from the product of concentration of ^{18}F activity measured in each sample and the volume of each sample for a subset of patients.

Safety

Safety parameters will be summarized using
descriptive statistics

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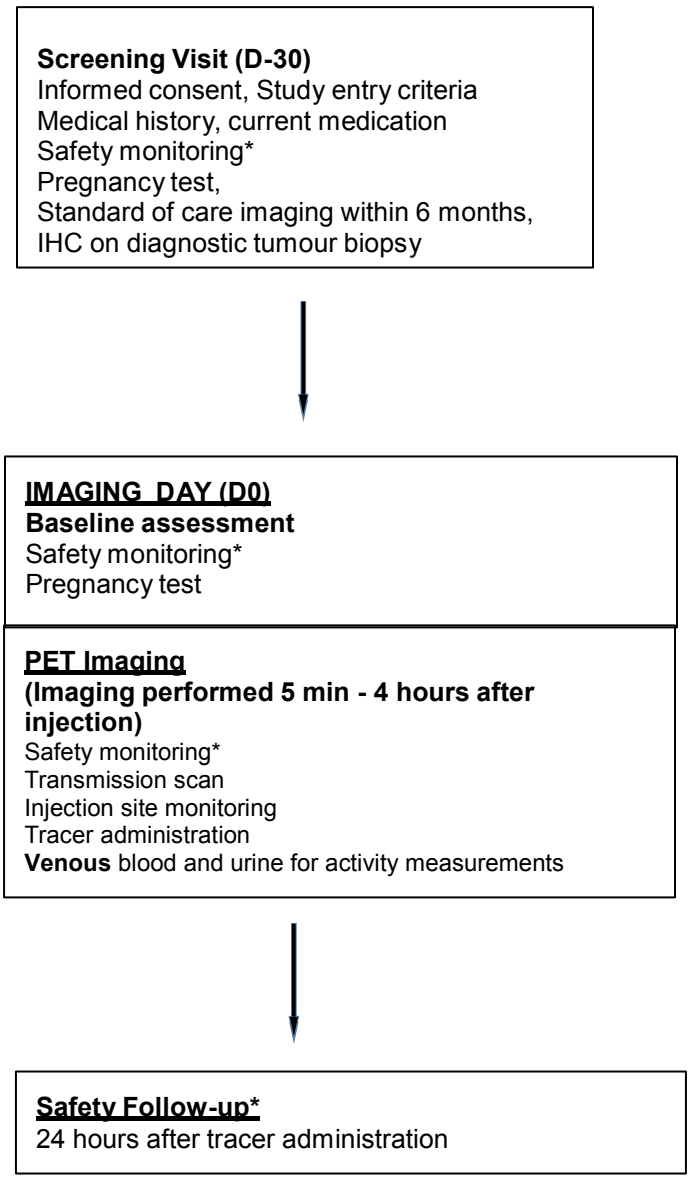
3. LIST OF ABBREVIATIONS and Definitions of Terms

^{18}F	Fluorine with an Atomic Mass of 18
^{68}Ga	Gallium with an Atomic Mass of 68
^{99m}Tc	Metastable Technetium with an Atomic Mass of 99
AE	Adverse Event
ARSAC	Administration of Radioactive Substances Advisory Committee
Bpm	Beats per Minute (Heart Rate)
CRF	Case Report Form
CT	Computed Tomography
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ED	Effective Dose (ie, the sum of risk weighted organ absorbed radiation dose used as a measure of stochastic radiation risk)
EUC	Electrolytes, Urine, Creatinine
GCP	Good Clinical Practice GLP Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
i.v.	Intravenous
MBq	Megabecquerel
MHRA	Medicines & Healthcare products Regulatory Agency
MIRD	Medical Internal Radiation Dose
NET	Neuroendocrine tumour
PET	Positron Emission Tomography
PK	Pharmacokinetics
SAE	Serious Adverse Event
SRS	Somatostatin Receptor Scintigraphy
SSTR	Somatostatin Receptor

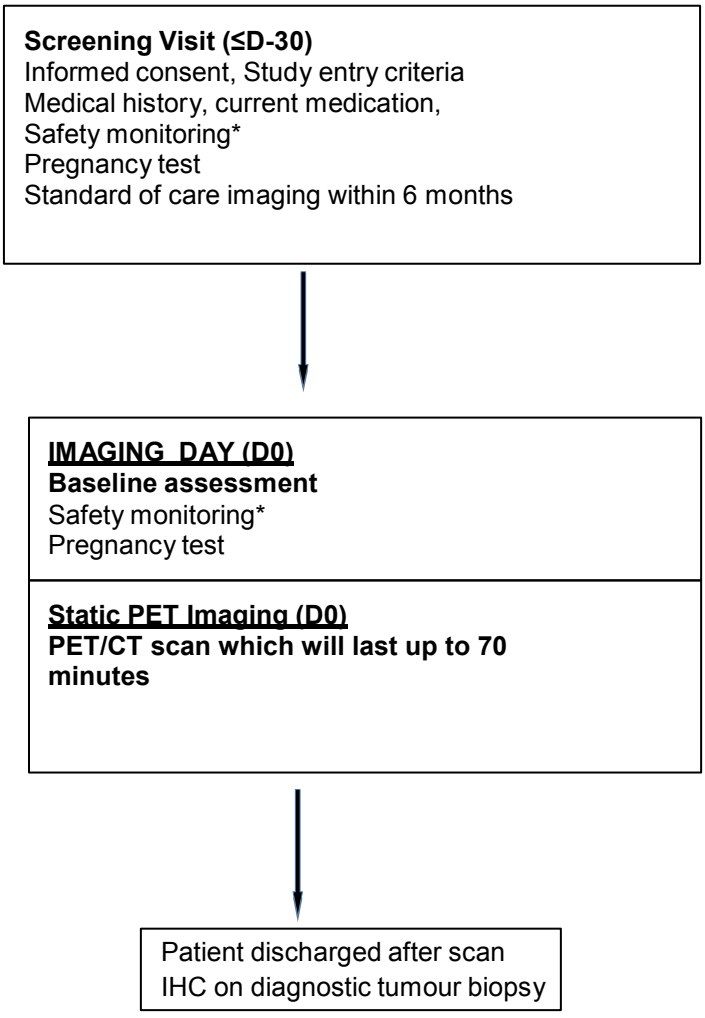
4. SUMMARY

4.1 Cohort 1. Dosimetry and safety study in patients with histological diagnosis of NETs of any site.



*For safety parameters please refer to the study schedules of events, Table 1 & Table 2

4.2 Cohort 2. Open label study comparing [^{18}F]-FET-βAG-TOCA – PET with [^{68}Ga]-DOTATATE-PET/CT in patients with histological diagnosis of NETs of any site.



