A Phase 3, Open-label Study to Assess the Clinical Utility of Fluciclovine (^{18}F) PET/CT in Patients with Prostate Cancer with Biochemical Recurrence after Radical Treatment

Blue Earth Diagnostics Study No: BED-004
Syne qua non Ltd Study No: BLS14004

Statistical Analysis Plan

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Date: 10th October 2018

For Syne qua non Ltd – Lead Statistician

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For Blue Earth Diagnostics

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ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BCR	Biochemical recurrence
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
CrCl	Creatinine clearance
CRF	Case report form
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events
EAS	Evaluable analysis set
ECG	Electrocardiogram
FAS	Full analysis set
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
LDH	Lactate dehydrogenase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
ms	Milliseconds
PCa	Prostate cancer
PET	Positron emission tomography
PPS	Per protocol set
PSA	Prostate specific antigen
PT	Preferred term
RBC	Red blood cell
RDW	Red cell distribution width
RP	Radical prostatectomy
RRT	Radical external beam radiotherapy
RT	Radiotherapy
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation

SOC	System organ class
TEAE	Treatment emergent adverse event
TNM	TNM classification of malignant tumours
WBC	White blood cell
WHO	World Health Organization
WHO DDE	WHO Drug Dictionary Enhanced

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the final protocol version dated 24th March 2015 and amendments 1-4 dated 30th November 2015, 5th April 2016, 2nd March 2017 and 4th June 2018.

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.

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.

For treatment response baseline prostate specific antigen (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 18F-fluciclovine positron emission tomography/computerised tomography (PET/CT) for non-salvage subjects. If no PSA measurement is available just prior to salvage therapy, baseline will be defined as the most recent PSA measurement prior to fluciclovine (^{18}F) scan. For all other variables, and for baseline PSA other than for treatment response, baseline is defined as the most recent value prior to fluciclovine (^{18}F) administration.

In general, there will be no imputation of missing data, however where dates are partially missing dates may be imputed for calculation purposes, details are given under relevant section.

3 STUDY OBJECTIVES AND DESIGN

3.1 Study Objectives

The primary objective of the study is to confirm the clinical benefit of fluciclovine (^{18}F) PET/CT in affecting management decisions in subjects with biochemical recurrence (BCR) being considered for radical salvage treatment (with curative intent).

The secondary objectives of the study are

- To assess possible improvement in outcome of radical salvage treatment based on fluciclovine (^{18}F) PET/CT being included in the assessment

- To assess the PSA threshold for positive lesion detection by fluciclovine (^{18}F) PET/CT in BCR
- To assess the safety of fluciclovine (^{18}F) injection in subjects undergoing PET/CT

