Statistical Analysis Plan

Protocol Title:
Enhanced Epidermal Antigen Specific Immunotherapy trial -1 (EE-ASI-1): A Phase 1a study of gold nanoparticles administered intradermally by microneedles to deliver immunotherapy with a proinsulin derived peptide in Type 1 diabetes.

Short title: EE-ASI – 1.

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Author: Wai-Yee Cheung Date: 13 Aug 2016

Approved by:

Chief Investigator signature: _____ Date:

Trial Statistician signature: Cheung Wai Yee Date: 19 Oct 2016

SAP Amendments:

Version	Description of Changes	Effective Date

Abbreviations and Definitions

CI	Chief Investigator
CRF	Case Report Forms
CTIMP	Clinical Trial of an Investigational Medicinal Product
DSMB	Data Safety Monitoring Board
GCP	Good Clinical Practice
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
SOP	Standard Operating Procedure
STU	Swansea Trials Unit
TM	Trial Manager
TMF	Trial Master File
TS	Trial Statistician
TSC	Trial Steering Committee
SAP	Statistical Analysis Plan

1. Synopsis of trial protocol

1.1. Introduction

This is the plan for analysing the safety, feasibility and efficacy endpoints from a Phase 1a study of gold nanoparticles administered intradermally by microneedles to deliver immunotherapy with a proinsulin derived peptide in Type 1 diabetes.

At diagnosis of Type 1 diabetes, most people have sufficient residual beta cell function to achieve good glycaemic control. This level of beta cell function, even if it declines or is lost over the next few years, has been shown to improve glycaemic control, reduce hypoglycaemia, improve quality of life and reduce long-term complications.

Antigen specific immunotherapy (ASI) is the preferred approach to beta cell preservation since this avoids the risks of immunosuppression. Attempts at ASI to date although successful in preclinical models have had limited efficacy in humans. There is therefore an urgent need for the development of novel approaches to deliver effective ASI.

The skin is a very effective means of antigen delivery to the immune system due to the very high density and specialised nature of its antigen presenting cells (APCs). Yet the density of APCs reduces rapidly just below the epidermis. The study will target antigen presentation through the superficial layers of the skin via the use of ultrashort needles to improve efficiency of antigen delivery.

To enhance uptake of antigen by dendritic cells and reduce inflammation, very small gold nanoparticles will be coupled to a peptide of proinsulin C19-A3. This peptide is a naturally processed and presented T cell epitope of proinsulin that is frequently targeted in patients with type 1 diabetes who carry the susceptibility molecule, HLADRB1*0401. Gold is an inert metal which has an extensive safety record and safety can be further enhanced by the use of very small nanoparticles. Preclinical data show that gold nanoparticles (GNP) coupled peptide has the potential to induce a regulatory T cell response not only in skin at the site of administration but at distance sites including the pancreas draining lymph nodes.

1.2. Objectives

The primary objective of the study is to examine the risk of C19-A3 GNP administration in terms of general safety and induction of hypersensitivity.

Secondary objectives are:

- To study the feasibility of delivering C19-A3 GNP via microneedles to humans.
- To study the size and nature of immune responses to C19-A3 GNP generated in blood and the draining (axillary) lymph node.

2. Study Methods

2.1. Trial design

The study is a two centre, open-label, uncontrolled single group phase 1A study of C19-A3 GNP peptide (10 µg peptide equivalent content) administered via Nanopass microneedles every 28 days for 8 weeks (3 doses), with follow-up for 12 weeks (20 weeks in total from first dose). Treatment will be given into the arm at a volume of 50ul. A schedule of study visits and procedures carried out at each study visit are shown in table 1.

2.2. Interim analysis and stopping guidance

2.2.1. No interim analysis planned

2.2.2. Guidelines for stopping a trial early

Injections and treatment will be immediately discontinued (but follow up will continue) in any subject who:

- Experiences a worsening local wheal or flare reaction at the injection site exceeding 5 cm.
- Experiences a serious adverse reaction or an allergic event suggestive of systemic hypersensitivity requiring more than local therapy (e.g. requiring steroids, bronchodilators, or adrenaline).
- Becomes pregnant

Data from these subjects will be included in the final analysis

If any individual in the study experiences a SUSAR, further dosing of all subjects at all sites will be suspended pending review by the Data Safety Monitoring Board (DSMB) and discussion with the CI and Sponsor. Advice will be sought from the DSMB regarding re-starting the study.