*For safety parameters please refer to the study schedules of events, Table 1 & Table 3

5. BACKGROUND

Neuroendocrine tumours (NETs) are tumours derived from enterochromaffin cells, which are characterised by the presence of neurosecretory granules composed of a variety of hormones and biogenic amines. These tumours can release vasoactive substances into the systemic circulation, resulting in episodic flushing, wheezing, diarrhoea, and eventual right-sided valvular heart disease. All of these symptoms negatively impact on patients' quality of life. NETs can originate at any site, however the common site of disease is the midgut comprising of 40% to 70% of all NETs[1]. Whilst initially thought to be relatively rare, it is evident from the US Surveillance Epidemiology and End Results database that the incidence and prevalence has increased substantially (approximately 500%) over the past 30 years, and unlike most other solid tumours, the incidence continues to rise [2]. Within the UK 3000 patients are diagnosed each year making it the 11th most common cancer in the UK, and the second most prevalent tumour of the gastrointestinal tract.

The management of NETs is primarily determined by the stage of the disease. For patients with localised or limited disease the primary modality of therapy is surgery, whilst in patients with metastatic disease, systemic therapy is employed with palliative intent. Accurate imaging is therefore central to the management of this disease.

Whilst computer tomography is useful in the initial localisation of NETs, nuclear imaging using tumour-specific radiolabelled receptor analogues or amine precursors are considerably more sensitive and specific methods for detecting NETs and their metastases. Five SSTR subtypes (1-5) have been identified in human tissues, with 70 – 90% of NETS expressing subtypes 2 and 5. Somatostatin analogues, such as octreotide, bind with high affinity to SSTR2 and SSTR5, and with varying affinity to SSTR3 and 4. When chelators such as diethylenetriamine pentaacetic acid (DTPA) or 1,4,7,10-tetraazacyclododedcane-*N, N', N'', N'''* – tetraacetic acid (DOTA) are coupled to these analogues, they can be labelled with [^{111}In] or [^{99m}Tc] for scintigraphy in order to stage NETs. Furthermore, positive uptake on these scans will predict the likelihood of patients responding to therapy utilising radiolabelled somatostatin analogues. Currently, [^{111}In]-DTPA-octreotide SRS is the clinical gold standard for the imaging of these tumours, however there is an emerging clinical trend for the use of PET based on improved sensitivity and specificity.

In a review of pooled data from over 1200 patients, [^{111}In]-DTPA-octreotide SRS showed a median detection rate of 89% (range 67% to 100%) and a median sensitivity of 84% (range 57% - 93%)[3]. Whilst SRS is accurate, false positive results can be seen from the presence of inflammatory conditions that can be associated with an increase in SSTR expression such as in Crohn's disease [4]. Furthermore, NETs that are either too small or do not express high levels of SSTRs will not be detected. Other reasons for scan failure include low signal in areas of high background activity such as the liver and low spatial resolution.

Acquisition time is also prolonged, up to 48hours, making it inconvenient for both patients and nuclear medicine departments. Therefore, there is clearly a need to develop more accurate imaging techniques. The utility of PET imaging for visualising NETs has been highlighted with the development of [68Ga]-labelled somatostatin analogues. PET has superior physical characteristics compared to SRS including spatial resolution, sensitivity and quantification, and [68Ga]-labelled ligands also show higher affinity for SSTR 2 and 5 and more rapid clearance from the blood compared with [111-In]-labelled tracers, with images being obtained 60-90min following tracer injection. Furthermore, the radiation dose is lower using these tracers.

Preclinical and clinical studies have described the use of a number of analogues including DOTA-Tyr^3 octreotide (DOTA-TOC), DOTA-Tyr^3,Thr^8octreotide (DOTA-TATE) and DOTA-1-Nal^3-octreotide (DOTA-NOC) in the imaging of NETs [5-8]. [^{18}F]-Fluorodeoxyglucose (FDG)-PET has been extensively studied in NETs however the sensitivity of this imaging technique is low, 25 to 73%, because of the relatively low metabolic activity of NETs, making [^{18}F]-FDG-PET not suitable for the routine clinical imaging, with its role currently limited to the visualisation of poorly differentiated tumours. Imaging with [^{68}Ga]-DOTA-TOC PET has been reported to be more sensitive than [^{18}F]-FDG PET in patients with primary or recurrent NETs [9]. Furthermore, clinical studies comparing [^{68}Ga]-DOTA-TOC PET with [^{111}In]-octreotide scintigraphy suggest that [^{68}Ga]-DOTA-TOC PET is more sensitive than SRS in detecting NETs as a result of greater signal-to-background contrast [10, 11]. Currently it is unclear which [^{68}Ga] tracer - DOTA-TOC, DOTA-TATE or DOTA-NOC - is the best and there is no consensus for their use partly due to lack of a robust supply mechanism for the radiotracers for clinical trials. It is clear, however, that the sensitivities of these tracers are better than SRS due to use of PET.

