

The Impact of ¹⁸F-fluciclovine (FACBC) PET/CT on Management of Patients with Rising PSA after Initial Prostate Cancer Treatment

Blue Earth Diagnostics Study No: BED-003
Syne qua non Ltd Study No: BLS15002

Statistical Analysis Plan

Version: Amendment 3 Draft Final

Date: 5th March 2018

For Syne qua non Ltd – Lead Statistician

DocuSigned by:
Elizabeth Gardener

 Signer Name: Elizabeth Gardener
Signing Reason: I am the author of this document
Signing Time: 05 March 2018 | 12:55 GMT
A40AC5551C6B49FBA379312B0D6DA509

For Blue Earth Diagnostics

DocuSigned by:
Albert Chau

 Signer Name: Albert Chau
Signing Reason: I approve this document
Signing Time: 05 March 2018 | 13:01 GMT
9E0EEC5DCDE944CCADB63BA0CE6CA8E

Contents

1	INTRODUCTION.....	4
2	GENERAL PRINCIPLES.....	4
3	STUDY OBJECTIVES AND DESIGN	4
3.1	Study Objectives	4
3.2	Study Design.....	5
3.3	Visit Structure.....	7
3.4	Sample Size	7
3.5	Changes from the Protocol Planned Analysis	7
4	STUDY SUBJECTS	8
4.1	Analysis sets	8
4.2	Disposition of Subjects	8
4.3	Protocol Deviations	8
4.4	Background and Demographic Characteristics	8
4.4.1	Demographic and Baseline Characteristics.....	8
4.4.2	Medical History	9
4.4.3	Prostate Cancer History.....	9
4.4.4	Cancer Therapies for Prostate Cancer	9
4.4.5	Prior and Concomitant Medications.....	10
4.4.6	Other Subject Characteristics	11
4.5	Administration of Investigational Product	11
5	EFFICACY EVALUATION.....	11
5.1	Primary Efficacy Variable.....	11
5.2	Secondary Efficacy Variables	11
5.3	Definition of Region Levels	11
5.4	Statistical Analysis	14
5.4.1	Primary Efficacy Analysis	14
5.4.2	Secondary Efficacy Analyses	18
5.4.3	Handling of Dropouts or Missing Data	22
5.4.4	Interim Analyses and Data Monitoring.....	22
5.4.5	Examination of Subgroups	22
6	SAFETY EVALUATION	22
6.1	Adverse Events.....	22
6.2	Clinical Laboratory Evaluation	23
6.2.1	Hematology.....	23
6.2.2	Biochemistry	23
6.2.3	Urinalysis dipstick	24
6.3	Vital Signs	24
6.4	Electrocardiography.....	24
7	References	24

ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
BCR	Biochemical recurrence
BMI	Body Mass Index
CI	Confidence Interval
CrCl	Creatinine clearance
CRF	Case Report Form
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events
EAS	Effectiveness Analysis Set
EKG	Electrocardiogram
FAS	Full Analysis Set
FN	False Negative
FP	False Positive
GFR	Glomerular Filtration Rate
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
ms	Milliseconds
NPV	Negative Predictive Value
PCa	Prostate Cancer
PET	Positron Emission Tomography
PPS	Per Protocol Set
PPV	Positive Predictive Value
PSA	Prostate Specific Antigen
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TN	True Negative
TNM	TNM Classification of Malignant Tumours
TP	True Positive
WHO	World Health Organization
WHO DDE	WHO Drug Dictionary Enhanced

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on protocol version 3 dated 7th June 2017.

The SAP describes the tables, listings and figures which will be provided upon completion of the study. The SAP will be finalised before locking the database.

The table, listing and figure shells will be supplied in a separate document.

The analyses relating to the fifth secondary objective “To explore differences in estimated cost of treatment plans determined prior to and following ¹⁸F-fluciclovine PET/CT” will be reported separately and are not covered in this SAP.

2 GENERAL PRINCIPLES

The analysis and statistical reporting will be conducted at Syne qua non using SAS version 9.2 or higher.

All listings will be based on all enrolled subjects unless specified otherwise. All tables will be presented by site and overall for the appropriate analysis population.

Descriptive summary statistics for continuous variables will include number of subjects (n), mean, standard deviation (SD), minimum, median, and maximum, unless specified otherwise. The precision of these summary statistics is defined in the table, figure and listing shells document.

Descriptive summary statistics for categorical variables will include frequency counts and percentages [N (%)]. Unless stated otherwise, the denominator for percentage calculations will be the number of subjects in the analysis set.

There will be no imputation of missing data.

3 STUDY OBJECTIVES AND DESIGN

3.1 Study Objectives

The primary objective of the study is to measure the fraction of subjects for whom ¹⁸F-fluciclovine PET/CT alters intended management through detection of disease after curative-intent treatment in a population of men with elevated prostatic specific antigen (PSA) levels indicative of persistent or recurrent prostate cancer and negative or equivocal findings on standard-of-care diagnostic imaging tests.