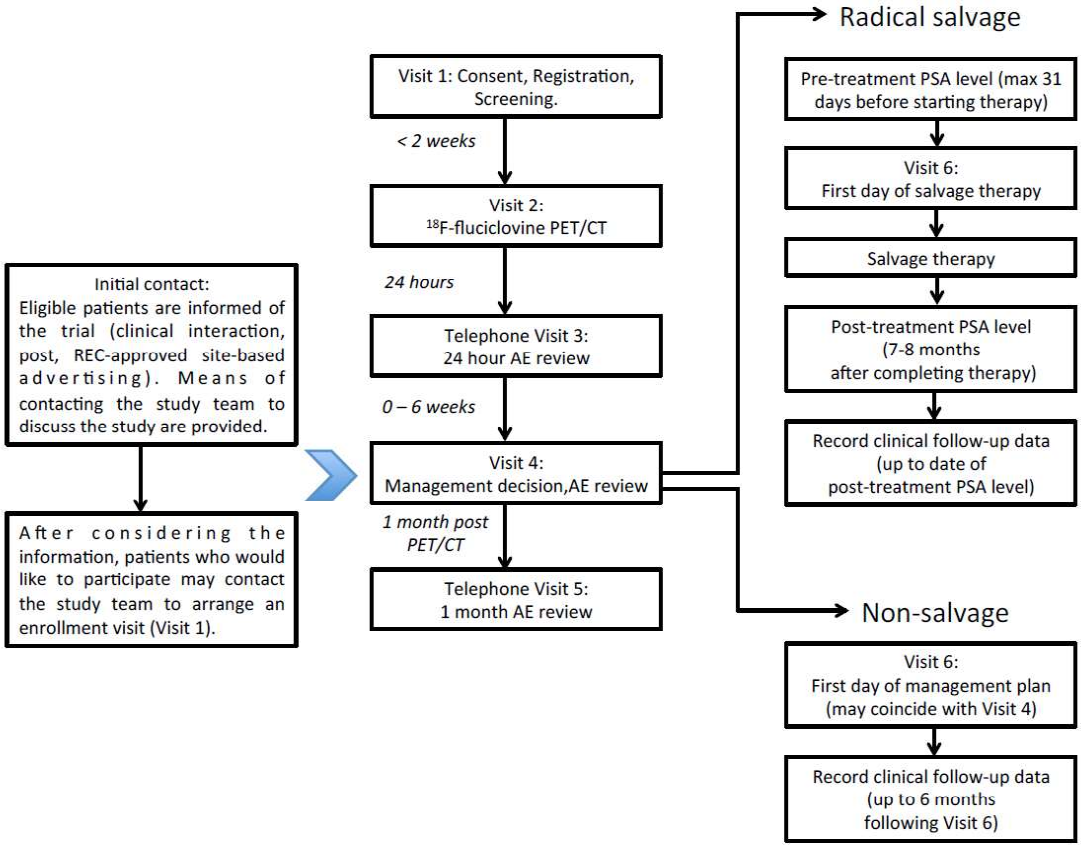
3.2 Study Design

This will be an open-labelled, multi-centred study in the United Kingdom.

The study group will include up to 180 subjects with a diagnosis of BCR of previous radically treated prostate cancer (PCa), and who are being considered for radical salvage therapy.

Subjects will have a fluciclovine (^{18}F) PET/CT scan in addition to standard work-up for radical salvage therapy. The clinical utility of fluciclovine (^{18}F) PET/CT will be assessed by recording changes to the recommended management plan influenced by the scan result.

The summary flow chart of the study design is as follows:



3.3 Visit Structure

The visit structure and scheduled assessments are detailed in Appendix A: Schedule of study procedures of the protocol.

3.4 Sample Size

For the primary objective of treatment change evaluation, a minimum of 171 subjects with complete primary endpoint data will be required to allow for a width of +/-6% in a two-sided 95% confidence interval (CI). This is based on the conservative assumption that 20% of subjects will have a treatment change, as fluciclovine (^{18}F) PET/CT has been shown to upstage 25.7% of subjects with recurrent prostate cancer, and also based on the management change studies reported on choline PET/CT. The aim is to recruit 180 subjects for this trial, based on an anticipated primary endpoint drop-out rate of 5%.

3.5 Changes from the Protocol Planned Analysis

The protocol specified “Improvement in outcome of radical salvage treatment based on fluciclovine (^{18}F) PET/CT being included in the assessment” as a secondary endpoint. This was to be assessed based on PSA and radiological response. Due to lack of data being recorded for radiological response this definition was not used, treatment response was instead assessed using PSA only (see section 5.4.2.1.).

4 STUDY SUBJECTS

4.1 Analysis sets

The list of subjects to be included in each of the analysis set 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 fluciclovine (^{18}F) will be included in the Safety Analysis Set (SAF).

Full Analysis Set (FAS): All subjects enrolled who have had a fluciclovine (^{18}F) 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 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 (weight (kg)/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 Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

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. This table will be repeated for all events, regardless of whether previous or current events.

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*(date of informed consent – date of initial prostate cancer diagnosis + 1)/365.25]
- TNM stage: Pathological TNM stage if available, otherwise Clinical TNM stage. A summary for T1 total, T2 total and T3 total will be provided as the sum of the number of subjects in each of the subgroups plus any subjects where only T1, T2 or T3 was recorded.
- Gleason total score: Gleason total score from surgery if available, otherwise Gleason total score from biopsy
- Time since adjuvant treatment (months), calculated as [12*(date of informed consent – stop date of adjuvant treatment + 1)/365.25]
- Duration of adjuvant treatment (months), calculated as [12*(stop date of adjuvant treatment – start date of adjuvant treatment + 1)/365.25]

- Time since diagnosis of biochemical recurrence (days), calculated as (date of informed consent – date of diagnosis of biochemical recurrence + 1). Time since diagnosis of BCR may be derived in months if more appropriate.
- Baseline PSA value
- Baseline PSA category (0 – 0.2, >0.2 – 0.5, >0.5 – 1, >1 – 2, >2 – 5, >5 – 10 and >10)

In addition, summary table to summarise baseline Prostate Specific Antigen (PSA) by Prior Radical Prostatectomy status (Prior Radical Prostatectomy vs No Prior Radical Prostatectomy) using descriptive statistics (number of subjects (n), mean, standard deviation (SD), minimum, median, and maximum), will be produced.