The main limitations with [^{68}Ga]-DOTA-analogues PET are the requirement for an on-site Gallium generator for tracer manufacture resulting from the much shorter half life of [^{68}Ga] compared to [^{18}F] tracers that can be shipped easily to several sites and the low throughput of such generators, the poorer resolution of [^{68}Ga] compared to [^{18}F] and the paucity of clinical grade GMP radiotracer for large multi-centre trials. We, therefore, sought to develop a fluorine-18 labelled octreotate analogue which can be effectively used to image NETs by employing a versatile two-step GMP-compatible click chemistry method; embodied in the design of these fluorinated analogues, strategies to improve tumour uptake and systemic PK [12]. Fluorinated somatostatin analogues have been previously developed due to their superior physical properties for PET imaging, however, their clinical utility have been limited by high background uptake making it very difficult to visualise tumours particularly those within the liver, the main site of metastatic disease. We have developed a novel [^{18}F] labelled somatostatin analogue with improved *in vivo* kinetics compared to previously published [^{18}F] labelled analogues.

5.1 [^{18}F]-FET-βAG-TOCA-PET

We have developed a novel [^{18}F]fluoroethyl triazole labelled [Tyr^3]Octreotate analogue, [^{18}F]-FET-βAG-TOCA, that has been shown to have more favourable kinetics compared to other fluorinated somatostatin analogues and [^{68}Ga]-DOTATATE *in vivo* [12, 13]. We propose to transition [^{18}F]-FET-βAG-TOCA-PET into humans within 2 cohorts of patients. Patients in cohort 1 will undergo 'whole body dynamic PET scanning' with assessment of PK and safety. We will then use this information to develop an optimal 'whole body static PET scanning' protocol that will be used for patients in cohort 2. We will directly compare the sensitivity and specificity of [^{18}F]-FET-βAG-TOCA-PET to [^{68}Ga]-DOTATATE PET/CT, in the accurate localisation of NETs. It is anticipated that this novel tracer will eventually be the new standard in the imaging of these tumours.

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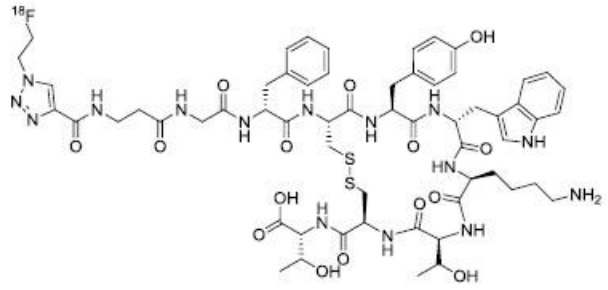
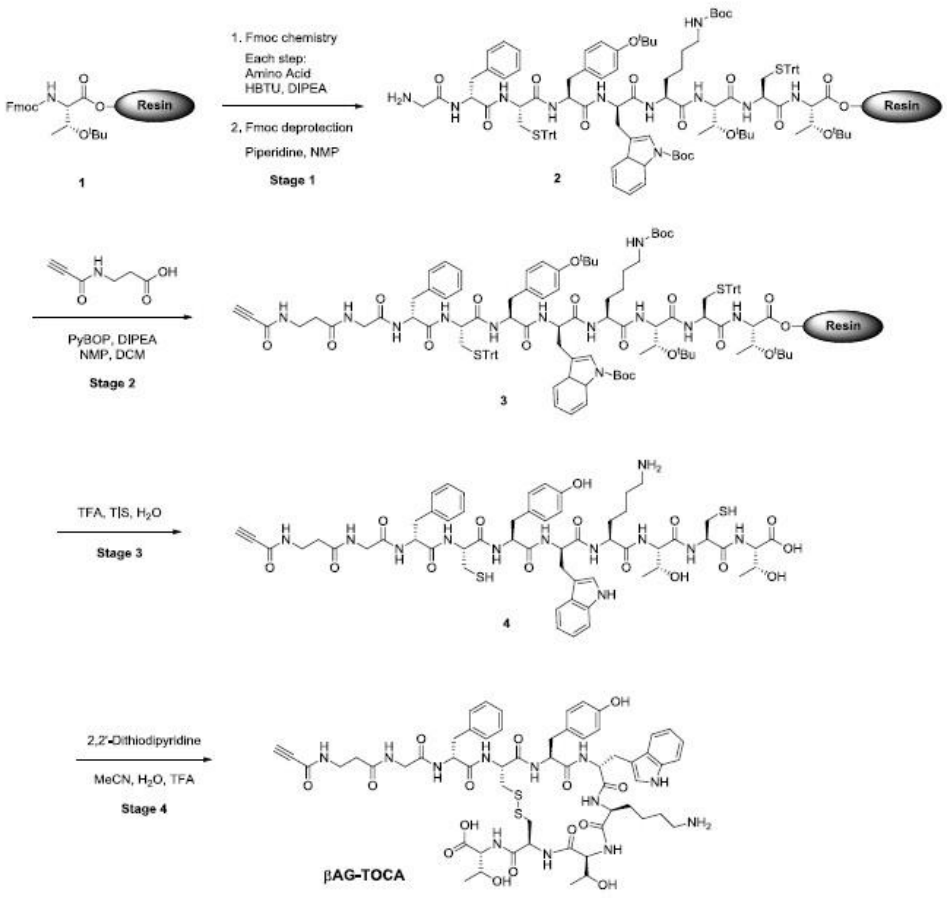
Figure 1. Structure of βAG-TOCA.

Structural Formula



Molecular Fomula	$C_{59}H_{76}FN_{15}O_{15}S_2$
Molecular Weight	1317.46 g.mol^{-1}

Figure 2. Flow Diagram for the synthesis of βAG-TOCA.



5.2 Rationale and evidence to date

NETs have a high density of SSTRs, in particular SSTR 2, on their cell surface. This characteristic allows the use of labelled somatostatin analogues to visualise these tumours. We developed five structurally-related [^{18}F]fluoroethyltriazole-[Tyr^3]octreotate analogues with suitable PK for PET imaging: [^{18}F]-FET-G-PEG-TOCA, [^{18}F]-FETE-PEG-TOCA, [^{18}F]-FET-G-TOCA, [^{18}F]-FETE-TOCA, and [^{18}F]-FET-βAG-TOCA. To select a lead compound we compared the tissue PKs of each novel compound to the recently described [^{18}F]-aluminium fluoride NOTA-octreotide ([^{18}F]-AlF-NOTA) and [^{68}Ga]-DOTA-TOCA, a radiotracer widely used in the clinical assessment of NETs [14]. All [^{19}F]fluoroethyltriazole-[Tyr^3]octreotate compounds retained high agonist binding affinity to SSTR2 *in vitro* (EC_{50} of 4-19 nM versus somatostatin at 5.6 nM)[12].