A substantial amendment application will be submitted to the Regulatory Agencies to resume the trial.

2.3. Timing of final analysis

Final statistical analysis should commence after the Statistical Analysis Plan (SAP) has been finalised and the study data locked. Prior to database lock, the SAP must be finalised and signed off by CI and Trial Statistician. All outcomes will be analysed collectively at the end of the trial and completed within the timeframe agreed by the study team.

Table 1: Schedule of study visits

	Screening			Treatment							Follow up			
Visit number	-2	-1	Pre V1	1	1b	1C	2	3	3b	3C	4	Pre V5	5	6
Weeks	These visits can be combined. Treatment must start within 3 months of screening commencing		A minimum of 72 hours prior to visit 1	0	1 day post visit1	3 to 5 days post visit 1	4	8	1 day post visit3	3 to 5 days post visit 3	9	A minimum of 72 hours prior to visit 5	14	20
Days				0			28	56			63		98	140 (85 days post final dose)
Informed consent	X													
Study drug administration				X			X	X						
Follow up telephone call 24 hours post IMP				X			X	X					X	
Physical Exam & ECG	X			X			X	X					X	
*Serum for AAbs and immune markers				X				X					X	
DRB1*0401 genotype	X													
MMTT				X									X	
Urine c-peptide post meal		X		X									X	
72 hour continuous glucose monitoring			Attach CGM	X								Attach CGM	X	
Serum for Cystatin C				X							X		X	X
Urinalysis for blood, protein, and beta-2 microglobulin		X		X			X				X		X	X
Serum and urine (morning) sample to measure gold concentrations				X pre dose	X*				X*		X	X	X	X
T cell (immune biomarker) assays (blood)				X				X			X		X	
*LN aspiration 0/3-5d				X		X		X		X				
*Safety blood samples		X		X			X				X		X	X
HbA1c measurement		X		X			X				X		X	
Vital signs	X	X		X			X	X			X		X	X
Adverse Event assessment/con meds		X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test		X		X			X	X					X	X
Record of insulin use	X			X			X	X					X	
*Blood glucose profile/insulin usage				X			X	X					X	X
Assessment of glycaemic control/review blood sugar recordings				X			X	X					X	
HFS survey				X									X	
ADDQoL				X									X	
DTSQs				X									X	
DTSQc													X	

3. Study Population

8 subjects with a diagnosis of Type 1 diabetes will be included in the study. Autoimmune diabetes will be confirmed by measurement of islet cell autoantibodies. Patients will be required to possess the HLA-DR4 (B1*0401) genotype. Eligibility of patients will be reviewed according to the inclusion and exclusion criteria listed below.

3.1. Inclusion Criteria

- Clinical diagnosis of type 1 diabetes for > 3 months (dated from the first insulin injection).
- Commenced on insulin treatment within 1 month of diagnosis.
- Age 16 to 40 years
- 2 hour post-meal UCPCR > 0.53 nmol/mmol on at least one occasion (maximum 3 tests on different days)
- Possession of 0401 allele at the HLA-DRB1 gene locus
- Use of highly effective birth control methods with a failure rate of less than 1% per year when used consistently and correctly (for details, please refer to study protocol)
- Written and witnessed informed consent to participate.

3.2. Exclusion Criteria

- HbA1c > 86mmol/L (10%).
- Females who are pregnant, breast-feeding or not using adequate forms of contraception.
- Previous diagnosis of renal disease including glomerulonephritis or nephropathy.
- Raised serum creatinine or abnormal urine albumin/creatinine ratio (ACR) (values above the laboratory reference range). If the initial ACR is raised, this should be repeated on two further occasions as first morning samples. The subject can be included if both of these samples are negative (within the reference range).
- Use of immunosuppressive or immunomodulatory therapies, including systemic steroids within 1 month prior to receiving the IMP and any monoclonal antibody therapy given for any indication. Note that previous exposure to proinsulin peptide C19-A3 in a clinical trial is an exclusion criterion.
- Use of cannabis within one month prior to trial entry.
- Use of any hypoglycaemia agents other than insulin, for more than 6 weeks, at any time prior to trial entry.
- Use of inhaled insulin.
- Known alcohol abuse, drug abuse, HIV or hepatitis.
- Allergies to drug components or any excipients.
- Any other medical condition which, in the opinion of investigators, could affect the safety of the subject's participation or outcomes of the study, including immunocompromised states and autoimmune conditions.