Details of prostate cancer history will be listed.

Date imputation for incomplete dates:

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

4.4.4 Cancer Therapies for Prostate Cancer

Cancer therapies for prostate cancer will be coded according to the World Health Organization Drug Dictionary Enhanced (WHO DDE) (Enhanced) version Sep 2015.

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 fluciclovine (^{18}F).

Concomitant/post-scan cancer therapies for prostate cancer are defined as those with a start date on or after the injection date of fluciclovine (^{18}F), or those with a start date before the injection date of fluciclovine (^{18}F) but which continued with a stop on or after the injection date of fluciclovine (^{18}F). Summaries for subjects with prior and post-scan radical prostatectomy will be presented separately.

Summary table to summarise time from ^{18}F-fluciclovine PET/CT to first post-^{18}F-fluciclovine treatment in days using descriptive statistics (number of subjects (n), mean, SD, minimum, median, and maximum) will be provided.

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 World Health Organization Drug Dictionary Enhanced (WHO DDE) (Enhanced) version Sep 2015.

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

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

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 centre and overall by medication class, standardised medication names sorted alphabetically 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.

4.5 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.

5 EFFICACY EVALUATION

All listings will be based on the FAS unless specified otherwise. The primary efficacy analysis will be based on the EAS and will be repeated on the PPS as a secondary analysis. The secondary efficacy analyses will be based on the FAS.

5.1 Primary Efficacy Variable

The primary efficacy variable is the record of the revised management plan post fluciclovine (^{18}F) PET/CT scan in comparison to the pre-scan intended management plan.

5.2 Secondary Efficacy Variables

The secondary efficacy variables are:

- The proportion of subjects who have a sustained response to radical salvage therapy.
- PSA levels in relation to scan positivity will be analysed to determine the optimal PSA threshold for detecting recurrent PCa by fluciclovine (^{18}F) PET/CT.

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
        - Peri-rectal left
        - Peri-rectal right
        - 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 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
  - Vertebra
    - 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
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  - 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 analysis of the primary outcome will be performed on the EAS as the primary analysis 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
		Watch and wait	Watch and wait
		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 (^{18}F) PET/CT	
Salvage radiotherapy to the prostate bed and whole pelvis	Salvage Radiotherapy	Salvage radiotherapy to the prostate bed and whole pelvis	Salvage Radiotherapy
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 (^{18}F) PET/CT	

Original Treatment Plan	Grouping for Original Tx Plan	Revised Treatment Plan	Grouping for Revised Tx Plan
Salvage cryotherapy	Salvage Cryotherapy	Salvage cryotherapy	Salvage Cryotherapy
		Salvage cryotherapy with boost to areas guided by fluciclovine (^{18}F) PET/CT	
Salvage brachytherapy	Salvage Brachytherapy	Salvage brachytherapy	Salvage Brachytherapy
		Salvage brachytherapy with boost to areas guided by fluciclovine (^{18}F) PET/CT	
		Salvage brachytherapy with treatment plan guided by fluciclovine (^{18}F) PET/CT	
Salvage HIFU	Salvage HIFU	Salvage HIFU	Salvage HIFU
		Salvage HIFU with treatment plan guided by fluciclovine (^{18}F) PET/CT	
Salvage prostatectomy	Salvage Prostatectomy	Salvage prostatectomy	Salvage Prostatectomy
		Salvage prostatectomy with targeted resection / sampling of fluciclovine (^{18}F) positive areas outside conventional surgical field	
Salvage prostatectomy and limited lymph node dissection		Salvage prostatectomy and limited lymph node dissection	

Original Treatment Plan	Grouping for Original Tx Plan	Revised Treatment Plan	Grouping for Revised Tx Plan
		Salvage prostatectomy and limited lymph node dissection with targeted resection / sampling of fluciclovine (^{18}F) 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 (^{18}F) positive areas outside surgical field	
		Targeted salvage treatment of fluciclovine (^{18}F) positive extra-pelvic / bony areas	Targeted salvage treatment
		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% CI of subjects with and without a change in management plan after the fluciclovine (^{18}F) scan results become available will be presented. In addition, the number and percentage of subjects with changes categorised as major or other will be presented. These summaries will be repeated separately for subjects with a positive and a negative fluciclovine (^{18}F) scan and for subjects without prostatectomy and with prostatectomy.

The number, percentage and 95% CI of subjects who agreed to the revised management plan after fluciclovine (^{18}F) scan results become available will be presented.

Details of the intended management plan, revised management plan and agreed management plan will be listed.