Utilising the AR42J pancreatic cancer xenograft model, which expresses a high level of SSTR-2, dynamic PET imaging was performed following administration of each tracer. Tumour uptake was maximal with FET-G-TOCA, followed by FET-βAG-TOCA and [^{18}F]-AlF-NOTA, with the least tumour uptake seen with [^{68}Ga]-DOTATATE. Incorporation of polyethylene glycol (PEG) linkers to reduce non-specific protein interactions and increase circulation time, as exemplified by [^{18}F]- FET-G-PEG-TOCA and FETE-PEG-TOCA, resulted in reduced uptake in high SSTR2 expressing AR42J pancreatic cancer xenografts, and these were not taken forward. Whilst tumour uptake was maximal with [^{18}F]-FET-G-TOCA, its slow hepatic clearance meant that this was not taken forward, and [^{18}F]-FET-βAG-TOCA, which showed the lowest non-specific uptake in liver, was selected for further development (^{13}).The specificity of [^{18}F]-FET-βAG-TOCA tumour uptake was illustrated through a number of experiments. Firstly, a radiolabelled scrambled peptide derived from [^{18}F]-FET-βAG-TOCA, [^{18}F]-FET-βAG-[W-c-(CTFTYC)K], did not show tumour uptake. Secondly, there was a 2-fold lower uptake of [^{18}F]-FET-βAG-TOCA in AR42J xenografts when mice were pre-treated with 10 mg/kg of unlabelled octreotide. Finally there was low uptake of [^{18}F]-FET-βAG-TOCA in low SSTR-2 expressing HCT116 xenografts.

The safety profile of [^{18}F]-FET-βAG-TOCA as a single microdose study in rats was assessed by a commercial GLP laboratory in accordance with MHRA/EMEA guidelines (see attached). There was no tracer (or precursor) related toxicity at 1000x the intended human dose. Rat radiation dosimetry studies, conducted by GE Healthcare are complete. The radiotracer showed a suitable organ dose profile. The new fluoroethyltriazole-[Tyr]^3-octreotate radioligand, FET-βAG-TOCA, combines high specific binding with rapid target localization for high contrast PET imaging.

6. STUDY OBJECTIVES

6.1 Primary objective

- To determine the bidistribution of [^{18}F] following single i.v administration of [18F]-FET-βAG-TOCA injection.
- To assess tumoural uptake of [^{18}F]-FET-βAG-TOCA

6.2 Secondary objectives

To assess efficacy of [^{18}F]-FET-βAG-TOCA PET/CT in patients with a histological diagnosis of NET and with measurable disease, who have and have not had [^{68}Ga]- DOTA-peptide imaging

6.3 Safety endpoints

The occurrence of one or more treatment-emergent adverse events (AEs) from administration of [^{18}F]-FET-βAG-TOCA injection throughout the study period, and changes in serum biochemistry, haematology, coagulation, immunology, urinalysis, vital signs, ECG, injection site and physical examination findings.

7.1 Cohort 1

7.1.1 Primary

1. To determine the biodistribution (clearance from whole blood and plasma, and urinary excretion) of [^{18}F] following single i.v. administration of [^{18}F]-FET-βAG-TOCA injection in patients with a histological diagnosis of NET
2. To calculate the internal radiation dosimetry and the Effective Dose (ED)

7.1.2 Translational end-points

1. To assess the safety of [^{18}F]-FET-βAG-TOCA
2. Assess expression of SSTR1-5 in biopsy specimens and compare with PET parameters

7.2 Cohort 2

7.2.1 Primary

1. To assess tumoural uptake of [^{18}F]-FET-βAG-TOCA –PET/CT

7.2.2 Secondary

2. Compare diagnostic efficacy of [18F]-FET-βAG-TOCA in those patients who have had or not had or are due to have [68Ga]-DOTA-peptide imaging. A power of ≥ 80% has been chosen to conclude non-inferiority equivalence.

Note***(All patients with a histological diagnosis of NET and lesion on CT is ≥1cm irrespective of whether they have had a [68Ga]-DOTA-peptide scan or are waiting for one as part of their management will be included in study).*

3. Comparison of [^{18}F]-FET-βAG-TOCA PET/CT scan and central review (nuclear medicine and radiology physician experts) of all imaging received by patient. (To account for any discrepancy that may exist between CT, [^{68}]Ga-DOTA-peptide imaging and [^{18}F]-FET-βAG-TOCA PET/CT scan, then patients will be offered an MRI scan.

7.2.3 Translational end-points

1. Assess expression of SSTR1-5 in biopsy specimens and compare with PET parameters

2. Evaluation of possible adverse effects

8. STUDY OUTLINE

8.1 Study design and rational of the chosen approaches

The total sample size will be 56 patients. Patients from cohort 1 (n=8-12), 4-6 female and 4-6 male (each cohort minimum 3) will be used in the final analysis. Patients with locally advanced or metastatic NETs of any site will be recruited from the Endocrinology, Surgical and Oncology Outpatients clinic, Hammersmith and Royal Free Hospitals. After obtaining informed consent, eligible patients will have blood taken at baseline for FBC, EUC, LFTs (routine clinical practice), and serum biomarkers. Patients will undergo routine staging. In addition, patients will undergo [^{18}F]-FET-βAG-TOCA PET/CT scanning at Imanova. Patients' original diagnostic tumour biopsy (paraffin fixed) will be obtained.

