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.

Data Review Report

EudraCT no: 2015-003934-28
Sponsor no: SPON1455-15

This page was intentionally left blank

Abbreviations and Definitions

AE	Adverse Events
C19-A3 GNP	Investigative medicine product comprising proinsulin peptide C19-A3 linked to Gold Nanoparticles
CI	Chief Investigator
CRF	Case Report Forms
CTIMP	Clinical Trial of an Investigational Medicinal Product
DSMB	Data Safety Monitoring Board
IMP	Investigational Medicinal Product
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
UCPCR	Urine C-peptide creatinine ratio (a measure of endogenous insulin production)

1. Summary of trial recruitment

As at 05/10/2018[1], 109 potential participants were referred, 6 have been enrolled and received the first injection. 103 were excluded according to at least one of the following criteria as set in Table 1. Details of participant recruitment were set in the CONSORT diagram in Appendix 1.

Table 1 Number of potential participants excluded according to the study inclusion/exclusion criteria-

	Ref to Protocol	Criteria	No
1	6.2.1	Clinical diagnosis of type 1 diabetes equal to or less than 3 months (dated from the first insulin injection).	**11**
2	6.2.2	Not commencing on insulin treatment within 1 month of diagnosis.	**0**
3	6.2.3	Age under 16 or over 40 years.	**6**
4	6.2.4	3 x Post meal UCPCR smaller than or equal to 0.2 nmol/mmol	**6**
5	6.2.5	Do not possession of 0401 allele at the HLA-DRB1 gene locus.	**12**
6	6.2.6	Inadequate contraception	**0**
7	6.3.1	HbA1c > 86 mmol/L (10%)	**0**
8	6.3.2	Females who are pregnant or breast-feeding	**0**
9	6.3.3	Previous diagnosis of renal disease including glomerulonephritis or nephropathy.	**0**
10	6.3.4	Raised serum creatinine or abnormal ACR	**0**
11	6.3.5	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.	**0**
12	6.3.6	Use of cannabis within one month prior to trial entry	**1**
13	6.3.7	Use of any hypoglycaemia agents other than insulin, for more than 6 weeks, at any time prior to trial entry.	**4**
14	6.3.8	Use of inhaled insulin.	**0**
15	6.3.9	Known alcohol abuse, drug abuse, HIV or hepatitis.	**0**
16	6.3.10	Allergies to drug components or any excipients.	**0**
17	6.3.11	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.	**3***
18	6.3.12	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 unless clinically essential.	**0**
19	6.3.13	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.	**0**
20	6.3.14	Abnormal ECG findings	**0**
21	6.2.7	Patient refuse consent	**37**

***** Participants trying to get pregnant

** Not included in table: Not eligible (other reasons=6, no response=23)

[1] The Trial Management Board decided to discontinue recruitment on 03/10/2018

2. Baseline characteristics of the enrolled participant

There were six participants enrolled (Cardiff n=5 participants, Linkoping n=1 participant). Data are available for all the six participants. One participant (114) withdrew after receiving the first injection due to competing time commitments but agreed to continue to provide information to the study team. Table 2 summarised the demographic characteristics of the enrolled participants.

Table 2 Baseline characteristics of enrolled participants

Mean (±SD) or *N* (%)	Enrolled (n=6)
Age at consent (years)	28.46 (8.06)
Range	18.29 – 37.34
Female (%)	33.3%
Ethnicity	
White (%)	100
Mixed race(%)	
Asian (%)	
Black (%)	
Chinese (%)	
Others (%)	
Age at diagnosis (years)	26.16 (9.45)
Duration of diabetes (months)	27.00 (31.47)

3. Delivery of the Investigational Medicinal Product (IMP)

Six participants received at least one IMP per schedule. One participant (114) withdrew after Injection 1. Another participant (122) did not receive Injection 2 or 3 because of Trial Management Board decision to discontinue treatment. A total of 14 doses of the right product confirmed to be within expiry date were administered to the right participants. There was one observed leakage during dosing.

Details for delivery of the IMP is set in Table 3.

Table 3 Delivery of the IMP

	Injection 1	Injection 2	Injection 3
No of participants expected to be injected	6	5	5
Injection per schedule[1]	6	4[2]	4[2]
Right drug confirmed	6	4	4
Confirmed to be within expiry date when administered	6	4	4
Any leakage observed	0	1	0
If yes Extent of leakage_1(complete/partial)	--	complete	--
Any leakage observed in the 1st repeated attempt (Y/N)	--	N	--
If yes Extent of leakage_2 (complete/partial)	--	--	--
Any leakage observed in the 2nd repeated attempt (Y/N)	--	--	--
If yes Extent of leakage_3 (complete/partial)	--	--	--
Pain assessment 0-100 mm Mean (±SD) [range] Due to needle insertion (mm) Due to vaccine (mm)	 7.5 (9.87) [0 – 20] 14.50 (10.44) [1 – 30]	 0 (0) [0 – 0] 10.75 (19.52) [0 – 40]	 3.50(4.51) [0 – 10] 3.75 (4.35) [0 – 10]

[1]Treatment visits 1, 2 and 3 should be every 28 days +/- 3 days

[2]One patient withdrew, the second patient had injection withheld

4. Immediate observations (up to 6 hours)

Every participant was kept under observations for 6 hours for their first injection. For subsequent injections, all participants were observed for 1 hour. Immediate observations post injection are summarised in Table 4.

Table 4 Immediate post injection observations (up to 6 hours)

	Injection 1 (n=6)	Injection 2 (n=4)	Injection 3 (n=4)
Participants with skin reactions	5	4	3
Largest erythema area size in mm^2	260 - 2000	225 - 1080	240 - 400
Largest erythema area > 10*10 mm^2?	5	4	3
If Y, time taken for node size to reduce to <10*10mm^2(in mins)	10 – 120	10 - 45	5 - 45
Participants with skin reaction reported in AE log			
Vital signs / observations (range) No of observations per participant	11[1]	4	4
Diastolic blood pressure (mmHg)	49 - 105	61 - 84	60 – 79
Systolic blood pressure (mmHg)	100 - 151	95 - 127	100 - 126
Highest heart Rate (BPM)	58 - 101	58 - 89	56 - 106
Highest temperature (°C)	36.3 - 37.4	36.7 - 37.4	36.1 - 37.3
No of participants with Vital signs / observations abnormal?	2	0	0
If any abnormal sign, clinically significant?	0	--	--
Adverse event?	--	--	--

[1] One participant has a 45-minute post injection observations missed. The other 5 participants had 11 observations made.

All erythemas > 10*10 mm^2 disappeared after 2 hours but some skin discoloration remained at the injection sites for all the participants. After assessment by the site PI, these skin reactions were reported as Adverse Events.

5. 24 Hour Report

The study team aimed to follow up all participants within 24 hours of their injections. Findings from the 24 hour contact is summarised in Table 5.