5.4.2 Secondary Efficacy Analyses

5.4.2.1 Treatment response as assessed by change in PSA

An assessment of treatment response, which is based on the percentage change in PSA from baseline to the last value reported, is defined as:

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

See section 2 General Principles for baseline definition.

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 FAS 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 following the ^{18}F-fluciclovine PET/CT scan. In addition, treatment response assessed by change in PSA will be summarised by disease location (local disease versus extra-prostatic disease) and treatment administered.

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, disease location and treatment administered.

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.

5.4.2.2 PSA threshold

The detection rate (DR) will be calculated as number of positive fluciclovine (^{18}F) scan results/total number of scans.

The point estimate (expressed in percentage) of the DR will be presented at the region level and at the subject level. 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. See section 2 General Principles for baseline definition.

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

All fluciclovine (^{18}F) and other imaging results will be listed.

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

A single interim analysis of the primary endpoint will be performed in the first 85 evaluable subjects. If the number of treatment changes is greater than 45 (52.9%, with a 97.5% two-sided CI of 40.3%-62.3%, so the lower limit is over 40%), the trial will be terminated early due to overwhelming effectiveness. If the number of treatment changes is 8 or fewer (9.4%, with a 97.5% two-sided CI of 3.6%-18.9%, so the upper limit in this population is below the 20% of the null hypothesis), the trial will be terminated early due to futility.

5.4.5 Examination of Subgroups

No subgroup analyses will be conducted during the study.

5.4.6 Site Specific Sub-study

A site specific sub-study will be conducted in order to compare the ordered subset expectation maximisation (OSEM) standard of care method of reconstructing PET/CT images with that of the Bayesian penalised likelihood method of PET/CT image reconstruction. The analysis of the sub-study results is beyond the scope of this SAP.

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.

6.1 Adverse Events

Adverse events (AE) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

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

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

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 (unrelated, possibly related, probably related, definitely related and related, where related adverse events are those classified as possibly, probably and definitely related to fluciclovine ^{18}F)

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 and relationship to 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 fluciclovine (^{18}F) administration will be flagged. All SAEs will be listed separately.

6.2 Clinical Laboratory Evaluation

6.2.1 Haematology

Haematology 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 (Cockroft DW, 1976) and the glomerular filtration rate (GFR) will be derived using the MDRD formula (Levey AS, 2006) as follows:

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

CrCl and GFR categories (≤30 mL/min, >30 - ≤60, >60 - ≤90, >90 mL/min) will be summarised by time window, and the shift table of baseline status against the worst status on or after fluciclovine (^{18}F) 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.

6.2.4 Urine microscopy

All urine microscopy results will be listed.

6.3 Vital Signs

Vital signs include pulse rate, systolic and diastolic blood pressure.

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 (ECG) interpretation is recorded at screening and visit 4.

ECG interpretations will be summarised by shift tables highlighting any changes between screening and visit 4.

7 REFERENCES

Cockroft DW, G. M. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*, 31-41.

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.

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Required hardware and software

Operating Systems:	Windows2000? or WindowsXP?
Browsers (for SENDERS):	Internet Explorer 6.0? or above
Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
Email:	Access to a valid email account
Screen Resolution:	800 x 600 minimum
Enabled Security Settings:	•Allow per session cookies •Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection

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A Phase 3, Open-label Study to Assess the Clinical Utility of Fluciclovine (^{18}F) PET/CT in Patients with Prostate Cancer with Biochemical Recurrence after Radical Treatment

Blue Earth Diagnostics Study No: BED-004
Syne qua non Ltd Study No: BLS14004

Statistical Analysis Plan

Version: Amendment 1 Final

Date: 10th October 2018

For Syne qua non Ltd – Lead Statistician

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Contents

ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BCR	Biochemical recurrence
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
CrCl	Creatinine clearance
CRF	Case report form
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events
EAS	Evaluable analysis set
ECG	Electrocardiogram
FAS	Full analysis set
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
LDH	Lactate dehydrogenase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
ms	Milliseconds
PCa	Prostate cancer
PET	Positron emission tomography
PPS	Per protocol set
PSA	Prostate specific antigen
PT	Preferred term
RBC	Red blood cell
RDW	Red cell distribution width
RP	Radical prostatectomy
RRT	Radical external beam radiotherapy
RT	Radiotherapy
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation

SOC	System organ class
TEAE	Treatment emergent adverse event
TNM	TNM classification of malignant tumours
WBC	White blood cell
WHO	World Health Organization
WHO DDE	WHO Drug Dictionary Enhanced

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the final protocol version dated 24th March 2015 and amendments 1-4 dated 30th November 2015, 5th April 2016, 2nd March 2017 and 4th June 2018.