8.1.1 Cohort 1. Dosimetry and safety study in patients with histological diagnosis of NETs of any site.

In this initial evaluation patients presenting for routine staging will be consented to undergo whole body dynamic scanning (multiple whole body scans up to 3.5 hours) with metabolite analysis in order to develop a suitable protocol for static scanning that will be used for patients in cohort 2. We will also calculate the internal radiation dosimetry, which may alter the administered dose in subsequent studies. Although we do not expect any toxicity, we will conduct detailed safety assessment in this group of patients. We require a minimum of 8 patients for final Dosimetry and safety analysis, which should include a minimum of either 3 male or 3 female subjects. To ensure both sexes are sufficiently represented in the final Dosimetry, for calculating effective dose, Cohort 1 will therefore include a minimum of 8, but up to 12 subjects.

8.1.2 Cohort 2. Open label study assessing tumoural uptake of [18F]-FET-βAG-TOCA –PET in patients with histological diagnosis of NETs of any site.

Patients presenting for routine staging will be consented to also undergo a static PET/CT imaging with [^{18}F]-FET-βAG-TOCA in order to compare the clinical utility of [^{18}F]-FET-βAG-TOCA – PET/CT with standard of care somatostatin receptor imaging . As a translational endpoint, patients will also be consented for retrieval of their pre-treatment biopsy specimen. Immunohistochemistry (IHC) will be performed for expression of SSTR1-5, which will be correlated with PET images from both tracers (see section 4.2 for Summary)

9. ELIGIBILITY

9.1 Inclusion criteria

1. Written informed consent
2. Age ≥ 18 years
3. Histological diagnosis of NET of any site, except where ENETS criteria does not mandate histology for confirmation of diagnosis or patients who have a positive ^{68}Gallium-peptide scan in whom NET diagnosis is pre-operatively definitive.
4. Locally advanced or metastatic disease
5. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 (appendix A)
6. Life expectancy > 3 months
7. Measurable disease defined as a lesion that can be accurately measured in at least one dimension with the longest diameter ≥10mm using conventional techniques
8. Somatostatin receptor imaging within 6 months. (if patient does not have somatostatin receptor imaging they may also be included provided they have measurable disease (≥10mm) on conventional imaging.
9. Adequate organ system function as defined in Table 1

Table 1 clinical laboratory parameters

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC) Hemoglobin[1] Platelets	≥ 1.5 X 10^9/L ≥ 9 g/dL (5.6 mmol/L) ≥ 100 X 10^9/L
Prothrombin time (PT) or international normalized ratio (INR)	≤ 1.2 X upper limit of normal (ULN)
Partial thromboplastin time (PTT)	≤ 1.2 X ULN
Hepatic[2]	
Total bilirubin AST and ALT	≤ 1.5 X ULN ≤ 2.5 X ULN
Renal	
Serum creatinine Or, if greater than 1.5 mg/dL: Calculated creatinine clearance	≤ 1.5 mg/dL (133 µmol/L) ≥ 50 mL/min

1	Subjects may not have had a transfusion within 7 days of screening assessment.
2	Concomitant elevations in bilirubin and AST/ALT above 1.0 x ULN are not permitted

9.2 Exclusion Criteria

1. Patients received chemotherapy within 3 weeks of study

2. Patients received radiotherapy within 4 weeks of study
3. Active uncontrolled infections, gastrointestinal disease, haemolysis or any serious co-existing medical illness
4. Psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
5. Pregnant or lactating women
6. Females of childbearing potential who are unwilling to avoid pregnancy, for the duration of the study
7. Presence of any underlying medical conditions which in the investigators opinion would make the patients unsuitable for treatment
8. Patient not expected to be able to tolerate the scanning sessions

10. COMPLETION OR EARLY WITHDRAWAL

10.1 Subject completion

A completed subject is one who has completed all phases of the study.
The end of the study is defined as the last subject's last visit.

10.2 Withdrawal criteria

Whatever the disease status, the treatment will always be discontinued in case of patient refusal.
Each patient is free to withdraw from the study at any time.
A complete final evaluation at the time of the subject's withdrawal will be made and an explanation given of why the patient is withdrawing or being withdrawn from the study.
The reason for non-completion and the date and time of the last contact with the patient must be noted in the case report form (CRF).
In the case of patients withdrawal before or after dosing (ie, non-evaluable subjects) additional patients may be enrolled to reach a total of 56 evaluable patients.

10.3 Blinding

This is an open label study, therefore blinding is not applicable.

11. STUDY PROCEDURES

Each patient will have one session of PET/CT scanning. Patients in cohort 1 will be required to have an overnight stay following their scan whilst those in cohort 2 will have up to a 70 minute scan and will be discharged home following the scan. All efficacy and safety measurements obtained during the

course of the study are summarised in the Study Schedule of Events in table 1 and 2.

Table 2. Study Schedule of Events for cohort 1.

	-30 days screening	-30 to –5 min	-2 min	Dose	+2 min	+5 min	+10 min	+15 min	+30 min	+ 1 hour	+1 hour 30 min	+2 h 30 min	+4 hours	+ 24 hours
Informed Consent	•													
Entry Criteria	•													
Demographic Information	•													
Medical History	•													
Prior/Concomitant Medication	•	•												
Physical Exam	•	•												•
Injection Site Monitoring			•			•			•				•	•
Pregnancy Test	•	•												
ECG [1]	•	•	•	•	•	•		•	•	•		•	•	•
Pulse Oximetry [2]	•	•	•		•	•		•	•	•		•	•	•
Vital Signs	•	•	•		•	•		•	•	•		•	•	•
Blood (Serum Biochemistry, Haematology, Coagulation)[3]	•	•							•			•	•	•
Urinalysis[4]	•	•							•	•		•	•	•
Pre-administration Events														
Transmission Scan		•												
[^{18}F]-FET-βAG-TOCA injection				•										
Post-administration Events[5]														
PET Imaging[6]														
Blood and Plasma for Activity Counting						•	•	•	•	•	•	•		
Urine[4] for Activity Counting														

min=minutes

1 Continuous ECG performed from –5 min to +15 min. Lead II may be used for continuous monitoring. 12-lead ECG should be recorded at the times indicated ECG should remain under continuous supervision and additional print outs obtained if any abnormality is detected

2 At baseline, before vital signs and pulse oximetry are measured, the subject should be resting for at least 5 minutes (if possible)

3 All blood samples for patients will be taken from venous blood.

4 Time points indicated are preferred time points, urine will be collected as voided

5 Events will be collected throughout the subjects participation in the study

6 PET Imaging will be taken at 4 discrete time points for up to 4 hours post administration, with resting periods in between

* Shaded areas depict continuous monitoring

Table 3. Study Schedule of Events for cohort 2.