Table 5 24 hour report

	Injection 1 n=6	Injection 2 n=4	Injection 3 n=4
Any contact failure for the post dose call/visit? If yes, reasons for contact failure	0	1 Participant uncontactable by phone. Unable to chase due to bank holiday. Emailed participant and invited to contact staff or diabetes research nurse if any problem	0
AEs reported	1*	1**	0
SAEs reported	0	0	0
New concomitant medications reported since screening / previous dose	1	0	0

*After receiving the 1st injection, one participant (122) reported an AE.
** Participant (201) made comments related to redness at the injection site.

6. Safety blood tests

General laboratory assessments were to be carried out for all participants at either screening or Visit 1, then at Visit 2, Visit 4, Visit 5, Visit 6 and Visit 7. For participants 114, 119, 122 and 201 general laboratory assessment were carried out at both screening and Visit 1.

This section summarised findings from safety blood tests, except for HbA1c and blood glucose assessments. Findings from HbA1c and blood glucose assessments will be shown at Section 7.1.(Fig 3 and Fig 4)

Majority of the results of the laboratory assessments for most participants were within normal range. A few assessments for some participants were outside normal range at some visits, but only two outside range results were clinically significant. (Table 6) None of them were associated with any adverse event.

Table 6 Summary of laboratory assessments across visits

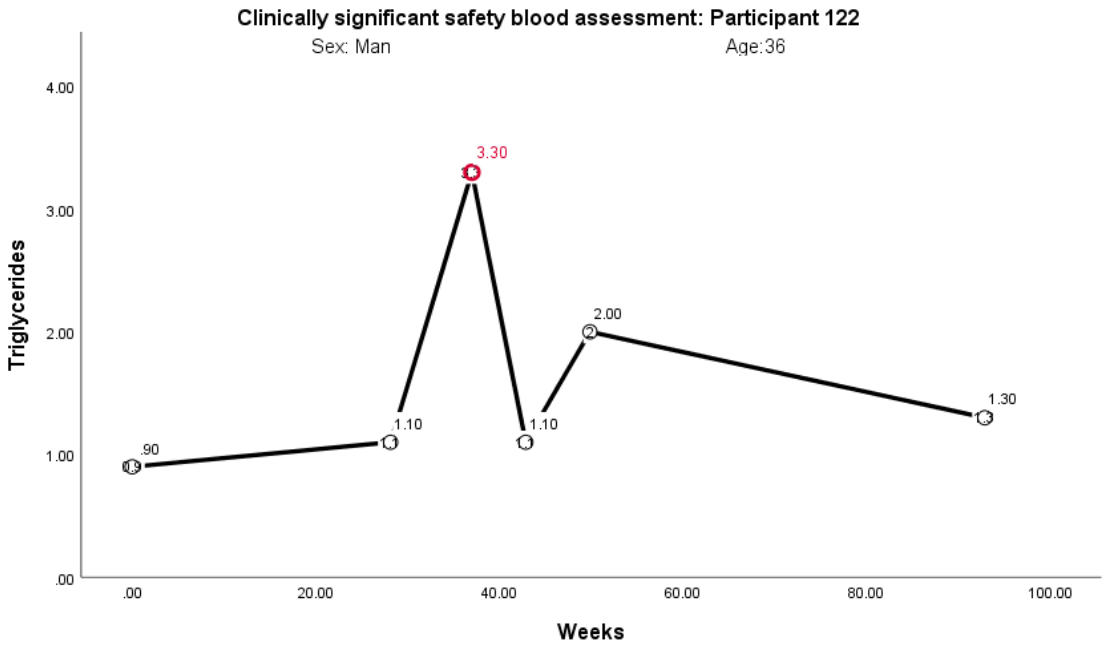
Total No of participants assessed	**S (n=6)**	**V1 (n=6)**	**V2 (n=5)**	**V4 (n=5)**	**V5 (n=5)**	**V6 (n=5)**	**V7 (n=5)**
Haematology							
Hb	0 | 0 (6)	0 | 0 (4)	0 | 0 (4)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)
Hct	0 | 0 (6)	0 | 0 (4)	0 | 0 (4)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)
MCV	0 | 0 (6)	0 | 0 (4)	0 | 0 (4)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)
MCH	0 | 0 (6)	0 | 0 (4)	1 | 0 (4)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)
WBC	1 | 0 (6)	1 | 0 (4)	1 | 0 (4)	1 | 0 (5)	1 | 0 (5)	0 | 0 (5)	0 | 0 (5)
RBC	0 | 0 (6)	1 | 0 (4)	0 | 0 (4)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)
Platelets	0 | 0 (6)	1 | 0 (4)	0 | 0 (4)	0 | 0 (5)	1 | 0 (5)	0 | 0 (5)	0 | 0 (5)
Neutrophils	0 | 0 (6)	0 | 0 (4)	0 | 0 (4)	1 | 0 (5)	1 | 0 (5)	0 | 0 (5)	0 | 0 (5)
Basophils	0 | 0 (6)	0 | 0 (4)	0 | 0 (4)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)
Eosinophils	0 | 0 (6)	0 | 0 (4)	1 | 0 (4)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)	1 | 0 (5)
Creatinine	0 | 0 (6)	0 | 0 (4)	0 | 0 (4)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)

Kidney Function							
Potassium	0 | 0 (6)	1 | 0 (4)	0 | 0 (4)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)
Urea	0 | 0 (6)	0 | 0 (4)	0 | 0 (4)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)
Liver Function							
Alkaline Phosphatase	0 | 0 (6)	0 | 0 (4)	0 | 0 (4)	0 | 0 (5)	1 | 0 (5)	0 | 0 (5)	1 | 0 (5)
Total Protein	0 | 0 (6)	0 | 0 (4)	0 | 0 (4)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)
Albumin	0 | 0 (6)	2 | 0 (4)	0 | 0 (4)	0 | 0 (5)	1 | 0 (5)	0 | 0 (5)	0 | 0 (5)
Total Bilirubin	2 | 0 (6)	2 | 0 (4)	1 | 0 (4)	3 | 0 (5)	1 | 0 (5)	1 | 0 (5)	0 | 0 (5)
AST (SGOT)	0 | 0 (6)	1 | 0 (4)	0 | 0 (4)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)
ALT(SGPT)	0 | 0 (6)	1 | 0 (4)	0 | 0 (4)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)
General Biochemistry							
Sodium	0 | 0 (6)	0 | 0 (4)	0 | 0 (4)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)
Calcium	0 | 0 (6)	0 | 0 (4)	0 | 0 (4)	0 | 0 (5)	1 | 0 (5)	0 | 0 (5)	0 | 0 (5)
Phosphate	0 | 0 (6)	1 | 0 (4)	0 | 0 (4)	1 | 0 (5)	0 | 0 (5)	1 | 0 (5)	0 | 0 (5)
Magnesium	0 | 0 (6)	0 | 0 (4)	0 | 0 (4)	0 | 0 (5)	0 | 0 (5)	2 | 0 (5)	0 | 0 (5)
TSH	0 | 0 (6)	1 | 0 (4)	1 | 0 (4)	0 | 0 (5)	1 | 1 (5)	1 | 0 (5)	0 | 0 (5)
Total Cholesterol	0 | 0 (6)	0 | 0 (4)	0 | 0 (4)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)
HDLC	1 | 0 (6)	1 | 0 (4)	0 | 0 (4)	0 | 0 (5)	1 | 0 (5)	0 | 0 (5)	0 | 0 (5)
LDLC	0 | 0 (6)	0 | 0 (4)	0 | 0 (4)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)
Triglycerides	1 | 0 (6)	0 | 0 (4)	0 | 0 (4)	1 | 1 (5)	0 | 0 (5)	3 | 0 (5)	0 | 0 (5)
Immunoglobulins							
IgA	2 | 0 (6)	2 | 0 (4)	0 | 0 (4)	1 | 0 (5)	1 | 0 (5)	1 | 0 (5)	1 | 0 (5)
IgM	0 | 0 (6)	0 | 0 (4)	0 | 0 (4)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)
IgG	0 | 0 (6)	0 | 0 (4)	0 | 0 (4)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)	0 | 0 (5)