- Subjects should not have had immunisations (flu and others) for 1 month prior to trial entry and should not receive any during their time in the trial – see section 5.6.
- Recent subject's involvement in other research studies which, in the opinion of investigators, may adversely affect the safety of the subjects or the results of the study.
- Abnormal ECG findings.

Number of patients screened and participated in the trial will be reported. Reasons for patients screened but not enrolled in the trial will be summarised. Baseline characteristics including but not restricted to age, gender, ethnicity, BMI, age of diagnosis and duration of diabetes of the enrolled and excluded patients will be summarised. The numeric variables will be summarised by mean and standard deviation. Both counts and percentages will be presented for the categorical variables. Baseline characteristics of the enrolled and the screened but not enrolled will be presented as set out in dummy table (i) in Appendix 1

3.3. Analysis populations

- Intention to treat population
  All patients enrolled in the study
- Per protocol population
  Patients receiving all three injections

4. Statistical Principle

The sample has not been powered to detect significant differences before and after treatments. Data will be analysed by simple descriptive statistics.

All patients enrolled will be followed up and included unless they withdrew from the study before the administration of the first dose. An intention to treat analysis will be carried out. Per protocol analyses may also be carried out alongside the intention to treat analysis if necessary.

Adherence to the intervention will be assessed by missed dose (protocol violation) and delayed / missed followup visits (protocol deviation).

4.1. Protocol violations

Patients will be allowed 28 days +/- 3 days between treatments. Where a dosing visit is > 3 days late it should be documented as a protocol violation.

Where the interval between 2 doses is > 42 days, the dose will be considered to have been missed. If a treatment is missed the subject will continue in follow-up but an additional subject will be recruited, so that a total of 8 subjects will receive all 3 doses.

Where the interval between two doses is between 32 to 42 days, this would be documented as protocol violations.

4.2. Protocol deviations

Patients will be allowed to attend for follow up visit 4 (week 9) +/- 1 day of schedule, visit 5 (week 14), +/- 1 week of visit schedule and visit 6 (week 20) must be a minimum of 85 days post final dose/+2 weeks. Any visits outside of this guidance will be considered a protocol deviation.

All protocol violations and deviations as well as number of patients involved will be enumerated at the end of the study. A patient will be defined as being compliant with the protocol if s/he has taken all the three injections on target (within window) dates. Adherence to intervention will be enumerated according to treatment/followup on target (within window), protocol violations/deviations and missed dose/followup across the study schedule as set out in dummy table (ii) in Appendix 1.

Data from all enrolled patient will be included in analysis of safety as specified in section 5.1.1. and 5.3. Metabolic and immunological outcomes of patients who have missed or delayed dose/followup will also be explored with analysis specified in section 5.1.2

5. Analysis strategy

5.1. Analysis of outcomes

5.1.1. Primary outcome

Assessment of the safety of C19-A3 GNP administration in terms of adverse events at the dose used is the primary outcome. This includes general safety concerns, induction of hypersensitivity and exacerbation of β-cell specific autoimmunity with accelerated β-cell loss. All enrolled patients will be included in the following analysis.

General Safety

To address general safety concerns at screening and 0, 4, 8 and 14 weeks a physical examination will be conducted. A review of AEs will be performed at all visits according to seriousness, causality and expectedness. Types of AEs, body systems involved and outcomes of the AE will be catagorised and analysed by incidence per person dose used. All AEs will be collated

Hypersensitivity

Patients will be observed for local and systemic reactions post injection. Number of local reactions will be analysed by incidence per person dose used, size of the erythema note and time taken for erythema note size to be reduced to < 1 cm will be analysed by mean and standard deviation. Systemic reactions will be analysed by incidence per person dose used. Therapies used and outcome will be counted and reported.

Exacerbation of β-cell specific autoimmunity with accelerated β-cell loss

Differences between week 0 and 14 will be calculated for each patient and summarised by mean and standard deviations for the following parameters:

- Measurement of islet cell autoantibodies (against insulin, GAD-65, IA-2 and ZnT8)
- Measurement of pro-inflammatory β-cell specific T cell responses (analytes to be defined)

5.1.2. Secondary outcomes

Differences in the parameters set below will be calculated for each patient and summarised by mean and standard deviations. Potential differences between patients receiving treatment within and outside treatment schedule will also be explored, if required.