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.

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.

For treatment response baseline prostate specific antigen (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 18F-fluciclovine positron emission tomography/computerised tomography (PET/CT) for non-salvage subjects. If no PSA measurement is available just prior to salvage therapy, baseline will be defined as the most recent PSA measurement prior to fluciclovine (^{18}F) scan. For all other variables, and for baseline PSA other than for treatment response, baseline is defined as the most recent value prior to fluciclovine (^{18}F) administration.

In general, there will be no imputation of missing data, however where dates are partially missing dates may be imputed for calculation purposes, details are given under relevant section.

3 STUDY OBJECTIVES AND DESIGN

3.1 Study Objectives

The primary objective of the study is to confirm the clinical benefit of fluciclovine (^{18}F) PET/CT in affecting management decisions in subjects with biochemical recurrence (BCR) being considered for radical salvage treatment (with curative intent).

The secondary objectives of the study are

- To assess possible improvement in outcome of radical salvage treatment based on fluciclovine (^{18}F) PET/CT being included in the assessment

- To assess the PSA threshold for positive lesion detection by fluciclovine (^{18}F) PET/CT in BCR
- To assess the safety of fluciclovine (^{18}F) injection in subjects undergoing PET/CT

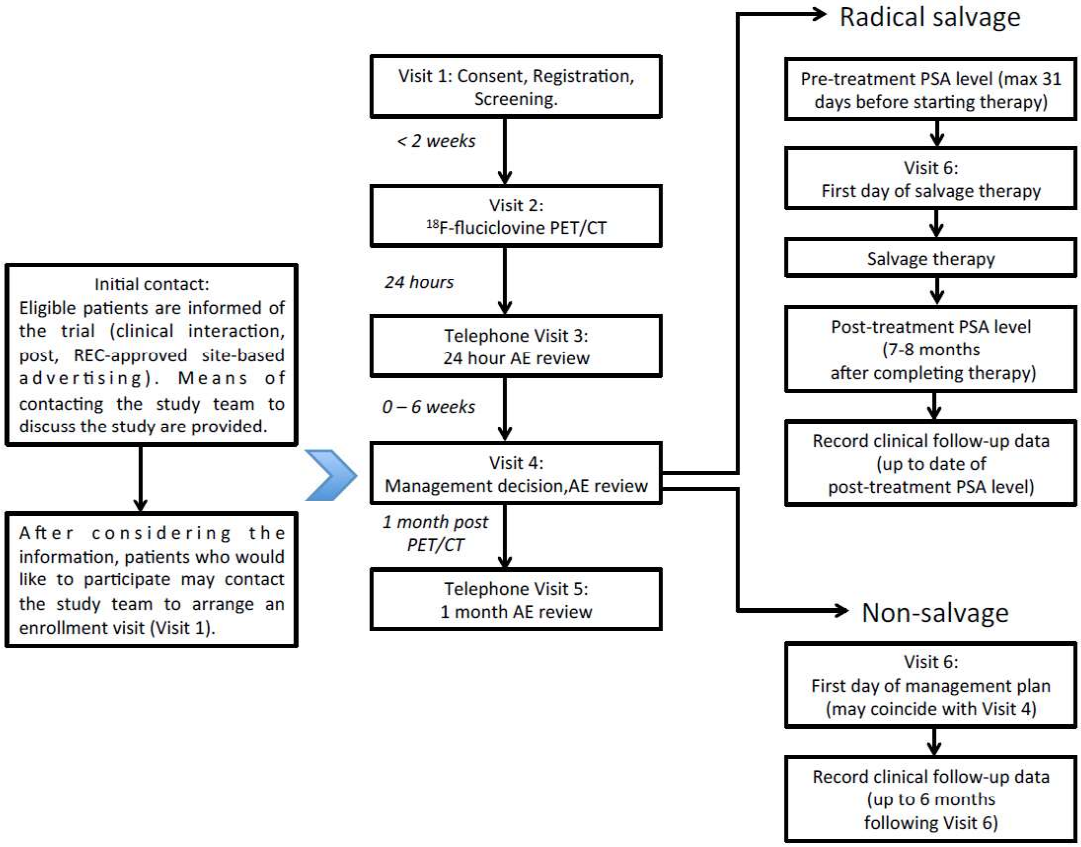
3.2 Study Design

This will be an open-labelled, multi-centred study in the United Kingdom.