Number on the top left of each cell is the number of participants with test values outside range. Number on the top right of each cell is the number of participants with outside range test values assessed by local PI as clinically significant. Number in brackets is the number of participants with a test value recorded in the database.

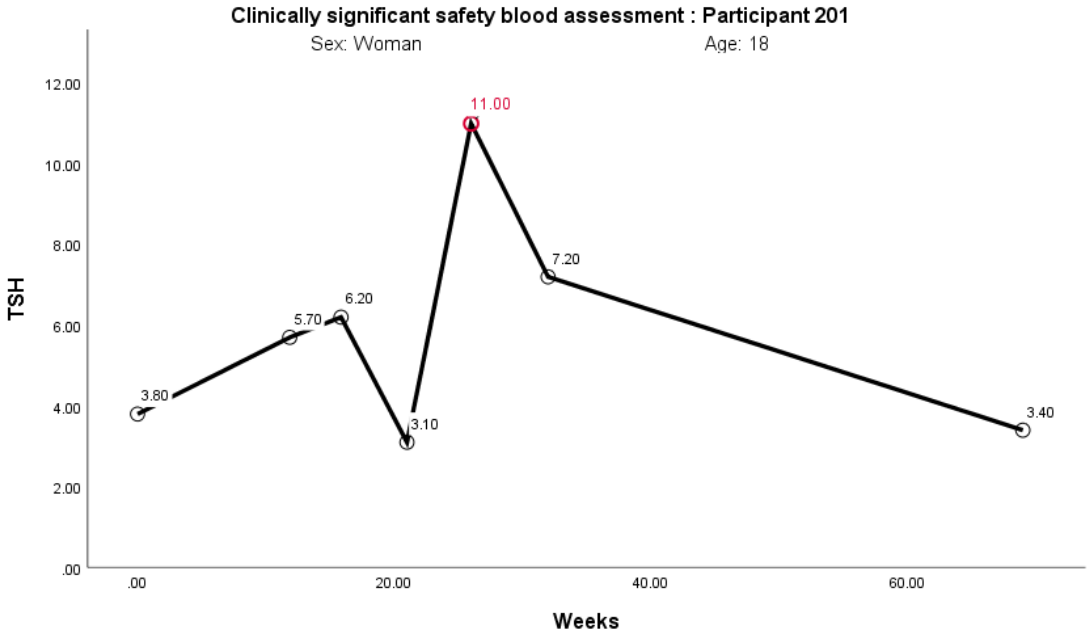
Participant 122 had an out-of-range triglycerides level which was clinically significant at Visit 4. Details of the triglycerides level across visits for this participant are shown in the following chart (Fig 1).

Fig 1



Participant 201 had an out-of-range TSH level which was clinically significant at Visit 5. Details of the TSH level across visits for this participant are shown in the following chart (Fig2).

Fig 2



7. Information on severity of disease

Information for severity of disease were collected with different means. These included :

- HbA1c and serum glucose assessed by general laboratory assessments
- Use of insulin
- Continuous Glucose Monitoring (CGM)
- Serum glucose assessed and serum C peptide level by Mixed Meal Tolerance Test (MMTT)
- Assessment of c peptide level in urine
- Assessment of autoantibodies
- Assessment of kidney health
- Symptomatic hypoglycaemia from Symptomatic Hypoglycaemia Log.

7.1 Glycaemic status from general laboratory assessments

HbA1c and serum glucose level were assessed at either screening or Visit 1, then at Visit 2, Visit 4, Visit 5, Visit 6 and Visit 7.

Fig 3

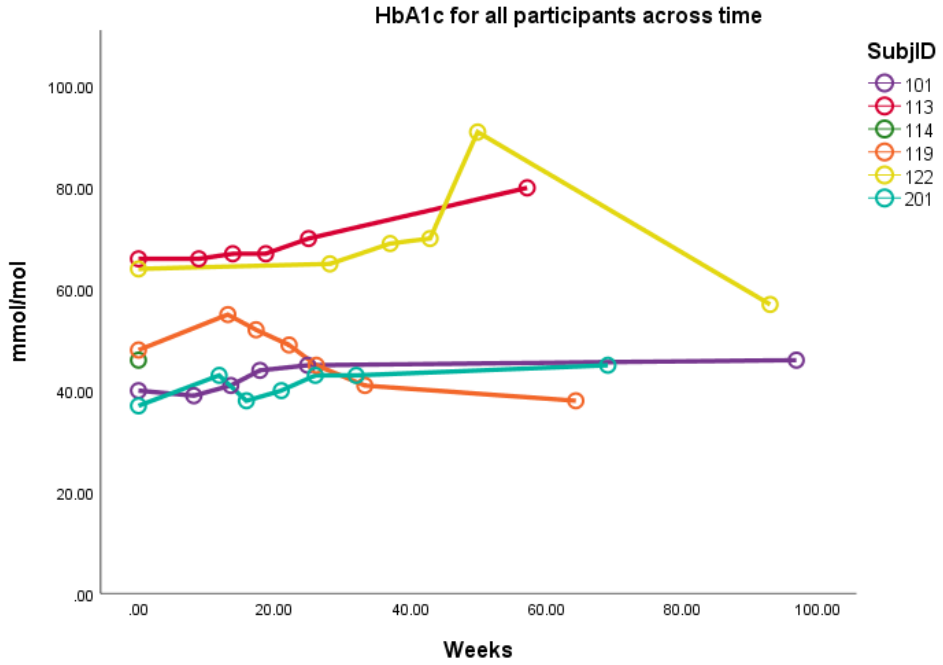
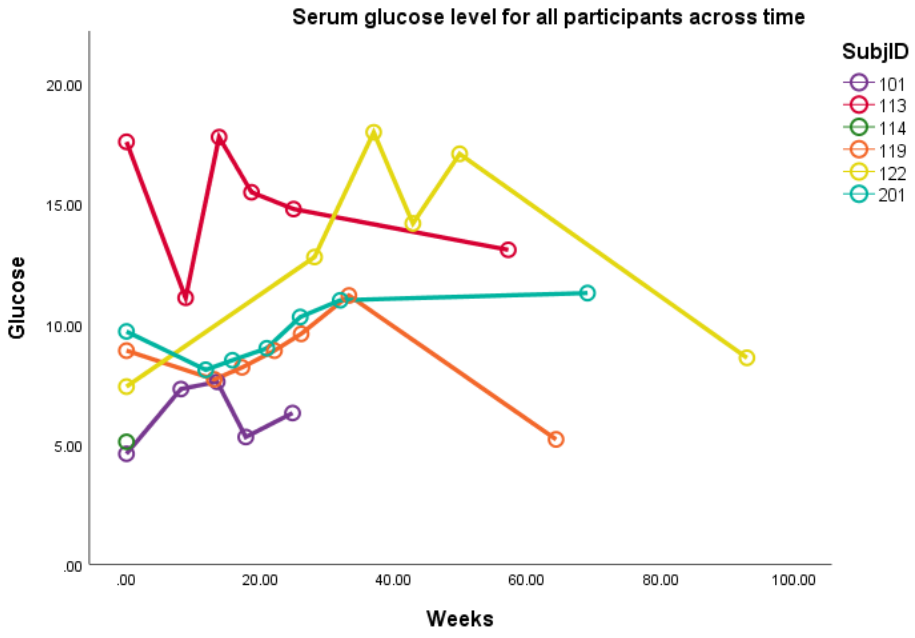