The secondary objectives of the study are

- To measure the fraction of subjects for whom ¹⁸F-fluciclovine PET/CT leads to a change in actual management by comparison with the intended management plan before ¹⁸F-fluciclovine PET/CT
- To estimate the fraction of subjects in whom ¹⁸F-fluciclovine PET/CT yields evidence of recurrent disease on the basis of imaging results
- To estimate:

- the rates of detecting regionally recurrent disease (i.e. prostatic bed-only and/or pelvic disease outside of the bed)
 - the rate of detecting distant metastases (i.e. bone metastases, visceral metastases, or non-regional nodal metastases)
- with ^{18}F -fluciclovine PET/CT in the study population
- To determine:
 - the positive predictive value (PPV) of ^{18}F -fluciclovine PET/CT to detect regionally recurrent disease
 - the PPV of ^{18}F -fluciclovine PET/CT to detect distant metastases in the study population in subjects who undergo optional biopsy of ^{18}F -fluciclovine PET/CT findings or have documentation of disease status based on other imaging and/or follow-up data
 - To explore differences in estimated cost of treatment plans determined prior to and following ^{18}F -fluciclovine PET/CT

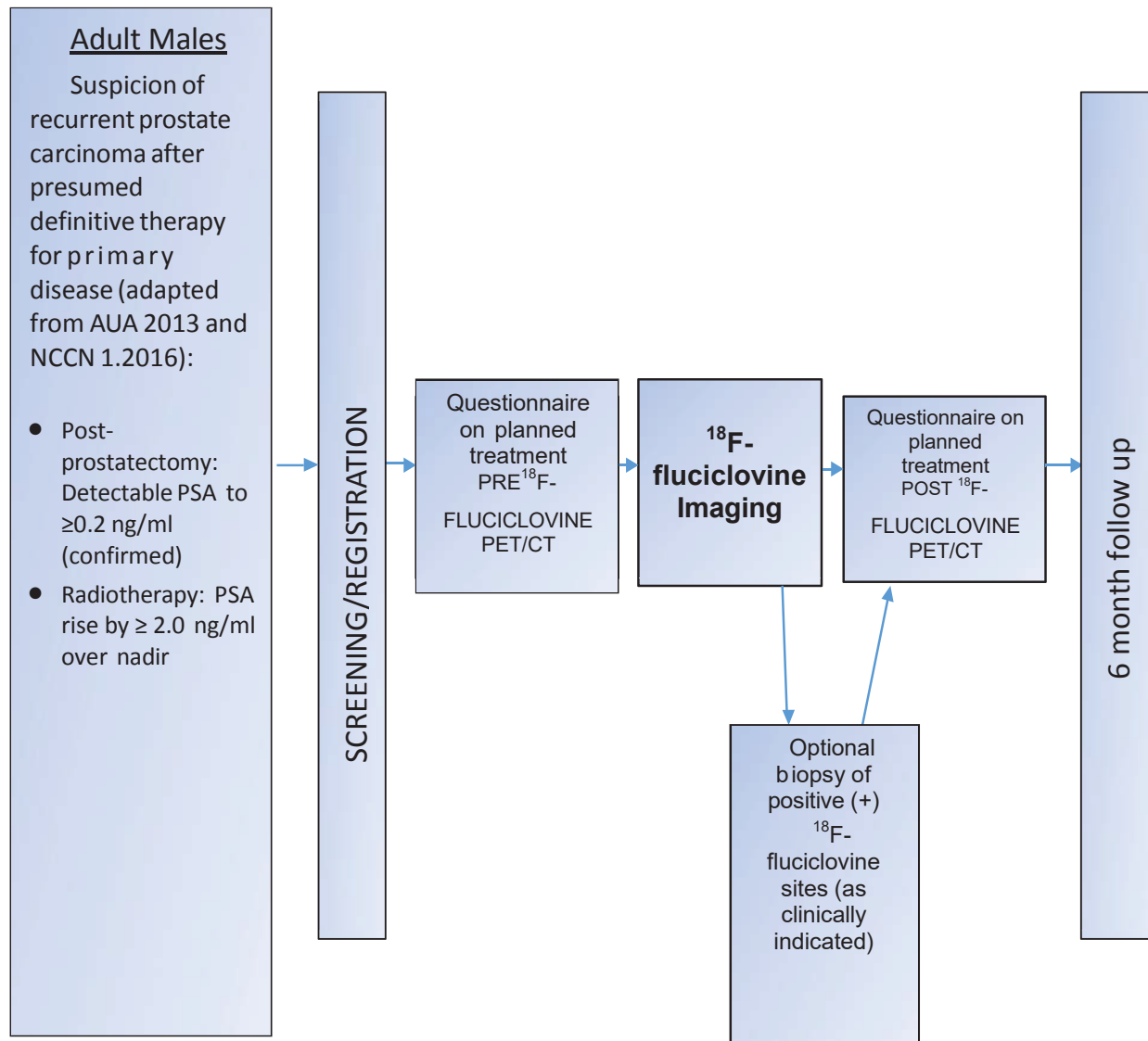
3.2 Study Design

This is a phase IIIb open-labelled, multi-centred study to assess the impact on subject management of ^{18}F -fluciclovine PET/CT in subjects with rising prostate specific antigen (PSA) after initial cancer treatment.