The study group will include up to 180 subjects with a diagnosis of BCR of previous radically treated prostate cancer (PCa), and who are being considered for radical salvage therapy.

Subjects will have a fluciclovine (^{18}F) PET/CT scan in addition to standard work-up for radical salvage therapy. The clinical utility of fluciclovine (^{18}F) PET/CT will be assessed by recording changes to the recommended management plan influenced by the scan result.

The summary flow chart of the study design is as follows:



3.3 Visit Structure

The visit structure and scheduled assessments are detailed in Appendix A: Schedule of study procedures of the protocol.

3.4 Sample Size

For the primary objective of treatment change evaluation, a minimum of 171 subjects with complete primary endpoint data will be required to allow for a width of +/-6% in a two-sided 95% confidence interval (CI). This is based on the conservative assumption that 20% of subjects will have a treatment change, as fluciclovine (^{18}F) PET/CT has been shown to upstage 25.7% of subjects with recurrent prostate cancer, and also based on the management change studies reported on choline PET/CT. The aim is to recruit 180 subjects for this trial, based on an anticipated primary endpoint drop-out rate of 5%.

3.5 Changes from the Protocol Planned Analysis

The protocol specified “Improvement in outcome of radical salvage treatment based on fluciclovine (^{18}F) PET/CT being included in the assessment” as a secondary endpoint. This was to be assessed based on PSA and radiological response. Due to lack of data being recorded for radiological response this definition was not used, treatment response was instead assessed using PSA only (see section 5.4.2.1.).

4 STUDY SUBJECTS

4.1 Analysis sets

The list of subjects to be included in each of the analysis set 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 fluciclovine (^{18}F) will be included in the Safety Analysis Set (SAF).

Full Analysis Set (FAS): All subjects enrolled who have had a fluciclovine (^{18}F) 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 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 (weight (kg)/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 Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

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. This table will be repeated for all events, regardless of whether previous or current events.

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*(date of informed consent – date of initial prostate cancer diagnosis + 1)/365.25]
- TNM stage: Pathological TNM stage if available, otherwise Clinical TNM stage. A summary for T1 total, T2 total and T3 total will be provided as the sum of the number of subjects in each of the subgroups plus any subjects where only T1, T2 or T3 was recorded.
- Gleason total score: Gleason total score from surgery if available, otherwise Gleason total score from biopsy
- Time since adjuvant treatment (months), calculated as [12*(date of informed consent – stop date of adjuvant treatment + 1)/365.25]
- Duration of adjuvant treatment (months), calculated as [12*(stop date of adjuvant treatment – start date of adjuvant treatment + 1)/365.25]

- Time since diagnosis of biochemical recurrence (days), calculated as (date of informed consent – date of diagnosis of biochemical recurrence + 1). Time since diagnosis of BCR may be derived in months if more appropriate.
- Baseline PSA value
- Baseline PSA category (0 – 0.2, >0.2 – 0.5, >0.5 – 1, >1 – 2, >2 – 5, >5 – 10 and >10)

In addition, summary table to summarise baseline Prostate Specific Antigen (PSA) by Prior Radical Prostatectomy status (Prior Radical Prostatectomy vs No Prior Radical Prostatectomy) using descriptive statistics (number of subjects (n), mean, standard deviation (SD), minimum, median, and maximum), will be produced.

Details of prostate cancer history will be listed.

Date imputation for incomplete dates:

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

4.4.4 Cancer Therapies for Prostate Cancer

Cancer therapies for prostate cancer will be coded according to the World Health Organization Drug Dictionary Enhanced (WHO DDE) (Enhanced) version Sep 2015.

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 fluciclovine (^{18}F).

Concomitant/post-scan cancer therapies for prostate cancer are defined as those with a start date on or after the injection date of fluciclovine (^{18}F), or those with a start date before the injection date of fluciclovine (^{18}F) but which continued with a stop on or after the injection date of fluciclovine (^{18}F). Summaries for subjects with prior and post-scan radical prostatectomy will be presented separately.

Summary table to summarise time from ^{18}F-fluciclovine PET/CT to first post-^{18}F-fluciclovine treatment in days using descriptive statistics (number of subjects (n), mean, SD, minimum, median, and maximum) will be provided.

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 World Health Organization Drug Dictionary Enhanced (WHO DDE) (Enhanced) version Sep 2015.

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

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

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 centre and overall by medication class, standardised medication names sorted alphabetically 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.

4.5 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.

5 EFFICACY EVALUATION

All listings will be based on the FAS unless specified otherwise. The primary efficacy analysis will be based on the EAS and will be repeated on the PPS as a secondary analysis. The secondary efficacy analyses will be based on the FAS.