Fig 4



Participant 101 missed blood glucose assessment at Visit 7

7.2 Use of insulin

Information on insulin use was collected over three days before Visit 1, 2, 3, 5, 6 and 7. The following chart showed the average daily dose of the different types of insulin used by participants, adjusted by their body weight.

Fig 5a

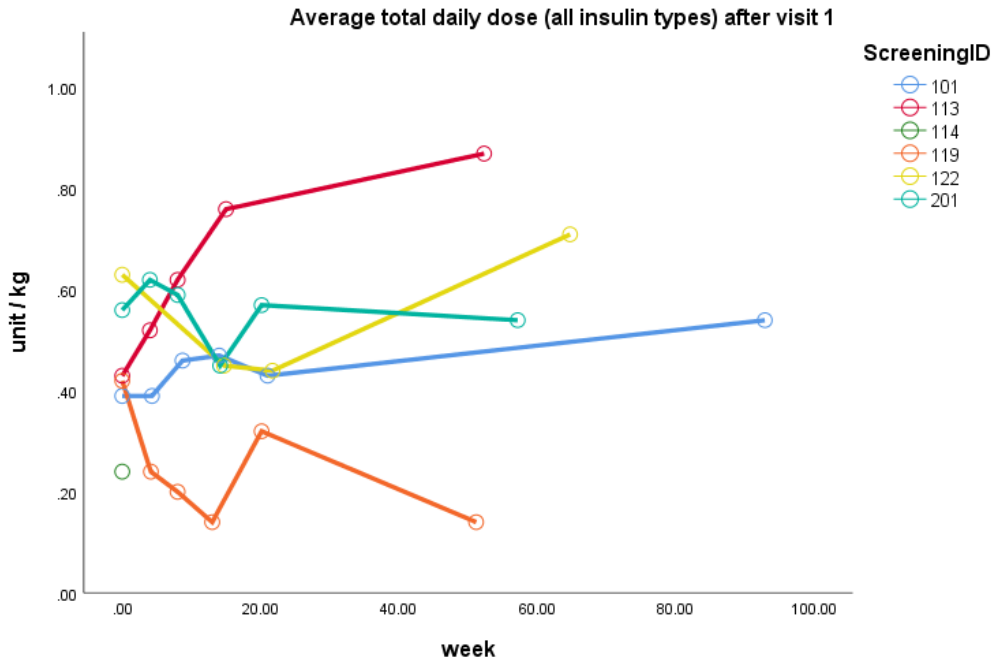
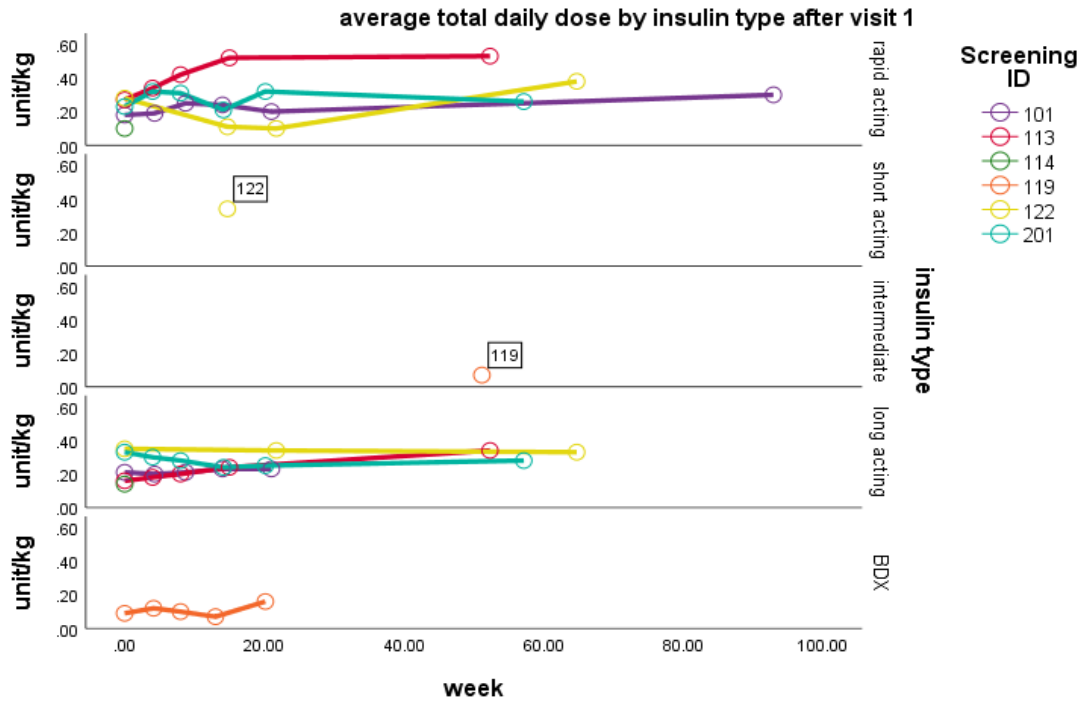


Fig 5b



7.3 Continuous Glucose Monitoring (CGM)

Continuous Glucose Monitoring (CGM) for at least 72 hours before Visit 1, Visit 5 and Visit 7 were performed for each participant. Findings from each participant were presented in the following figures (Fig 6a and 6b) and tables (Table 7a, Table 7b, Table 7c, Table 7d, Table 7e and Table 7f).