The prospective study will enrol up to 330 men with PSA-recurrent prostate cancer after curative-intent primary therapy and negative or equivocal findings on standard-of-care imaging. Consenting participants will be imaged with ^{18}F -fluciclovine PET/CT. Site clinicians will manage study subjects per standard practices and will document any change in treatment based on review of the ^{18}F -fluciclovine PET/CT findings. Additionally, as clinically indicated, optional biopsy will be performed. All participants will be followed for up to 6 months, with clinical data collected for this study: PSA measurement from scan for 6 months. Treatment response will be assessed 6 months post scan.

The summary flowchart of the study design is as follows:

STUDY SCHEMA



3.3 Visit Structure

The visit structure and scheduled assessments are detailed in Appendix 1: Schedule of Events of the protocol.

3.4 Sample Size

The primary objective of this study is to measure the fraction of subjects for whom ¹⁸F-fluciclovine PET/CT alters the intended management plan. The sample size consideration is primarily based on the binding width of its 95% confidence interval, i.e. precision analysis. The prevalence of positive ¹⁸F-fluciclovine PET/CT findings in this population is assumed to be approximately 40%. About 30% of the positive scans are expected to change the physician's intended management plan. The goal is to accurately assess the fraction of change in intended management in these subjects. The table below lists the calculated sample sizes with respect to binding different 95% CI widths at the proportion of 30%. The Clopper-Pearson Exact method was used in PASS 12 (Hintze, 2013).

Confidence Level	Sample Size (N)	Target Width	Actual Width	Proportion (P)	Lower Limit	Upper Limit	Width If P=0.5
0.950	341	0.100	0.100	0.300	0.252	0.352	0.109
0.950	89	0.200	0.199	0.300	0.207	0.406	0.216
0.950	40	0.300	0.300	0.300	0.166	0.465	0.324

If the goal is to bind the 95% CI width at 0.20 then 89 FACBC positive subjects will be needed for the assessment of the primary aim. Since the positivity rate is assumed to be approximately 40% in the study population, 223 subjects need to be enrolled. After accounting for the random nature of the observed numbers of subjects meeting the clinical criteria in a prospective study and potential data loss, it is planned to enrol at least 292 and up to 330 subjects in order to obtain 89 evaluable subjects.

3.5 Changes from the Protocol Planned Analysis

PPV efficacy variable (section 5.2) will be determined using adjudication panel decision rather than only using biopsy or biopsy/MRI data. This is consistent with the study objectives.

4 STUDY SUBJECTS

4.1 Analysis sets

The list of subjects to be included in each of the analysis sets is to be agreed between the Syne qua non statistician and Blue Earth Diagnostics once all study data are available and prior to database lock.

Enrolled Set: All subjects who entered screening.

Safety Analysis Set (SAF): All subjects who have been included in the database and have been administered ^{18}F -fluciclovine will be included in the Safety Analysis Set (SAF).

Full Analysis Set (FAS): All subjects enrolled who have had an ^{18}F -fluciclovine PET/CT scan will be included in the Full Analysis Set (FAS).

Evaluable Analysis Set (EAS): All subjects from the FAS who have an intended treatment management plan completed and a revised management plan page completed will be included in the Evaluable Analysis Set (EAS).

Per Protocol Set (PPS): All subjects in the EAS who meet the second and third protocol inclusion criteria (see protocol section 6.2) and any other subject without major significant deviation following review of the protocol deviation list.

4.2 Disposition of Subjects

The number and percentage of all subjects enrolled, included in each analysis set, who completed the study and who prematurely withdrew, including a breakdown of the primary reasons for withdrawal, will be presented.

All enrolled subjects will be listed indicating their membership to the evaluable analysis set along with the reason for exclusion.

Completion and withdrawal information will be listed, including individual reasons for withdrawal.

4.3 Protocol Deviations

Failed inclusion criteria and failed exclusion criteria will be listed for screening failures.

The number and percentage of subjects within each deviation category will be presented by deviation type (Major Significant, Major or Minor) and by site and overall. The deviation category and type will be provided by Blue Earth Diagnostics. All protocol deviations will be listed.

4.4 Background and Demographic Characteristics

4.4.1 Demographic and Baseline Characteristics

Demographic characteristics (age, ethnic origin and race collected at Screening), body measurements (height, weight collected and BMI derived at Visit 2) will be summarised for the enrolled set, FAS, EAS and PPS populations.

Body mass index (BMI) is calculated as $(\text{weight (kg)}/\text{height (m)}^2)$.

Individual demographic characteristics and body measurements data will be listed.