5.1 Primary Efficacy Variable

The primary efficacy variable is the record of the revised management plan post fluciclovine (^{18}F) PET/CT scan in comparison to the pre-scan intended management plan.

5.2 Secondary Efficacy Variables

The secondary efficacy variables are:

- The proportion of subjects who have a sustained response to radical salvage therapy.
- PSA levels in relation to scan positivity will be analysed to determine the optimal PSA threshold for detecting recurrent PCa by fluciclovine (^{18}F) PET/CT.

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
        - Peri-rectal left
        - Peri-rectal right
        - 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 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
  - Vertebra
    - 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
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  - 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 analysis of the primary outcome will be performed on the EAS as the primary analysis 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
		Watch and wait	Watch and wait
		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 (^{18}F) PET/CT	
Salvage radiotherapy to the prostate bed and whole pelvis	Salvage Radiotherapy	Salvage radiotherapy to the prostate bed and whole pelvis	Salvage Radiotherapy
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 (^{18}F) PET/CT	

Original Treatment Plan	Grouping for Original Tx Plan	Revised Treatment Plan	Grouping for Revised Tx Plan
Salvage cryotherapy	Salvage Cryotherapy	Salvage cryotherapy	Salvage Cryotherapy
		Salvage cryotherapy with boost to areas guided by fluciclovine (^{18}F) PET/CT	
Salvage brachytherapy	Salvage Brachytherapy	Salvage brachytherapy	Salvage Brachytherapy
		Salvage brachytherapy with boost to areas guided by fluciclovine (^{18}F) PET/CT	
		Salvage brachytherapy with treatment plan guided by fluciclovine (^{18}F) PET/CT	
Salvage HIFU	Salvage HIFU	Salvage HIFU	Salvage HIFU
		Salvage HIFU with treatment plan guided by fluciclovine (^{18}F) PET/CT	
Salvage prostatectomy	Salvage Prostatectomy	Salvage prostatectomy	Salvage Prostatectomy
		Salvage prostatectomy with targeted resection / sampling of fluciclovine (^{18}F) positive areas outside conventional surgical field	
Salvage prostatectomy and limited lymph node dissection		Salvage prostatectomy and limited lymph node dissection	

Original Treatment Plan	Grouping for Original Tx Plan	Revised Treatment Plan	Grouping for Revised Tx Plan
		Salvage prostatectomy and limited lymph node dissection with targeted resection / sampling of fluciclovine (^{18}F) 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 (^{18}F) positive areas outside surgical field	
		Targeted salvage treatment of fluciclovine (^{18}F) positive extra-pelvic / bony areas	Targeted salvage treatment
		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% CI of subjects with and without a change in management plan after the fluciclovine (^{18}F) scan results become available will be presented. In addition, the number and percentage of subjects with changes categorised as major or other will be presented. These summaries will be repeated separately for subjects with a positive and a negative fluciclovine (^{18}F) scan and for subjects without prostatectomy and with prostatectomy.

The number, percentage and 95% CI of subjects who agreed to the revised management plan after fluciclovine (^{18}F) scan results become available will be presented.

Details of the intended management plan, revised management plan and agreed management plan will be listed.

5.4.2 Secondary Efficacy Analyses

5.4.2.1 Treatment response as assessed by change in PSA

An assessment of treatment response, which is based on the percentage change in PSA from baseline to the last value reported, is defined as:

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

See section 2 General Principles for baseline definition.

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 FAS 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 following the ^{18}F-fluciclovine PET/CT scan. In addition, treatment response assessed by change in PSA will be summarised by disease location (local disease versus extra-prostatic disease) and treatment administered.

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, disease location and treatment administered.

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.

5.4.2.2 PSA threshold

The detection rate (DR) will be calculated as number of positive fluciclovine (^{18}F) scan results/total number of scans.

The point estimate (expressed in percentage) of the DR will be presented at the region level and at the subject level. 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. See section 2 General Principles for baseline definition.

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

All fluciclovine (^{18}F) and other imaging results will be listed.

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

A single interim analysis of the primary endpoint will be performed in the first 85 evaluable subjects. If the number of treatment changes is greater than 45 (52.9%, with a 97.5% two-sided CI of 40.3%-62.3%, so the lower limit is over 40%), the trial will be terminated early due to overwhelming effectiveness. If the number of treatment changes is 8 or fewer (9.4%, with a 97.5% two-sided CI of 3.6%-18.9%, so the upper limit in this population is below the 20% of the null hypothesis), the trial will be terminated early due to futility.