Fig 6a

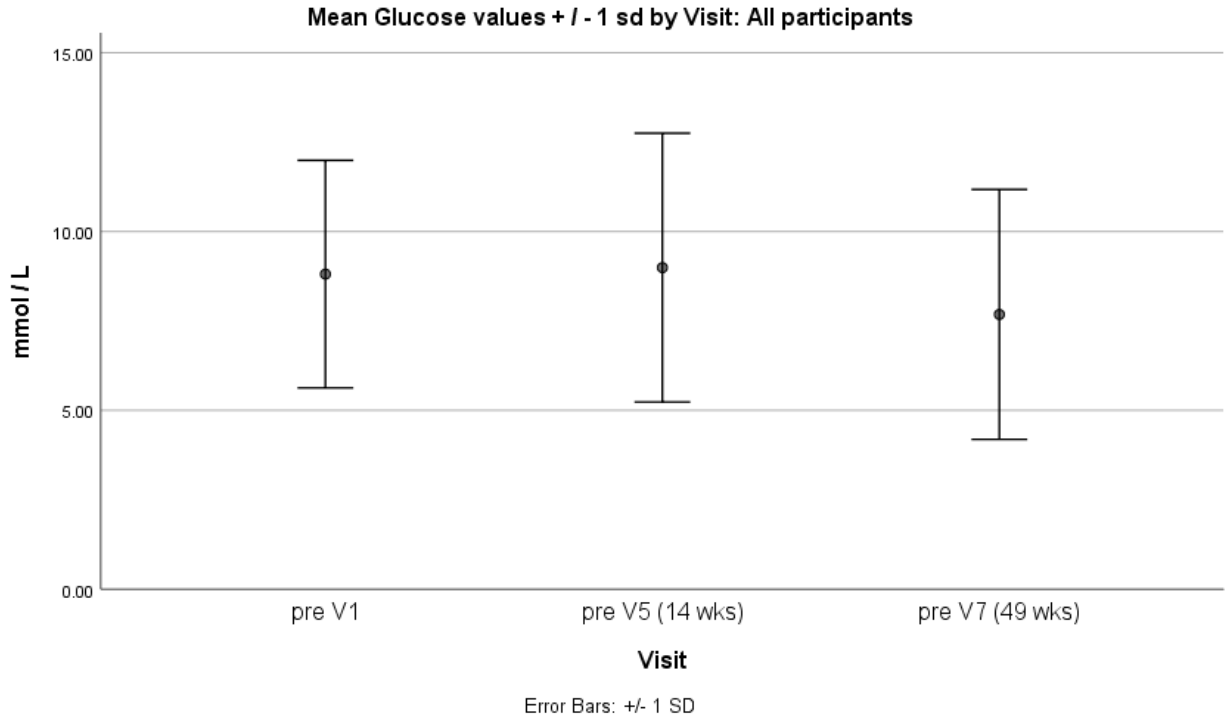


Fig 6b

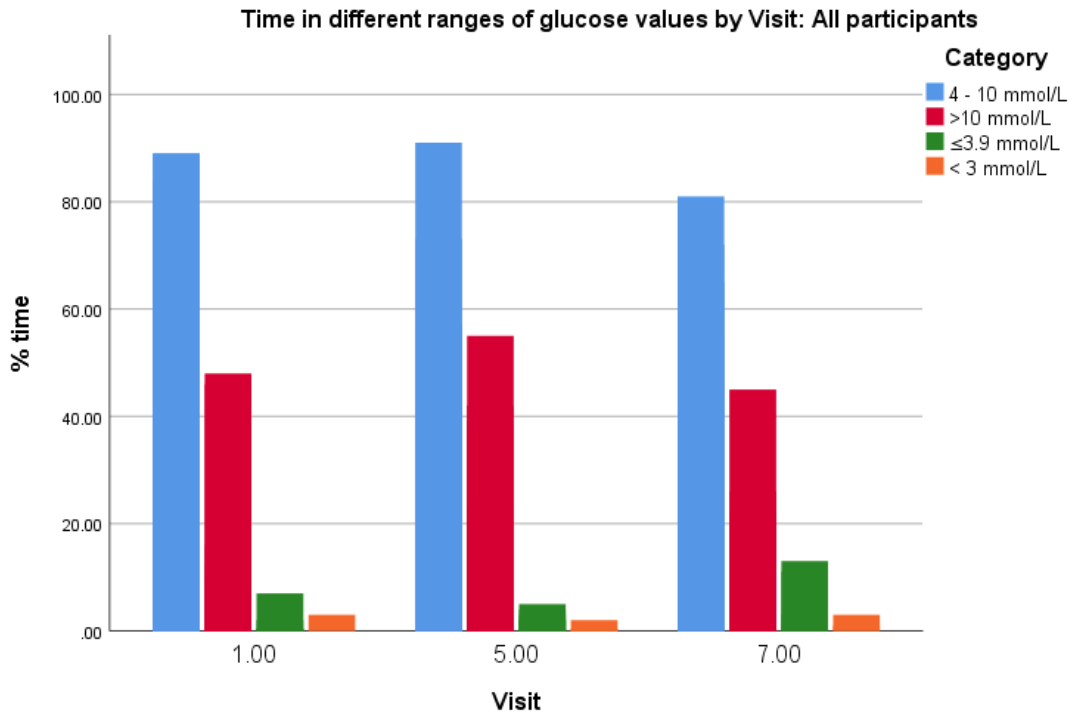


Table 7a Ranges of blood glucose level pre-Visit 1, 4 and 7 – Participant 101

Participant 101	Visit 1	Visit 5	Visit 7
Hours monitored	111.83	116.49	88.75
Min –Max	3.22 - 11.93	2.77 - 15.76	2.22 – 21.31
Mean (sd)	7.07 (1.86)	7.94 (2.88)	7.54 (3.84)
% of time in the range of 4 - 10 mmol/L	89%	73%	65%
% of time >10 mmol/L	9%	23%	22%
% of time less than or equal to 3.9	2%	4%	13%
% of time less than 3	0%	0.2%	3%

Table 7b Ranges of blood glucose level pre-Visit 1, 4 and 7 – Participant 113

Participant 113	Visit 1	Visit 5	Visit 7
Hours monitored	112.41	265.49	93.74
Min –Max	4.72 – 20.09	2.22 – 21.20	3.61 – 22.09
Mean (sd)	9.90 (2.91)	10.91 (3.78)	10.18 (3.66)
% of time in the range of 4 - 10 mmol/L	52%	43%	55%
% of time >10 mmol/L	48%	55%	45%
% of time less than or equal to 3.9	0%	2%	1%
% of time less than 3	0%	0.3%	0%