4.4.2 Medical History

Medical history events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

The number and percentage of subjects from the FAS with previous medical history and current events will be tabulated by system organ class (SOC), preferred term (PT). SOCs will be ordered in decreasing frequency of the total number of subjects with medical history events reported in each SOC and PTs will be ordered within a SOC in decreasing frequency of the total number of subjects with each medical history event.

All medical history events will be listed.

4.4.3 Prostate Cancer History

Details of prostate cancer history will be summarised for subjects from the FAS, and will consist of:

- Time since initial diagnosis (months), calculated as $[12 * (\text{date of informed consent} - \text{date of initial prostate cancer diagnosis} + 1) / 365.25]$
- TNM stage: Pathological TNM stage if available, otherwise Clinical TNM stage
- Gleason total score: Gleason total score from surgery if available, otherwise Gleason total score from biopsy
- Time since adjuvant treatment (months), calculated as $[12 * (\text{date of informed consent} - \text{stop date of adjuvant treatment} + 1) / 365.25]$
- Duration of adjuvant treatment (months), calculated as $[12 * (\text{stop date of adjuvant treatment} - \text{start date of adjuvant treatment} + 1) / 365.25]$
- Time since diagnosis of biochemical recurrence (BCR) in days, calculated as $(\text{date of informed consent} - \text{date of diagnosis of biochemical recurrence} + 1)$. Time since diagnosis of BCR may be derived in months if more appropriate.
- Baseline PSA value, baseline being defined as the last value prior to fluciclovine (^{18}F) administration

Details of prostate cancer history will be listed.

Date imputation for incomplete dates:

- If day part missing, use 15th of the month
- If day and month parts missing, use 01 July.

4.4.4 Cancer Therapies for Prostate Cancer

Cancer therapies for prostate cancer will be coded according to the latest version of the World Health Organization Drug Dictionary Enhanced (WHO DDE).

Cancer therapies will be categorised as follows:

Subjects with radical prostatectomy:

- Radiotherapy
- No radiotherapy

Subjects without radical prostatectomy:

- Radiotherapy only
 - EBRT only
 - Brachytherapy only
 - EBRT and brachytherapy
- Radiotherapy and other therapies
 - EBRT and other therapies
 - Brachytherapy and other therapies
- Other therapies

Prior cancer therapies for prostate cancer are defined as those for which the end date is prior to the date of injection of ^{18}F -fluciclovine.

Concomitant cancer therapies for prostate cancer are defined as those with a start date on or after the injection date of ^{18}F -fluciclovine, or those with a start date before the injection date of ^{18}F -fluciclovine but which continued with a stop date on or after the injection date of ^{18}F -fluciclovine.

If cancer therapy dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

The number and percentage of subjects per category of prostate cancer therapy will be presented for all subjects from the SAF, separately for subjects with and without radical prostatectomy. This summary will be repeated for prior and concomitant cancer therapies.

All therapies for prostate cancer will be listed including type of therapy, reported therapy name, medication class, standardised medication name, dose, dose unit, route of administration, start date and end date or 'ongoing' flag, therapy comments.

4.4.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded according to the latest version of the WHO DDE.

Prior medications are defined as those for which the end date is prior to the date of injection of ^{18}F -fluciclovine.

Concomitant medications are defined as those with a start date on or after the injection date of ^{18}F -fluciclovine, or those with a start date before the injection date of ^{18}F -fluciclovine but which continued with a stop date on or after the injection date of ^{18}F -fluciclovine.

If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

The number and percentage of subjects who took any medications will be presented by center and overall by medication class, standardised medication names sorted in decreasing frequency for all subjects from the SAF, separately for prior medications and concomitant medications.

All prior and concomitant medications will be listed including reported name, medication class, standardised medication name, indication, dose, dose unit, frequency, route of administration, start date and end date or 'ongoing' flag.

4.4.6 Other Subject Characteristics

Not applicable

4.5 Administration of Investigational Product

The volume of undiluted fluciclovine, activity of fluciclovine and injection site reaction during and following fluciclovine administration will be summarised for subjects in the SAF.

All fluciclovine administration data will be listed in full.

5 EFFICACY EVALUATION

All listings will be based on the FAS unless specified otherwise.

5.1 Primary Efficacy Variable

The primary efficacy variable is the change in management plan assessed by comparing pre ^{18}F -fluciclovine PET/CT management plan with the post ^{18}F -fluciclovine PET/CT management plan, for subjects with a positive ^{18}F -fluciclovine PET/CT scan.

5.2 Secondary Efficacy Variables

The secondary efficacy variables are:

- Per subject impact (yes/no) of ^{18}F -fluciclovine PET/CT on pre-PET intended versus post-PET actual subject management
- The rate of detection of any disease site by ^{18}F -fluciclovine PET/CT in the study population
- The rate of detection of:
 - Prostatic bed and other pelvic disease
 - Distant metastases (i.e. bone metastases, visceral metastases or non-regional nodal metastases)with ^{18}F -fluciclovine PET/CT in the study population
- The PPV of ^{18}F -fluciclovine PET/CT to detect regionally recurrent disease compared to adjudication panel decision.
- The PPV of ^{18}F -fluciclovine PET/CT to detect distant metastases compared to adjudication panel decision.