- T cell responses to C19-A3 GNP as determined by changes from baseline of interferon gamma and IL-10 ELISPOT responses to this peptide in blood following treatment at weeks 0, 9 and 14.
- T cell responses to C19-A3 GNP as determined by changes from baseline of interferon gamma and IL-10 ELISPOT responses to this peptide in

draining axillary lymph node before treatment and following the last treatment administration (four aspirations: before and after visit 1 and visit 3)

- Changes in additional immunological biomarkers (e.g. flow cytometry profiles, T reg assays, autoantibodies, beta cell and T cell free DNA markers) from baseline at week 0, 9 and 14.
- Effects on residual insulin requirement and c-peptide secretion at week 14 as compared to baseline as assessed by secreted C peptide AUC after a mixed meal tolerance test and a stimulated urine c-peptide test.
- Effects on glycaemic control assessed by blood sugar profiles and HbA1c at week 14 as compared to baseline
- Scores on quality of life and diabetes self-management (week 0 and week 14).

5.2. Handling of missing data

Every effort will be made by the study team to capture full data. In case of any missing data, three methods will be used to impute the missing data points: worst case imputation, last observation carried forward and, mean value of the non-missing cases. Sensitivity analysis will be carried out with the three imputed data sets and the complete case data set.

5.3. Summary of safety data

All enrolled patients will be included in the safety analysis. Details for analysis of AEs and hypersensitivity already reported in 5.1.1.

5.3.1. Safety blood test

In addition, results of blood tests at screening, weeks 4, 9, 14 & 20 will be reviewed to identify any abnormalities in the full blood count; urea, electrolytes and creatinine; liver function tests; (prothrombin time, total bilirubin, total protein, albumin, AST (SGOT), SGPT (ALT), alkaline phosphatase; thyroid stimulating hormone; immunoglobulins (G, A, M); calcium; magnesium, phosphate, lipid profile (total cholesterol, LDL, HDL, triglyceride). Types and frequency of abnormal blood test results per patient over time will be enumerated.

5.3.2 Safety urinalysis

Urinalysis for pH blood, protein, urine beta-2-microglobulin and albumin/creatinine ratio will be done at screening and visits 1, 2, 4, 5 and 6 and urine for cystatin-c will be collected at visits 1, 4, 5 & 6. A urine pregnancy test will be completed on females only, at all trial visits. Frequency of abnormal urine PH blood and protein per patient over time and positive pregnancy tests will be enumerated.

In addition to the final report, interim safety reports will be circulated to DSMB for review after the sentinel patient and the 4th patient receiving his/her first injection.

5.3.3 Gold concentration

At visits 1, 1b, 3b, 4, 5 and 6 blood and urine samples will be taken for gold concentrations to enable assessment of gold excretion. Laboratory measurements for these will be performed at the LGC laboratory, Cambridgeshire. Concentration of gold for each patient over time will be analysed by half-life of elimination at the end of the study.

The major organ of accumulation and excretion of the gold nanoparticles is the kidney. Safety reports on markers of kidney function in blood (levels of electrolytes, urea, creatinine, calcium, phosphate, and magnesium) and urine (blood in urine, protein in urine, cystatin-c and beta-2-microglobulin) have already been covered in 5.3.1 and 5.3.2.

5.3.4 Pregnancy outcome

If a patient or their partner got pregnant during the study or within 85 days of receiving the final injection, they will be followed up until child birth. Pregnancy outcomes will be enumerated at the end of the follow up. A final safety report will be provided to DSMB for review.

6. Presentation of Data for Analysis

- The trial manager working in conjunction with the data manager and consult the trial statistician if required should ensure all data presented to the trial statistician are clean and validated.
- The study database should be frozen by the data manager or the person responsible for the data.
- The statistician/designee should work on a copy of the study database that has been downloaded for them by the data manager.
- Any amendments to the study database should be documented and a new version supplied to the statistician.
- Presentation of data depends on purpose of the analysis and the method of data capture. For detailed specification of data for analysis, please see Appendix 2.

7. Statistical Software

Analysis will be carried out using SPSS version 22 or later.

8. Amendments

Amendments of the SAP will be circulated to DSMB for review and ratification.