Table 7c Ranges of blood glucose level pre-Visit 1, 4 and 7 – Participant 114

Participant 114	Visit 1	Visit 5	Visit 7
Hours monitored	121.74	--patient withdrew	
Min –Max	2.22 – 21.20	--	
Mean (sd)	10.60 (3.57)	--	
% of time in the range of 4 - 10 mmol/L	89.%		
% of time >10 mmol/L	10%		
% of time less than or equal to 3.9	0.4%	--	
% of time less than 3	0.1%	--	

Participant 114 withdrew after Visit 1, CGM findings of Visit 1 was displayed

Table 7d Ranges of blood glucose level pre-Visit 1, 4 and 7 – Participant 119

Participant 119	Visit 1	Visit 5	Visit 7
Hours monitored	114.66	165.58	157.58
Min –Max	5.16 – 13.49	3.00 - 11.76	2.66 – 12.43
Mean (sd)	8.56 (1.64)	6.01 (1.75)	6.14 (2.11)
% of time in the range of 4 - 10 mmol/L	84%	91%	81%
% of time >10 mmol/L	16%	4%	8%
% of time less than or equal to 3.9	0%	5%	11%
% of time less than 3	0%	0%	1%

Table 7e Ranges of blood glucose level pre-Visit 1, 4 and 7 – Participant 122

Participant 122	Visit 1	Visit 5	Visit 7
Hours monitored	156.67	157.75	Not available
Min –Max	3.27 – 23.00	2.55 – 23.00	
Mean (sd)	10.85 (4.10)	9.59 (3.65)	
% of time in the range of 4 - 10 mmol/L	54%	56%	
% of time >10 mmol/L	46%	42%	
% of time less than or equal to 3.9	0.4%	2%	
% of time less than 3	0%	0.3%	

Table 7f Ranges of blood glucose level pre-Visit 1, 4 and 7 – Participant 201

Participant 201	Visit 1	Visit 5	Visit 7
Hours monitored	136.75	109.25--	114
Min –Max	2.00 – 16.32	--2.00 – 20.75	3.20 – 21.80
Mean (sd)	7.09 (2.60)	--9.40 (3.59)	8.52 (3.25)
% of time in the range of 4 - 10 mmol/L	--81%	-57%-	72%
% of time >10 mmol/L	--12%	--39%	26%
% of time less than or equal to 3.9	--7%	--3%	3%
% of time less than 3	--3%	--2%	0%

7.4 Mixed Meal Tolerance Test (MMTT)

As at the data cut-off point on 1 May 2020, MMTT blood glucose and serum c peptide data were available for all participants at Visit 1, Visit 5 and V7, except for 4 of the 6 participants (101, 113, 119, 201). Participant 114 withdrew after Visit 1. Samples for participant 122 at Visit 7 were stored and would be analysed when laboratory facilities re-open after the COVID-19 pandemic lockdown ease off. Findings from the MMTT are presented in the following charts (Fig 7a, 7b and Fig 8a, 8b).

Fig 7a

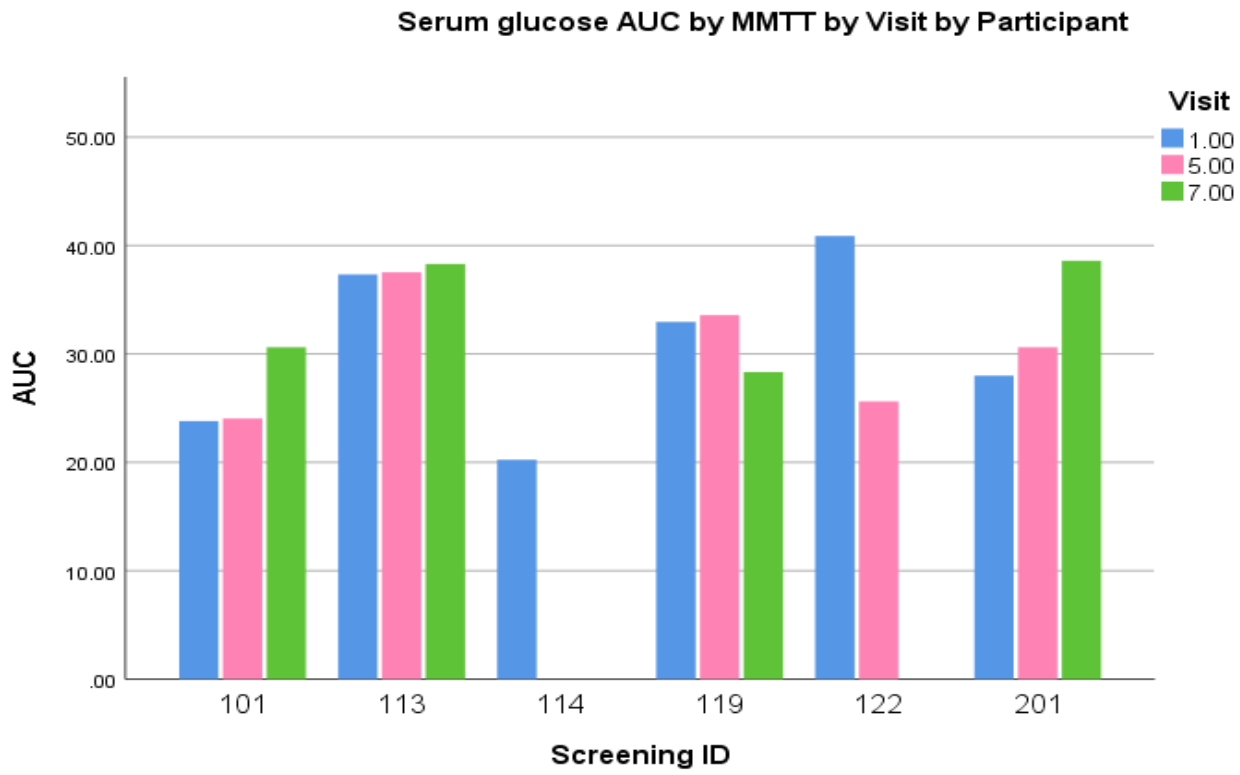
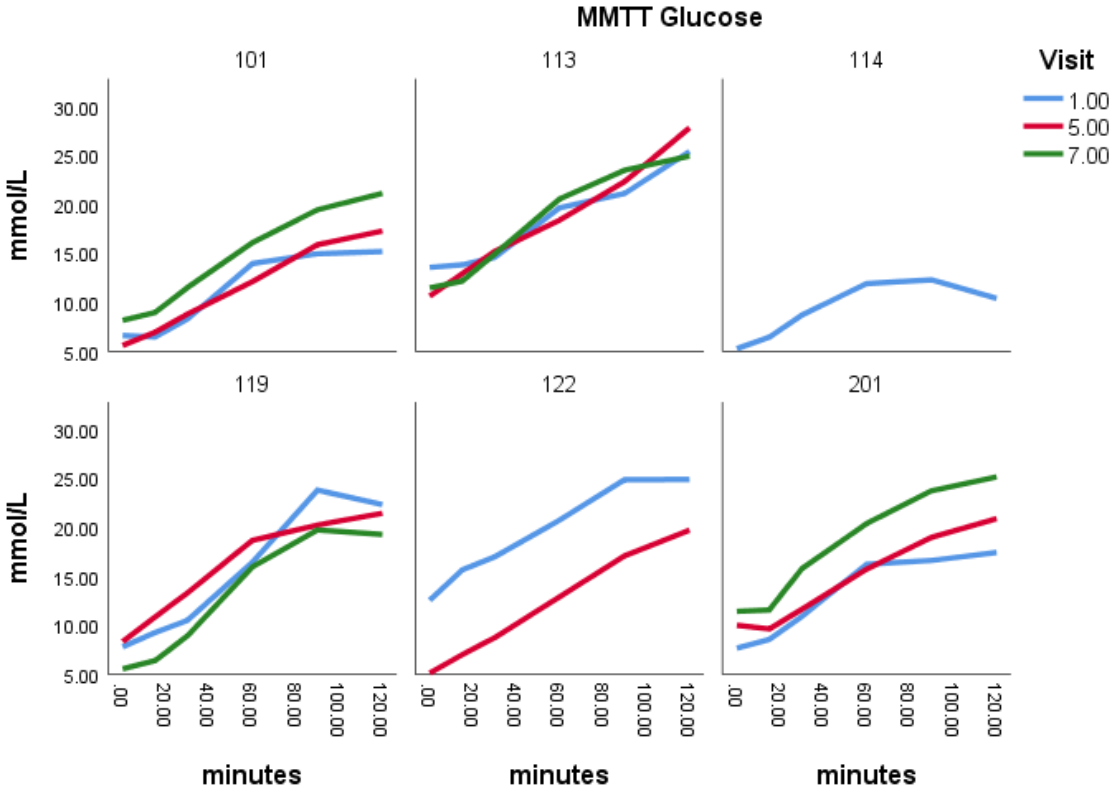