5.3 Definition of Region Levels

Two main regions will be analysed, the prostate and prostate bed and the extra-prostatic region.

The prostate and prostate bed include the following lesion locations:

- Prostate bed left
- Prostate bed right

- Peripheral zone left
- Peripheral zone right
- Central gland left
- Central gland right
- Left seminal vesicle
- Right seminal vesicle

The extra-prostatic regions include the following lesion locations

- Lymph nodes
 - Pelvic lymph nodes
 - Common iliac left
 - Common iliac right
 - Internal iliac left
 - Internal iliac right
 - External iliac left
 - External iliac right
 - Obturator left
 - Obturator right
 - Pre-sacral left
 - Pre-sacral right
 - Peri-rectal anterior
 - Peri-rectal posterior
 - Inguinal left
 - Inguinal right
 - Retroperitoneal lymph nodes
 - Para-aortic
 - Retro-aortic
 - Para-caval
 - Retro-caval
 - Aorto-caval
 - Retrocrural left
 - Retrocrural right
 - Other lymph nodes
 - Intra-peritoneal
 - Mediastinal left
 - Mediastinal right
 - Axillary left
 - Axillary right
 - Cervical left
 - Cervical right
- Soft tissues/parenchyma
 - Lung upper lobe left
 - Lung upper lobe right
 - Lung middle lobe left
 - Lung middle lobe right
 - Lung lower lobe left
 - Lung lower lobe right

- Brain left
- Brain right
- Liver left
- Liver right
- Spleen
- Subcutaneous/cutaneous
- Muscle
- Bowel
- Bones
 - Skull
 - Skull base/maxilla left
 - Skull base/maxilla right
 - Mandible left
 - Mandible right
 - Neck
 - Vertebra C1
 - Vertebra C2
 - Vertebra C3
 - Vertebra C4
 - Vertebra C5
 - Vertebra C6
 - Vertebra C7
 - Vertebra T1
 - Vertebra T2
 - Vertebra T3
 - Vertebra T4
 - Vertebra T5
 - Vertebra T6
 - Vertebra T7
 - Vertebra T8
 - Vertebra T9
 - Vertebra T10
 - Vertebra T11
 - Vertebra T12
 - Vertebra L1
 - Vertebra L2
 - Vertebra L3
 - Vertebra L4
 - Vertebra L5
 - Sacrum left
 - Sacrum right
 - Sacrum central
 - Chest
 - 1st rib left
 - 1st rib right
 - 2nd rib left
 - 2nd rib right
 - 3rd rib left
 - 3rd rib right
 - 4th rib left
 - 4th rib right
 - 5th rib left
 - 5th rib right

- 6th rib left
- 6th rib right
- 7th rib left
- 7th rib right
- 8th rib left
- 8th rib right
- 9th rib left
- 9th rib right
- 10th rib left
- 10th rib right
- 11th rib left
- 11th rib right
- 12th rib left
- 12th rib right
- Sternum
- Clavicle left
- Clavicle right
- Scapula left
- Scapula right
- Pelvis
 - Ilium left
 - Ilium right
 - Superior pubic ramus left
 - Superior pubic ramus right
 - Inferior pubic ramus left
 - Inferior pubic ramus right
 - Pubic body left
 - Pubic body right
 - Ischium left
 - Ischium right
- Appendicular
 - Proximal humerus left
 - Proximal humerus right
 - Proximal femur left
 - Proximal femur right

5.4 Statistical Analysis

5.4.1 Primary Efficacy Analysis

The primary efficacy analysis will be based on the EAS and will be repeated on the PPS as a secondary analysis. Comparisons between the original treatment plan and the revised treatment plan will be categorised as no change, major change or other change. The definitions of the change categories are listed below.

- No change: the original treatment plan is the same as the revised treatment plan
- Major change: the original treatment plan is not the same as the revised treatment plan and the grouping for the original treatment plan is not the same as the grouping for the revised treatment plan

These will be further split and presented according to the following categories:

- Salvage or Non-curative systemic therapy to Watchful waiting
 - Salvage therapy to Non-curative systemic therapy
 - Non-curative systemic therapy to Salvage therapy
 - Alternative Major change
- Other change: the original treatment plan is not the same as the revised treatment plan but the grouping for the original treatment plan is the same as the grouping for the revised treatment plan

These will be further split and presented according to the following categories:

- Modified RT field plan
- Modified androgen-deprivation regimen
- Alternative Other change

Groupings of treatment plans are detailed in the following table:

Original Treatment Plan	Grouping for Original Tx Plan	Revised Treatment Plan	Grouping for Revised Tx Plan
Was androgen deprivation therapy planned	Androgen Deprivation Therapy	Androgen deprivation therapy	Androgen deprivation therapy
		Active surveillance	Active surveillance
		Chemotherapy	Chemotherapy
Salvage radiotherapy to the prostate bed	Salvage Radiotherapy	Salvage radiotherapy to the prostate bed	Salvage Radiotherapy
Salvage radiotherapy to the prostate bed, with boost to areas guided by conventional imaging		Salvage radiotherapy to the prostate bed, with boost to areas guided by conventional imaging	
		Salvage radiotherapy to the prostate bed with boost to areas guided by fluciclovine (18F) PET/CT	
Salvage radiotherapy to the prostate bed and whole pelvis	Salvage Radiotherapy	Salvage radiotherapy to the prostate bed and whole pelvis	Salvage Radiotherapy

Original Treatment Plan	Grouping for Original Tx Plan	Revised Treatment Plan	Grouping for Revised Tx Plan
Salvage radiotherapy to the prostate bed and whole pelvis, with boost to areas guided by conventional imaging		Salvage radiotherapy to the prostate bed and whole pelvis, with boost to areas guided by conventional imaging	
		Salvage radiotherapy to the prostate bed and whole pelvis with boost to areas guided by fluciclovine (18F) PET/CT	
Salvage cryotherapy		Salvage cryotherapy	
	Salvage Cryotherapy	Salvage cryotherapy with treatment plan guided by fluciclovine (18F) PET/CT	Salvage Cryotherapy
Salvage brachytherapy		Salvage brachytherapy	
	Salvage Brachytherapy	Salvage brachytherapy with treatment plan guided by fluciclovine (18F) PET/CT	Salvage Brachytherapy
Salvage HIFU		Salvage HIFU	
	Salvage HIFU	Salvage HIFU with treatment plan guided by fluciclovine (18F) PET/CT	Salvage HIFU
Salvage prostatectomy		Salvage prostatectomy	
	Salvage Prostatectomy	Salvage prostatectomy with targeted resection /	Salvage Prostatectomy

Original Treatment Plan	Grouping for Original Tx Plan	Revised Treatment Plan	Grouping for Revised Tx Plan
		sampling of fluciclovine (18F) positive areas outside conventional surgical field	
Salvage prostatectomy and limited lymph node dissection		Salvage prostatectomy and limited lymph node dissection	
		Salvage prostatectomy and limited lymph node dissection with targeted resection / sampling of fluciclovine (18F) positive areas outside surgical field	
Salvage prostatectomy and extended lymph node dissection (including internal and external iliac, and obturator nodes)		Salvage prostatectomy and extended lymph node dissection (including internal and external iliac, and obturator nodes)	
		Salvage prostatectomy and extended lymph node dissection (including internal and external iliac, and obturator nodes) with targeted resection / sampling of fluciclovine (18F) positive areas outside surgical field	
		Targeted salvage treatment of fluciclovine (18F)	Targeted salvage treatment

Original Treatment Plan	Grouping for Original Tx Plan	Revised Treatment Plan	Grouping for Revised Tx Plan
		positive extra-pelvic / bony areas	
		Other	Other

The classification and sub-classification of change in treatment management plan will be agreed prior to data base lock.

The number, percentage and exact 95% confidence interval (CI) of subjects with and without a change in management plan after ¹⁸F-fluciclovine PET/CT scan results become available will be presented for the EAS. In addition, the number and percentage of subjects with changes categorised as major or other will be presented along with its 95% CI. These summaries will be repeated separately for subjects with a positive and a negative ¹⁸F-fluciclovine PET/CT scan and for subjects without prostatectomy and with prostatectomy. All these summaries will be repeated using the PPS.

Details of the intended management plan, revised management plan and categorisation of change in management plan will be listed.

5.4.2 Secondary Efficacy Analyses

5.4.2.1 Change in actual management plan

The number, percentage and exact 95% CI for the percentage of subjects in the EAS with clinically significant deviations in actual management from the revised management plan after ¹⁸F-fluciclovine PET/CT scan results become available will be presented for overall and for subjects with positive and with negative ¹⁸F-fluciclovine PET/CT scans.

All management plan deviations will be listed in full.

5.4.2.2 Diagnostic performance of ¹⁸F-fluciclovine

Diagnostic performance will be assessed by calculating sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV), using subject based analyses. Further calculations will be made for intra-prostatic / prostate bed and extra-prostatic disease. Reference tests will be the adjudication panel decision. The Adjudication Panel will follow the Adjudication Manual that prospectively documents the processes to be used to determine a decision concerning the result of the ¹⁸F-fluciclovine PET/CT scan vs standard of truth. The number and percentage of indeterminate responses will be reported.

The sensitivity, specificity, PPV and NPV will be calculated as:

- Sensitivity = $TP / (TP + FN)$
- Specificity = $TN / (FP + TN)$
- PPV = $TP / (TP + FP)$
- NPV = $TN / (FN + TN)$

where TP, TN, FP and FN refer to true positive, true negative, false positive and false negative results respectively.

Definitions of these summaries will be based on the table below.