Appendix 1

Table (i) Baseline Characteristics of the enrolled and not enrolled

Mean (±SD) or *N* (%)	Enrolled	Screened but not enrolled
Age (years) Range		
Female (%)		
Ethnicity White (%) Mixed race(%) Asian (%) Black (%) Chinese (%) Others (%)		
Body mass index		
Age of diagnosis		
Duration of diabetes		

Table (ii) Adherence to intervention

N (%)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
On target (Within window)						
Protocol Violations / Deviations						
Missed dose/ followup						

Appendix 2

The following tables summarised formats of data files required for the current study according to the purpose of analysis (and method of data capture where appropriate)

- Eligibility assessment

  Table 1 shows the headings of the data file for eligibility assessment

Screening No	Centre No	Satisfy screening criteria (Y/N)	If N, additional report[1]

[1]List all reasons of failure for each screened subject as captured in CRF in a separate spreadsheet.

- Description of baseline characteristics (demographical and clinical data)

  Table 2 shows the headings of the data file to describe baseline characteristics with demographic and clinical data

Screening No	Centre No	DOB	Sex	Date of assessment at Visit -2	Date of diagnosis	Date of 1st insulin

Cont'd

Ongoing med plm (Y/N)	If Y, additional report[1]	Ever smoked (Y/N)	If Y, duration of smoking	Current smoker (Y/N)	If Y, additional report[2]

Cont'd

Former smoker (Y/N)	If Y, additional report[3]	Recreational drug use (Y/N)	Consume alcohol (Y/N)	If Y, separate list[4]

Cont'd

Type 1 insulin used (Y/N)	If Y, total daily dose of Type 1	Type 2 insulin used (Y/N)	If Y, total daily dose of Type 2	Type 3 insulin used (Y/N)	If Y, total daily dose of Type 3	CSII used (Y/N)[5]

Cont'd

Sbp at Visit -2	Dbp at Visit -2	Heart rate Visit -2	T°C Visit -2	Ht	Wt at Visit -2	ECG performed (Y/N)	If N, separate list[6]	If Y, (normal / abnormal, not sig/ abnormal and sig)

Cont'd

Phy exam at Visit -2 (Y/N)	If N, list reason[7]	If Y, Any system abnormal ? (Y/N)	If abnormal, separate list[8]	Abnormality, clinically sig? (Y/N)	If Y, separate list[9]

Cont'd

Date of assessment at Visit -1	Sbp at Visit -1	Dbp at Visit -1	Heart rate Visit -1	T°C Visit -1	Wt at Visit -1

[1]List ongoing medical problems for each subject in a separate spreadsheet. [2]List smoking details as captured in CRF for each current smoker in a separate spreadsheet. [3]List smoking details as captured in CRF for each former smoker in a separate spreadsheet. [4]List alcohol consumption details as captured in CRF for each drinker. [5]List CSII details as captured in CRF for each CRF user. [6]List reason for not performing ECG for each subject in a separate spreadsheet. [7] List reasons for not completing physical examination for each non-completer in a separate spreadsheet. [8]List all information about the abnormalities for each subject as captured in CRF in a separate spreadsheet. [9]List all clinically significant abnormalities as captured in CRF in a separate spreadsheet.

- Description of baseline characteristics (laboratory assays)

Table 3 shows the headings of the data file to describe baseline characteristics with laboratory assays

Screening No	Centre No	Visit No	HbA1c at Visit -1	Serum Aabs	DRB1*0401	A*02	Pregnancy test (Y/N)

Cont'd

Urine C peptide	Albumin/creatinine ratio	Beta 2 microglobulin	Insulin cell free DNA

KCL

- Table 4 shows the headings of the data file for assessing adherence to study intervention

Screening No	Centre No	Visit 1 date*	Visit 2 date*	Visit 3 date*	Visit 4 date	Visit 5 date	Visit 6 date

*Please flag up withdrawn patients or patients with treatment received date different from the visit date

- Endpoints Analysis (clinical observations)

Table 5 shows the headings of the data file for endpoints assessment with clinical observations

Screening No	Centre No	Visit No	Rx No	Sbp (pre-Rx)	Dbp (pre-Rx)	Heart rate (pre-Rx)	T°C (pre-Rx)	Wt

Cont'd

ECG performed (Y/N)	If N, separate list[1]	If Y, (normal / abnormal, not sig/ abnormal and sig)	Phy exam performed (Y/N)	If N, list reason[2]	If Y, Any system abnormal ? (Y/N)	If abnormal, separate list[3]

Cont'd

Abnormality, clinically sig? (Y/N)	If Y, separate list[4]	Capillary blood glucose	Taking insulin? (Y/N)	If Y, TDD Day 1	If Y, TDD Day 2	If Y, TDD Day 3

Cont'd

Any change in insulin (Y/N)	IF Y, separate list[5]	Concomitant medication? (Y/N)	If Y, separate list[6]	Injection per scheduled (Y/N)	If N, delayed /missed	Reason as per CRF