5.4.5 Examination of Subgroups

No subgroup analyses will be conducted during the study.

5.4.6 Site Specific Sub-study

A site specific sub-study will be conducted in order to compare the ordered subset expectation maximisation (OSEM) standard of care method of reconstructing PET/CT images with that of the Bayesian penalised likelihood method of PET/CT image reconstruction. The analysis of the sub-study results is beyond the scope of this SAP.

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.

6.1 Adverse Events

Adverse events (AE) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

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

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

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 (unrelated, possibly related, probably related, definitely related and related, where related adverse events are those classified as possibly, probably and definitely related to fluciclovine ^{18}F)

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 and relationship to 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 fluciclovine (^{18}F) administration will be flagged. All SAEs will be listed separately.

6.2 Clinical Laboratory Evaluation

6.2.1 Haematology

Haematology 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 (Cockroft DW, 1976) and the glomerular filtration rate (GFR) will be derived using the MDRD formula (Levey AS, 2006) as follows:

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

CrCl and GFR categories (≤30 mL/min, >30 - ≤60, >60 - ≤90, >90 mL/min) will be summarised by time window, and the shift table of baseline status against the worst status on or after fluciclovine (^{18}F) 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.

6.2.4 Urine microscopy

All urine microscopy results will be listed.

6.3 Vital Signs

Vital signs include pulse rate, systolic and diastolic blood pressure.

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 (ECG) interpretation is recorded at screening and visit 4.

ECG interpretations will be summarised by shift tables highlighting any changes between screening and visit 4.

7 REFERENCES

Cockroft DW, G. M. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*, 31-41.

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.

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A Phase 3, Open-label Study to Assess the Clinical Utility of Fluciclovine (^{18}F) PET/CT in Patients with Prostate Cancer with Biochemical Recurrence after Radical Treatment

Blue Earth Diagnostics Study No : BED-004
Syne qua non Ltd Study No : BLS14004

Statistical Analysis Plan Addendum 2

Version: Final

Date: 08 March 2019

For Syne qua non Ltd – Lead Statistician

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Contents

LIST OF ABBREVIATIONS

PSA	Prostate specific antigen
SAP	Statistical analysis plan

1 INTRODUCTION

This the second addendum to the final statistical analysis plan (SAP) Amendment 1 dated 10th October 2018, documenting additional analyses following database lock. Full details of the changes are detailed below.

2 CHANGES TO THE FINAL SAP

2.1 Change 1

Section 5.4.2.1 Treatment response as assessed by change in PSA

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 for subjects in the FAS who had salvage therapy. The summary will include an overall summary and separate summaries for subjects who had therapy guided by fluciclovine and for subjects whose therapy was not guided by fluciclovine.

This additional table will be of the same format as *Table 14.2.2.1 Treatment Response Assessment as Assessed by PSA - by Disease Location*, with the categories "Overall", "Local Disease" and "Extra-prostatic disease", replaced with "Salvage Therapy – All", "Salvage Therapy Guided by Fluciclovine" and "Salvage Therapy Not Guided by Fluciclovine" respectively.

This description is considered sufficient and a shell is not required. The title will be "*Table 14.2.2.5 Treatment Response Assessment as Assessed by PSA in Subjects with Salvage Therapy - by Guided by/Not Guided by Fluciclovine*".

Subjects will be determined to have a therapy guided by fluciclovine if they have an agreed therapy which contains the text string "GUIDED BY FLUCICLOVINE".

Reason for the change

To assess possible improvement in outcome of radical salvage treatment based on 18F fluciclovine PET/CT being included in the assessment.

2.2 Change 2

Section 5.4.2.3 Summary of disease location in subjects who had a change in management plan from salvage therapy to non-salvage therapy

The number and percentage of subjects who had positive extra-prostatic findings and negative extra-prostatic findings will be presented for subjects who had a change in management plan from salvage therapy to non-salvage therapy.

Subjects who had a change in management plan from salvage therapy to non-salvage therapy will be identified where the change of management plan is "SALVAGE THERAPY TO NON-CURATIVE SYSTEMIC THERAPY".

Positive/negative extra-prostatic findings will be determined from the imaging results.

This description is considered sufficient and a shell is not required. The title will be "*Table 14.2.2.6 Presence of Extra-prostatic Disease in Subjects with Change of Management Plan from Salvage Therapy to Non-salvage Therapy*".

Reason for the change

This is an exploratory descriptive analysis to aid interpretation of the change in management plan data.

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Email:	Access to a valid email account
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