	≤30 days	-180to –5 min	Dose	≤70 - min	END OF SCAN
Informed Consent	•				
Entry Criteria	•				
Demographic Information	•				
Medical History	•				
Prior/Concomitant Medication	•				
Physical Exam	•				
Pregnancy Test[4,5]	•	•			
Pulse Oximetry[1,5]	•	•			
Vital Signs[1,5]	•	•			
Blood (Serum Biochemistry, Haematology)[2]	•				
[^{18}F]-FET-βAG-TOCA injection (max 370MBq)			•		
PET/CT Imaging					
Adverse event monitoring[3]					

min=minutes

[1] At baseline, before vital signs and pulse oximetry are measured, the subject should be resting for at least 5 minutes (if possible)

[2] All blood samples for patients will be taken from venous blood. If blood results are available which have been taken as part of subjects standard care (within 30 days of study scan), these do not need to be repeated.

[3] Events will be collected throughout the subjects participation in the study

[4] Women of childbearing potential.

[5] Where screening and PET scan are on same day, procedure is done once

*Shaded areas depict continuous monitoring

11.1 Screening period (Day -30 to Day 0)

- Patients will be screened up to 30 days before tracer administration and confirm eligibility. At the screening visit demographic data/baseline characteristics, medical history, and medication will be recorded. All female subjects of childbearing potential will undergo a pregnancy test.
- Signed and dated informed consent must be obtained from all subjects prior to any protocol specific procedures being performed.
- Blood samples for serum biochemistry and haematology, will be drawn from venous blood if not already taken as part of subjects standard care within 30 days of tracer administration. ;.
- Vital signs and pulse oximetry, will be recorded and a physical examination including a limited neurological examination will be performed.
- If [^{68}Ga]-DOTA-peptide imaging PET/CT has been performed within 6 months of [^{18}F]-FET-βAG- TOCA PET/CT, scans will be retrieved.

11.2 PET Procedure (Day 0)

The tracer is made at GMP standards, at Imanova Limited which are GMP certified

- PET/CT scans will be carried out in the Imanova Limited, at the Hammersmith hospital site, Du Cane Road, London
- Transportation will be arranged as required for patients
- Between 30 min to 2 min before dosing the different parameters will be assessed as reported in Table 2 (Cohort 1). Between 180 min to 5 min before dosing the different parameters will be assessed as reported in Table 3 (Cohort 2).
- For patients in cohort 1 two Intravenous cannulae will be placed in the arm in order to inject the tracer, [^{18}F]-FET-βAG-TOCA and for metabolites (approximately 200ml of blood samples will be taken from this line). For patients in cohort 2 one Intravenous needle will be placed in the arm in order to inject the tracer, [^{18}F]-FET-βAG-TOCA.
- Patient will be asked to lie flat on the PET-CT scanner bed
- The bed will move into the scanner which looks like a short tunnel
- Patients in cohort 1 will have ECG monitoring. Vitals will be assessed (pre-specified time points, as reported in Table 2).
- A non contrast enhanced CT will be performed to define the region of interest. [^{18}F]-FET-βAG-TOCA will be injected intravenously. PET/CT scanning will be then subsequently performed. In cohort 1 patients will undergo 5-6 whole body sweeps (vertex to mid thighs) lasting approximately 3-4 hours with a gap in between. Patients in cohort 2 will have a PET/CT scan which will last up to 70 minutes
- Patients in cohort 1 will be admitted for overnight stay.
- Tumour biopsies at diagnosis will be retrieved for analysis of SSTR1-5 expression after Day 0 on successful completion of subject scan.

11.3 Radiation dosimetry.

Table 4. Radiation dosimetry description for [^{18}F]-FET-βAG-TOCA PET and CT.

Tracer	[^{18}F]-FET-βAG-TOCA	CT
Maximum dose per scan(MBq)	165	
Conversion factor (mSv/MBq)	0.04	
Effective dose per scan (mSv)	5.11	2.4
No of scans	1	2 (cohort 1) 1 (cohort 2)
Total effective dose (mSv)/ patient	5.11 mSv cohort 1 12 mSv cohort 2	4.8 (cohort 1), 2.4 (cohort 2)

Therefore total effective dose per patient is 12mSv for cohort 1 and 14mSv for cohort 2 (max dose injected 370Mbq).

11.4 PET parameters

Attenuation corrected images will be reconstructed. Regions of interest will be drawn around the tumour to derive semi-quantitative uptake parameters, SUV (standardized uptake value) and AUC (area under curve, total activity over scanning time). Venous blood samples will be taken for assessment of counts during the [^{18}F]-FET-βAG-TOCA scan in cohort 1. These bloods will be used to generate the blood input function that is required to derive uptake tracer

parameters such as Ki (rate constant for net irreversible uptake) and FRT (fractional retention of tracer) which will be used to set scanning parameters for cohort 2.

12. ASSESSMENT AND FOLLOW-UP

12.1 Clinical Assessments

12.1.1 Screening

<u>Confirm eligibility</u>

- Complete clinical history, including concomitant medications
- Full clinical examination
- Vital signs
- ECG
- Retrieve original tumour biopsies
- Somatostatin receptor imaging within 6 months of study entry

12.1.2 Cohort 1: day of scan (Day 0)

- Confirm eligibility
- Concomitant medication recording
- Physical examination
- Vital signs
- ECG
- Bloods
- Urinalysis
- Urine pregnancy test
- [^{18}F]-FET-βAG-TOCA PET/CT imaging
- Baseline adverse event reporting
- Cohort 1: Admit for overnight observation at the Phase I unit, Hammersmith Hospital

12.1.3 Cohort 1: Day 1 post scan

- Physical examination
- Vital signs
- ECG
- Bloods

- Urinalysis
- Adverse events reporting

12.1.4 Cohort 2: day of scan

- Confirm eligibility
- Vital signs
- [^{18}F]-FET-βAG-TOCA PET/CT imaging
- Baseline adverse event reporting
- Urine pregnancy test

13. COMPLICATIONS AND RADIATION DOSE

13.1 Complications

All patients will be recruited strictly according to protocol following the principles of the Declaration of Helsinki. All inclusion criteria would be satisfied before approaching patients. There are no immediate complications of the PET scan except for a potential mild bruising at the site of insertion of the cannula which should resolve in 1-2 weeks.