Cont'd

Batch no	Correct drug (Y/N)	Correct patient (Y/N)	Within expiry date (Y/N)	Adm intradermally (Y/N)	Date adm	Time adm

Cont'd

Site (L/R)	Pain (needle)	Pain (vaccine)	Skin Reaction (Y/N)	IF Y, separate list[7]	Post-injection vital signs abnormal?	If abnormal, separate list[8]

[1]List reason for not performing ECG by subject and visit no in a separate spreadsheet. [2]List reasons for not completing physical examination by subject and visit no in a separate spreadsheet. [3]List all information about the abnormalities as captured in CRF by patient and visit no in a separate spreadsheet. [4]List all clinically significant abnormalities as captured in CRF by patient and visit no in a separate spreadsheet. [5]List changes in insulin as captured in the change of insulin log by patient in a separate spreadsheet. [6]List concomitant medications as captured in concomitant medication log by patient in a separate spreadsheet. [7]List reaction details as captured in post injection skin reaction log by patient and visit no in a separate spreadsheet. [8]List whether the observation was judged to be clinically significant and whether it is an AE.

- Endpoints Analysis (laboratory assays)

  Table 6 shows the headings of the data file for endpoints assessment with laboratory assays

  For each of the analytes: eg GAD65

Screening No	Centre No	Treatment No	Visit -2	Visit -1

Cont'd

Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6

For a full list of all the analytes, please refer to the Data Transferral Plan in Section 10 of the Data Management Plan

- Questionnaire Data

  Table 7 shows the headings of the data file for endpoints assessment with questionnaire data

  At Visit 1

Screening No	Centre No	Visit No	Rx No	HFS items*	ADDQoL items*	DTSQs items*

Multiple columns

At Visit 5

Screening No	Centre No	Visit No	Rx No	HFS items*	ADDQoL items*	DTSQs items*	DTSQc items*

Multiple columns

- Safety data

  Table 8 shows the headings of the data file for AE assessment

Screening No	Centre No	Rx No	AE no	Start date	End date	Serious? 1=Y / 2=N	If Y, print full SAE form

Cont'd

Severity 0=no AE, 1=mild, 2=moderate,3=severe	Study drug action 0=none 1=temp interrupt 2=permanently withdraw	Outcome 0=resolved 1=resolved with sequelea 2=not resolved	Relationship to study drug 0=not related 1=unlikely 2=possibly 3=probably 4=very likely

Table 9 shows the headings of the data file for safety blood test reporting

Screening No	Centre No	Visit No	Hb (Males) Normal (Y/N)	Hb (Females) Normal (Y/N)	Hct Normal (Y/N)	MCV Normal (Y/N)

Cont'd

MCH Normal (Y/N)	WBC Normal (Y/N)	RBC Normal (Y/N)	Platelets Normal (Y/N)	Neutrophils Normal (Y/N)	Basophils Normal (Y/N)	Eosinophils Normal (Y/N)

Cont'd

Prothrombin Time Normal (Y/N)	HbA1c Normal (Y/N)	Glucose Normal (Y/N)	Creatinine Normal (Y/N)	Potassium Normal (Y/N)	Urea Normal (Y/N)	Sodium Normal (Y/N)

Cont'd

Calcium Normal (Y/N)	Phosphate Normal (Y/N)	Magnesium Normal (Y/N)	Alkaline Phosphatase Normal (Y/N)	Total Protein Normal (Y/N)	Albumin Normal (Y/N)	Total Bilirubin Normal (Y/N)

Cont'd

AST (SGOT) Normal (Y/N)	ALT (SGPT) Normal (Y/N)	TSH Normal (Y/N)	Total Cholesterol Normal (Y/N)	HDLC Normal (Y/N)	LDLC Normal (Y/N)	Triglycerides Normal (Y/N)

Cont'd

IgA Normal (Y/N)	IgM Normal (Y/N)	IgG Normal (Y/N)

List details as captured in CRF for parameter not within the normal range for the patient, visit and parameter concerned

Table 10 shows the headings of the data file for safety urine test reporting

Screening No	Centre No	Visit No	PH Blood Normal (Y/N)*	Protein Normal (Y/N)*	Pregnancy test (+ve, -ve)**

* List details as captured in CRF for parameter not within the normal range for the patient, visit and parameter concerned

**Please flag patients with positive pregnancy test