		Reference tests		
		Positive	Negative	
Fluciclovine (¹⁸ F) scan results	Positive	True Positive (TP)	False Positive (FP)	TP+FP
	Negative	False Negative (FN)	True Negative (TN)	FN+TN
		TP+FN	FP+TN	n

The number, percentage and exact 95% CIs of TP, FP, FN and TN, as well as the point estimates (expressed in percentages) and their associated exact 95% CIs, of the Sensitivity, Specificity, PPV and NPV, will be presented at the subject level and the region level for the FAS, where the region level estimates will be calculated separately for each region: prostatic region and extra-prostatic region. The region level results will be derived at the subject level for each region resulting in one outcome for each subject in each region. For the subject level analysis, if a subject has at least one positive result, the subject will be categorised as positive. If all of a subject's results are negative the subject will be categorised as negative. For the region level analysis, if a subject has at least one positive result from the prostatic region the subject will be categorised as positive for the prostatic region. If all results related to the prostatic region are negative for a subject, that subject will be categorised as negative for the prostatic region. Similar classification rules apply for the extra-prostatic region.

Note that the subgroup analyses will only be performed if there are sufficient data for these analyses to be meaningful.

These estimates will be repeated separately for regionally recurrent disease (prostate/prostate bed), pelvic lymph nodes and distant metastases (retroperitoneal lymph nodes, other lymph nodes, soft tissue/parenchyma and bones), a summary for lymph nodes (overall) will also be presented. Once again the region level results will be derived at the subject level and subjects will be categorised as positive or negative for each region in a similar manner to that described above for the prostatic region.

These subject and location level summaries will be repeated by the following baseline PSA subgroups:

- 0 – 0.2
- >0.2 – 0.5
- >0.5 – 1.0
- >1.0 – 2.0
- 2.0 – 5.0
- 5.0 – 10.0
- >10.0

and across the following baseline Gleason score categories: ≤ 6 , 7, 8 and ≥ 9 . All these summarise will be repeated for the PPS.

All ^{18}F -fluciclovine PET/CT results, other imaging results and adjudication decision data will be listed.

5.4.2.3 Detection rates

The detection rate (DR) will be calculated as $(\text{TP}+\text{FP})/n$ from the above table.

The point estimate (expressed in percentage) of the DR will be presented at the region level and at the subject level, as well as for the prostatic bed, other pelvic disease and distant metastases. These rates will be presented for all subjects from the FAS and PPS, overall and across a range of baseline PSA values:

- 0 – 0.2
- >0.2 – 0.5
- >0.5 – 1.0
- >1.0 – 2.0
- 2.0 – 5.0
- 5.0 – 10.0
- >10.0

to determine the optimum PSA threshold for lesion detection.

The detection rates will also be summarised across the following baseline Gleason score categories: ≤ 6 , 7, 8 and ≥ 9 .

All detection rate data will be listed.

5.4.2.4 Treatment response as assessed by change in PSA

Baseline PSA is the most recent PSA measurement prior to salvage therapy for subjects who had salvage treatment and the most recent PSA measurement prior to the ^{18}F -fluciclovine PET/CT for non-salvage subjects. Treatment response, which is based on the percentage change in PSA from baseline to the last value reported, is defined as:

- $\geq 30\%$ decrease in PSA will be considered to be a response to treatment
- $<25\%$ increase or $<30\%$ decrease will be classified as stable disease
- $\geq 25\%$ increase in PSA will be classified as disease progression

The number, percentage and exact 95% CI of subjects having a treatment response, stable disease and disease progression, as assessed by change in PSA, will be presented overall and separately for subjects in the EAS who had salvage treatment, for subjects who had non-salvage treatment, for those with a change in management plan and for subjects with no change in management plan, by treatment and by disease location (Local disease/Extra-prostatic disease) following the ^{18}F -fluciclovine PET/CT scan.

In addition, the percentage change in PSA from baseline to the last value reported will be summarised overall and by subjects who had a change in management plan versus those who did not have a change in management plan following the ^{18}F -

fluciclovine PET/CT scan. The percentage change in PSA from baseline to the last value reported will also be summarised for subjects who had disease in the prostate only and for subjects who have extra-prostatic disease and by treatment.

Finally, a waterfall plot of the maximum percentage reduction in PSA during the 4-8 month window will be presented on the y-axis and each subject will be represented by a bar on the x-axis. The bars will be ordered in descending order of the magnitude of the percentage change in PSA value.

Treatment response and the factors used to assess the response will be listed in full.

5.4.3 Handling of Dropouts or Missing Data

Subjects who withdrew from the study prior to completion will be summarised. Withdrawn subjects will not be directly replaced and no imputation of missing data will be conducted

5.4.4 Interim Analyses and Data Monitoring

No interim analysis is planned for this study.

5.4.5 Examination of Subgroups

No subgroup analyses will be conducted during the study.

6 SAFETY EVALUATION

All safety evaluations will be performed on the safety analysis set (SAF) unless specified otherwise.

All safety tables will be presented by centre and overall.

Subjects will be included and counted in summary tables only if they have available data.