13.2 Radiation dose

The total effective dose (ED) received from the PET-CT scan is estimated to be 12mSv for cohort 1 and 14 mSv for cohort 2. In a dosimetry study such as this, the estimate is necessarily uncertain but a conservative approach has been taken that will overestimate the effective dose by using a high dose conversion factor of 0.04 mSv/MBq injected activity. The total effective dose of 14 mSv (cohort2) is equivalent to about 6 times the average yearly exposure (2.3 mSv) from natural background radiation in the United Kingdom. For an adult in good health, this exposure would result in a risk of around 1 in 1600 (cohort1) and 1 in 1400 (cohort2) of contracting a fatal cancer, However, for someone in the planned study groups who have shorter life expectancy than the general population it represents a significantly lower risk.
Note that as part of the standard practice for patients included in this study, a single [68Ga] Dotatate PET/CT scan will be performed; this is one of the entry qualifications but is not an additional examination that is part of the research protocol.

14. STATISTICAL ANALYSIS AND SAMPLE SIZE CALCULATION

14.1 Cohort 1

Using results of dynamic scanning and metabolite analysis, in particular the time course of tumour radiotracer uptake, we will design the appropriate protocol by which we will analyse the diagnostic, static scans in cohort 2. We will calculate

the internal radiation dosimetry as well as biodistribution of the tracer. Depending on these results we may alter the administered dose in cohort 2.

14.1.1 Safety

Safety data will be collected at baseline and after the administration of the tracer. The safety of the regimen will be evaluated by the frequency and grade of adverse events. Rates will be reported with a 90% Binomial exact confidence interval. With a sample size of N=12 the maximum half-width to the confidence interval will be 0.25.Using results of dynamic scanning and metabolite analysis, in particular the time course of tumour radiotracer uptake, we will design the appropriate protocol by which we will analyse the diagnostic, static scans in sub-study 2.Rates of adverse events will be reported by grade and summarized using 95% Binomial exact confidence interval.

14.1.2 Biodistribution

The temporal variations of ^{18}F activity concentrations in whole blood and plasma and the rate and amount of ^{18}F activity excreted through the urinary pathway will be measured in patients and to evaluate the bio-distribution.

14.1.3 Dosimetry

We will calculate the internal radiation dosimetry as well as biodistribution of the tracer. Descriptive statistics will be used to summarize the biodistribution of [^{18}F] following single i.v. administration of [^{18}F]-FET-βAG-TOCA injection (mean, median, range, interquartile range, and standard deviation).Depending on these results we may alter the administered dose in sub-study 2.

14.1.4 Somatostatin receptor expression

SUV measures from [^{18}F]-FET-βAG-TOCA PET/CT will be summarized by lesion. The correlation of SUV measures to ordinal measures of SSTR1-5 detected by IHC staining of the diagnostic biopsy (-,+,++,+++) will be evaluated using non-parametric Kruskal-Wallis tests.

14.2 Cohort 2

Comparison will be made between FET-βAG-TOCA PET and the standard of acre somatostatin receptor imaging based on both a per-patient and per-lesion based analysis. Non-parametric McNemar test with Bonferroni correction for multiple comparisons will be used. The association between SSTR1-5 expression and imaging parameters obtained will be assessed. Data will be analyzed using SPSS 16.0 for Windows.

14.2.1 Power and sample size determination

Power for the Wilcoxon signed-rank test is calculated by simulation using a truncated log-normal distribution parameterized according to Kabasakal et al.[15] (median = 5, range = 1 to 25) to sample the total number of lesions in patients

across a range of samples. With a total of N = 48 patients assessed by both modalities, there will be 80% power to conclude non-inferiority equivalence if the two methods are equivalent ($\Delta = 0$).
The distributions of number of lesions detected by [^{18}F]-FET-βAG-TOCA – PET/CT and by [^{68}Ga]-DOTA-peptide-PET/CT will be summarized, and will be compared using the Wilcoxon signed-rank test with the pre-specified level of equivalence of $\Delta = 0.64$ and a one-sided alpha= 0.1.

14.2.3 Somatostatin receptor expression

SUV measures from [^{18}F]-FET-βAG-TOCA will be summarized by lesion. The correlation of SUV measures to ordinal measures of SSTR1-5 detected by IHC staining of the diagnostic biopsy (-,+,++,+++) will be evaluated using non-parametric Kruskal-Wallis tests.

15. PHARMACOVIGILANCE

15.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. *An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.*

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered. *All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.*

Unexpected Adverse Reaction: an AR, the nature or severity of which is not consistent with the applicable product information (eg investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product*). When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the SmPC which occur in a more severe form than anticipated are also considered to be unexpected.*

Serious Adverse Event (SAE) or **Serious Adverse Reaction:** any untoward medical occurrence or effect that at any dose

Results in death

Is life-threatening – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*

Requires hospitalisation, or prolongation of existing inpatients' hospitalisation

Results in persistent or significant disability or incapacity

Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious.

15.2 CAUSALITY

Most adverse events and adverse drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related toxicities due to the drugs used in this study. The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below.

If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigators. The pharmaceutical companies and/or other clinicians may be asked to advise in some cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view.

15.3 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the study coordination centre in the first instance. A flowchart is given below to aid in the reporting procedures.