Fig 7b



Screening ID	Visit 1	Visit 5	Visit 7
Glucose AUC (0-120 min)			
101	23.80	24.05	30.61
113	37.32	37.53	38.29
114	20.23	Participant withdrew	
119	32.95	33.58	28.33
201	27.99	30.62	38.60
122	40.88	26.62	*

*To be analysed when laboratory re-opens

Fig 8a

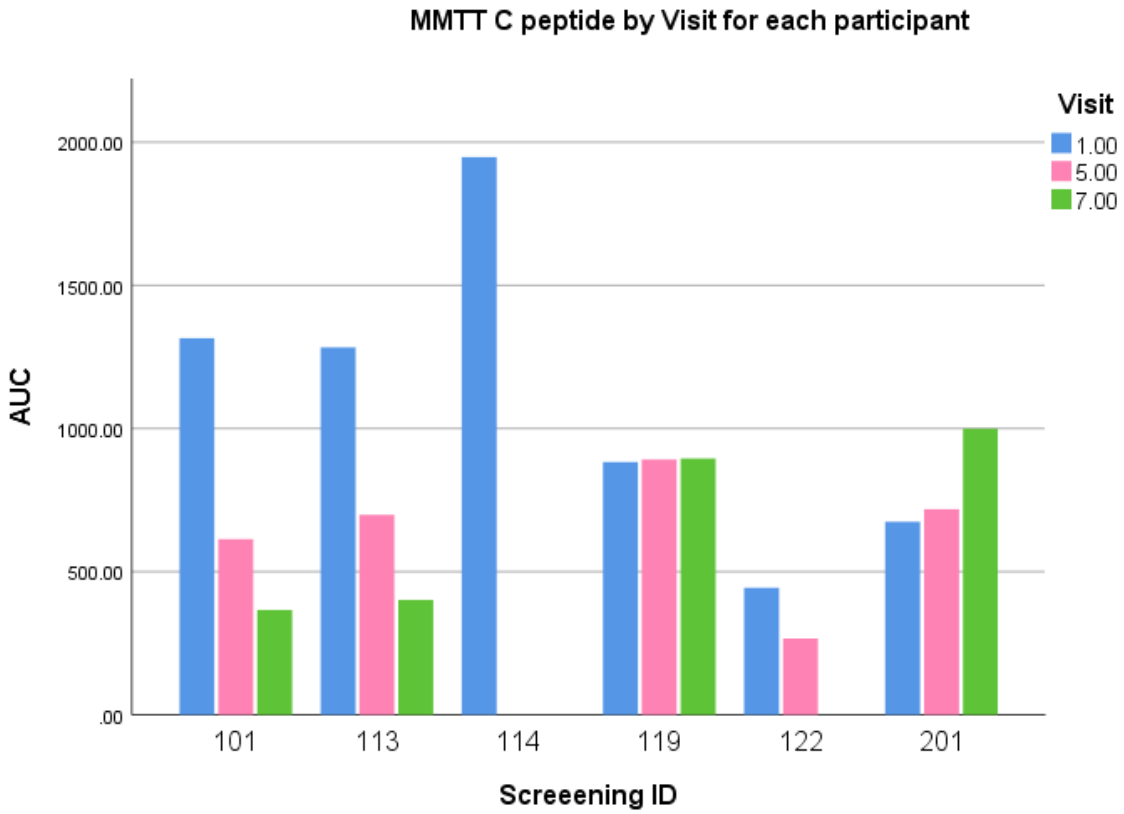
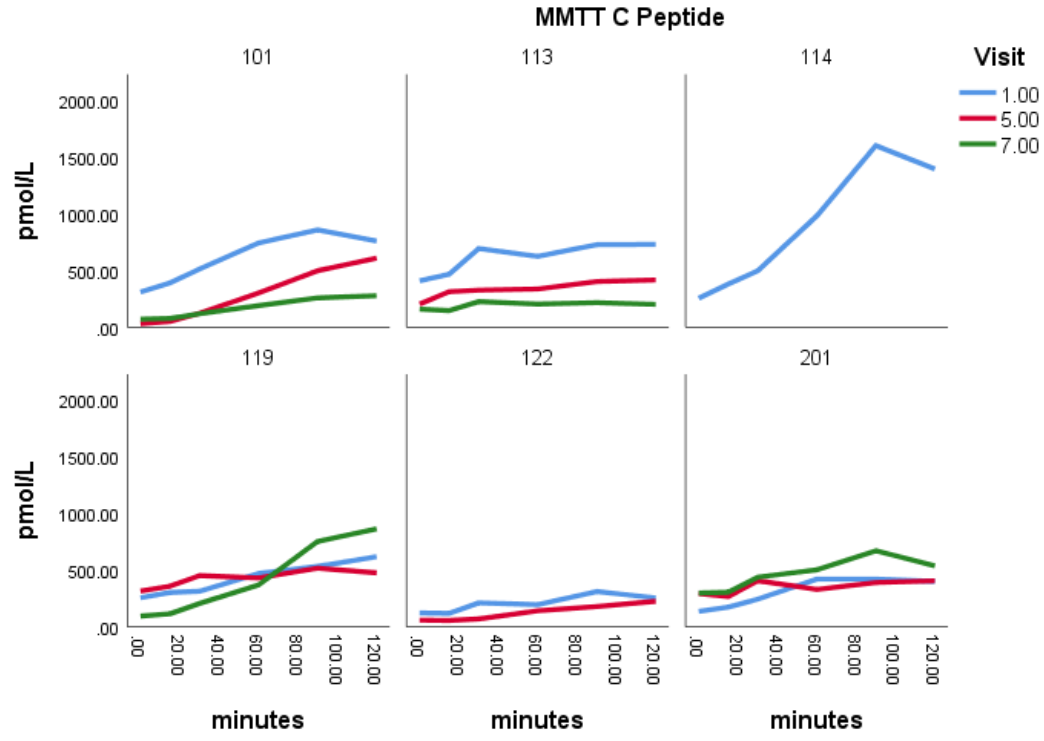