For laboratory parameters, vital signs and ECG, baseline will be defined as the last measure prior to fluciclovine (^{18}F) administration including day of administration if available.

6.1 Adverse Events

Adverse events (AE) will be coded using the latest version of the MedDRA dictionary.

A treatment-emergent adverse event (TEAE) is defined as an AE with start date/time on or after the start date/time of ^{18}F -fluciclovine administration, or AEs with worsening intensity on or after the start date/time of ^{18}F -fluciclovine administration, or when the AE has a start time within 1 minute prior to the start time of ^{18}F -fluciclovine administration.

AEs with unknown start date/time will be assumed to be treatment-emergent unless the end date/time is known to be before the ^{18}F -fluciclovine administration.

Summary tables will be produced for all TEAEs occurring up to 42 days after the ^{18}F -fluciclovine administration (i.e. occurring between day 1 and day 43).

An overall summary of TEAEs will be created including:

- number of TEAEs and number of subjects with TEAEs,

- number of TEAEs and number of subjects with TEAEs associated with the injection site,
- number of serious TEAEs and number of subjects with serious TEAEs,
- number of subjects with TEAEs by CTCAE grade (Grade 1 to Grade 5),
- number of subjects with TEAEs by relationship to fluciclovine (definitely, probably, possibly, unrelated)
- number of subjects with TEAEs that are related to or unrelated to fluciclovine, where related TEAEs are those classified as definitely, probably and possibly related

The number and percentage of subjects experiencing TEAEs will be presented by system organ class (SOC) and preferred term (PT). System organ class and preferred term will be presented in decreasing frequency of the total number of subjects with TEAEs. If a subject experienced more than one treatment-emergent adverse event, the subject will be counted once for each system organ class and once for each preferred term.

The number and percentage of subjects experiencing TEAEs will be presented by SOC, PT and CTCAE grade. SOC and PT will be presented in decreasing frequency of the total number of subjects with TEAEs. If a subject experienced more than one TEAE, the subject will be counted once for each SOC and once for each PT at the worst severity.

The number and percentage of subjects experiencing TEAEs will be presented by SOC, PT, relationship to study drug and whether the TEAE is related to the study drug. SOC and PT will be presented in decreasing frequency of the total number of subjects with TEAEs. If a subject experienced more than one TEAE, the subject will be counted once for each SOC and once for each PT at the closest relationship to study drug.

All adverse events will be listed and TEAEs will be identified. AEs occurring up to 42 days after ¹⁸F-fluciclovine administration will be flagged. All SAEs will be listed separately.

6.2 Clinical Laboratory Evaluation

6.2.1 Hematology

Hematology values will be summarised by parameter and visit, and also for change from baseline (last pre-scan value vs first post-scan value).

All haematology values will be listed showing reference ranges (flagging abnormal findings).

6.2.2 Biochemistry

Biochemistry values will be summarised by parameter and visit, and also for change from baseline (last pre-scan value vs first post-scan value).

Additionally, from the serum creatinine levels (mg/dL), creatinine clearance (CrCl) will be derived using the Cockcroft Gault formula (Cockcroft DW, 1976) and the glomerular filtration rate (GFR) will be derived using the modification of diet in renal disease (MDRD) formula (Levey AS, 2006) as follows:

- Cockcroft-Gault formula: $\text{CrCl (mL/min)} = (140 - \text{age}) * (\text{Weight in kg}) * (0.85 \text{ if female}) / (72 * \text{Creatinine})$
- MDRD formula: $\text{GFR (mL/min)} = 175 * \text{Creatinine}^{-1.154} * \text{age}^{-0.203} * 1.212$ (if subject is black) * 0.742 (if female)

CrCl and GFR categories (≤ 30 mL/min, $>30 - \leq 60$, $>60 - \leq 90$, >90 mL/min) will be summarised, and a shift table of baseline status against the status on or after ^{18}F -fluciclovine administration will be presented.

All biochemistry values will be listed showing reference ranges and flagging abnormal findings.

6.2.3 Urinalysis dipstick

All urinalysis results will be listed.

6.3 Vital Signs

Vital sign values will be summarised by parameter and time point, and also for change from baseline.

Details of vital signs data will be listed.

6.4 Electrocardiography

Electrocardiogram (EKG) interpretation is recorded pre-dose/pre-scan and within 7 days of the scan. EKG observed QTc and change from baseline will be summarised by visit. In addition, a summary of the incidence of outliers in absolute QTc intervals (>450 , >480 and >500 msec), and the change from baseline in QTc intervals (>30 and >60 msec both positive and negative changes) will be presented.

The overall interpretation of the EKG (Normal, Abnormal NCS, and Abnormal CS) will also be summarised by visit. All EKG results will be listed, including overall interpretation and change from baseline.

7 REFERENCES

- Cockcroft DW, G. M. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*, 31-41.
- Hintze, J. (2013). Pass 12. NCSS, LLC. Available: www.ncss.com. Kaysville, Utah, USA.
- Levey AS, C. J. (2006). Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*, 247-254.