15.3.1 Non serious AR/AEs

All such toxicities, whether expected or not, should be recorded in the toxicity section of the relevant case report form and sent to the study coordination centre within one month of the form being due.

15.3.2 Serious AR/AEs

Fatal or life threatening SAEs and SUSARs should be reported on the day that the local site is aware of the event. The SAE form asks for nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible investigator

should sign the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.

SAEs

An SAE form should be completed and faxed to the study coordination centre for all SAEs within 24 hours. However, relapse and death due to <condition>, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

SUSARs

In the case of suspected unexpected serious adverse reactions, the staff at the site should:

Complete the SAE case report form & send it immediately (within 24 hours, preferably by fax), signed and dated to the study coordination centre together with relevant treatment forms and anonymised copies of all relevant investigations.

Or

Contact the study coordination centre by phone and then send the completed SAE form to the study coordination centre within the following 24 hours as above. The study coordination centre will notify the MHRA, REC and the Sponsor of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study.

16. DATA MANAGEMENT

Data will be collected on electronic CRFs.

17. ADMINISTRATIVE AND LEGAL CONSIDERATIONS

To ensure compliance of this trial with Good Clinical Practice (GCP) principles, the following procedures will be followed by the Investigators.

17.1 Pre-Trial Requirements

Treatment within this study will only start if the following prerequisites have been fulfilled and documentation is at hand:

Signed copy (original) of the approved protocol

EC approval of the protocol, consent form and information sheet

Approval / notification of local authorities

The Investigator will hold an Investigator's File containing the relevant study documents.

17.2 General Legal Requirements

The study will be conducted in agreement with the following directives and guidelines:

- The Declaration of Helsinki (version of Edinburgh, Scotland, October 2000)

- The respective guidelines of the European Community: Guideline for Good Clinical Practice (Note for Guidance on Good Clinical Practice / ICH E6)

- Statutory Instrument 2004 No. 1031 – The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended.

All clinical work conducted under this protocol will be subject to Good Clinical Practice rules. This includes an inspection by health authority representatives at any time. The Investigator agrees to the inspection of study-related records by health authority representatives and/or the sponsor.

17.3 Protection of Subjects

17.3.1 Ethics Committee

The protocol and a copy of the subject information and informed consent form will be submitted to the competent EC(s). Written approval of the protocol and the proposed information and consent form will be obtained prior to the start of the trial.

17.3.2 Informed Consent

It is the Investigator's responsibility to explain to each subject the study procedure, potential benefits and hazards of trial participation, the right to withdraw from the study at any time, and to obtain written informed consent prior to any study-specific procedures. The original copy of the signed and dated Informed Consent Form must be filed in the patient's notes. The subject, the subject's legally authorized representative, or both will be given a copy of the

signed and dated Informed Consent Form.

17.3.3 Privacy protection

In order to maintain subject privacy, all CRFs, study drug accountability records, study reports and communications will identify the subject by initials and the assigned subject number.

The investigator will grant monitor(s) and auditor(s) access to the subject's original medical records for verification of data gathered on the CRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

17.4 Protocol Amendments

The protocol must be read thoroughly and the instructions must be followed exactly.

Any changes in the protocol will require a formal amendment. Such amendments will be agreed upon and approved in writing by the Principal Investigator. Amendments to the protocol will be submitted to the relevant authorities and the EC for approval prior to implementation.

Administrative changes which have no significant impact on the medical or scientific validity of the study will be documented in a statement. The EC will be notified of administrative changes, if applicable.

17.5 Premature Termination of the Trial

The Investigator reserves the right to terminate the trial for well-documented reasons. Instructions will be provided in a separate document should it be determined that assessments beyond those defined by the protocol are required.

Further recruitment of subjects will not take place under the following conditions:

- Premature termination of the trial.

- Drug-related events, i.e. SUSARs, emerging adverse effects that are serious and the risk/benefit ratio is unacceptable.

- Procedure-related events, i.e., the recruitment rate is too low or the number of dropouts for administrative reasons is too high.

An ‘End of Trial Form’ must be completed for each subject who completes the study or who withdraws prematurely from this study.

17.6 Record Retention

After the end of study, the Investigator will maintain all site study records in a safe and secure location. The records will be stored in a location allowing easy and timely retrieval when needed (for example, for an audit or inspection). Where permitted by local regulations or institutional policy, some or all of these records may be maintained in a format other than hard copy (for example, in an electronic format), but caution should be exercised. The Investigator will ensure that all reproductions are legible and are a true and accurate copy of the original. All study records must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until (1) there are no pending or contemplated marketing applications in an ICH region; or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The PI/institution should retain subject identifiers for at least 15 years after the completion or discontinuation of the study. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 15 years. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements. The PI must be notified and will assist with retention should institution be unable to continue maintenance of subject files for the full 15 years. It is the responsibility of PI to inform the institution as to when these documents no longer need to be retained.

If an Investigator moves, withdraws from an investigation, retires, requests to move records to another location or to assign these records to another party or (e.g. other Investigator) who will accept the responsibility, written notice of this transfer must be made to and agreed upon by each party.

17.7 Study Monitoring

The Investigator is responsible for ensuring that the study is monitored appropriately in order to ensure compliance with GCP and local regulatory guidelines. The monitor will check the completeness of medical records, verify the accuracy of entries in the CRF, and ensure adherence to the protocol and compliance with local regulatory requirements.

17.8 Final Report

A final integrated report will be prepared under the responsibility of the Investigator(s). It will include the tabulated raw data and the biostatistical report on the data.

17.9 Publications

Publication of the results of the study, whether in whole or in part, shall be within the sole and absolute discretion of the Investigator.

17.10 Liability and insurance

All patients participating in the study will have insurance coverage by the sponsor which is in line with all applicable laws and/or regulations.

17.11 Audits and Inspections

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit in accordance with their local internal procedures.

Audits and/or inspections may also be carried out by local authorities, or authorities to which information on this trial has been submitted. All documents pertinent to the trial must be made available for such inspection after an adequate announcement.

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19. Appendix A: WHO performance status scale

Grade	Performance scale
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.