MMTT C peptide by Visit for each participant
Visit
1.00
5.00
7.00
AUC
2000.00
1500.00
1000.00
500.00
.00
101
113
114
119
122
201
Screeening ID

Fig 8b


MMTT C Peptide
Visit
1.00
5.00
7.00
101
113
114
119
122
201
pmol/L
2000.00
1500.00
1000.00
500.00
.00
.00
20.00
40.00
60.00
80.00
100.00
120.00
minutes

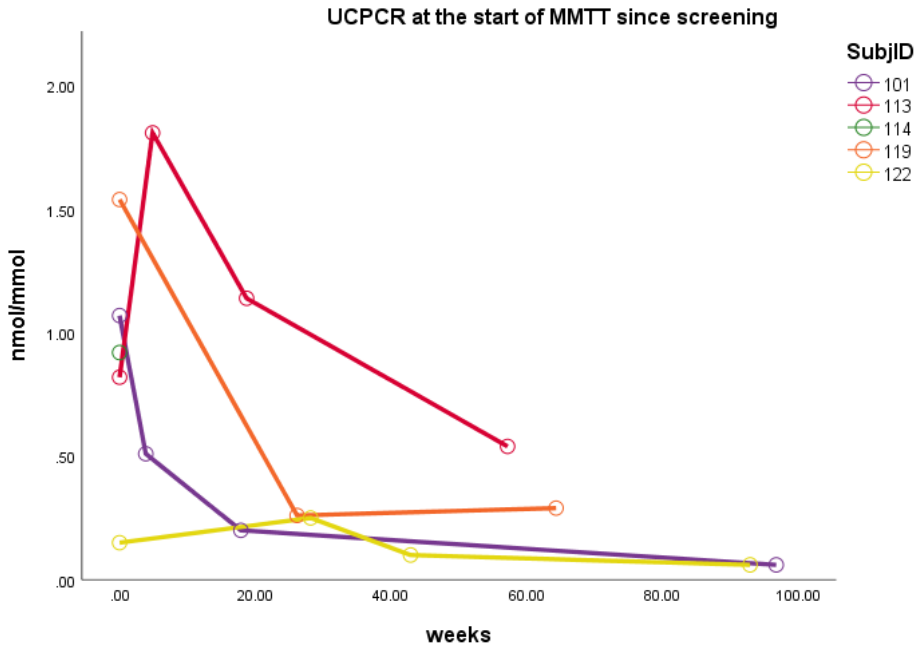
Screening ID	Visit 1	Visit 5	Visit 7
C Peptide AUC (0-120 min)			
101	1315.38	613.63	365.63
113	1283.38	698.50	401.00
114	1947.38	Participant withdrew	
119	882.38	891.88	895.50
201	674.38	718.25	999.13
122	443.50	266.63	*

*To be analysed when laboratory re-opens

7.5 UCPCR

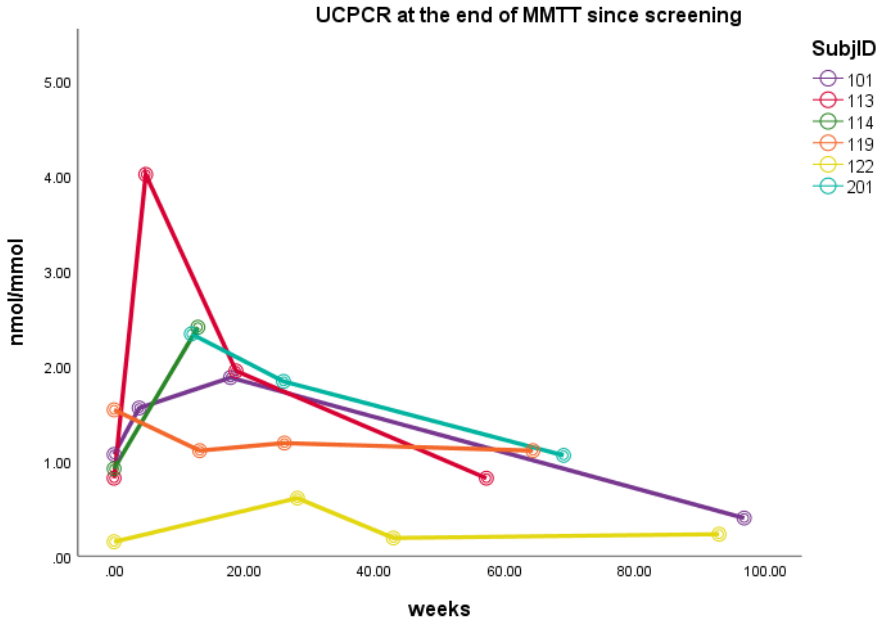
UCPCR samples were collected at the beginning and end of MMTT at Visit 1, 5 and 7 were collected for each participant. At screening, only a random UCPCR sample was available for each participant. UCPCR findings were shown in Fig 9 and Fig 10.

Fig 9



No Visit 1 UCPCR sample was collected for participant 119 at the beginning of MMTT.
No UCPCR samples were collected for participant201 at the start of MMTT throughout the trial.

Fig 10



No UCPCR samples was collected for participant201 at screening.

7.6 Autoantibodies

Samples for measuring GAD, IA2 and ZnT8 autoantibodies were collected for every participant at screening, Visit 1,4,5,6 and 7. Levels of these antibodies were assessed at screening, Visit 1,4,5 and 6. Visit 7 samples for all participants and samples for participant 122 after screening would be analysed when laboratory facilities re-open after the COVID-19 pandemic lockdown ease off. Findings were shown in Fig 11, 12 and 13.

Fig 11

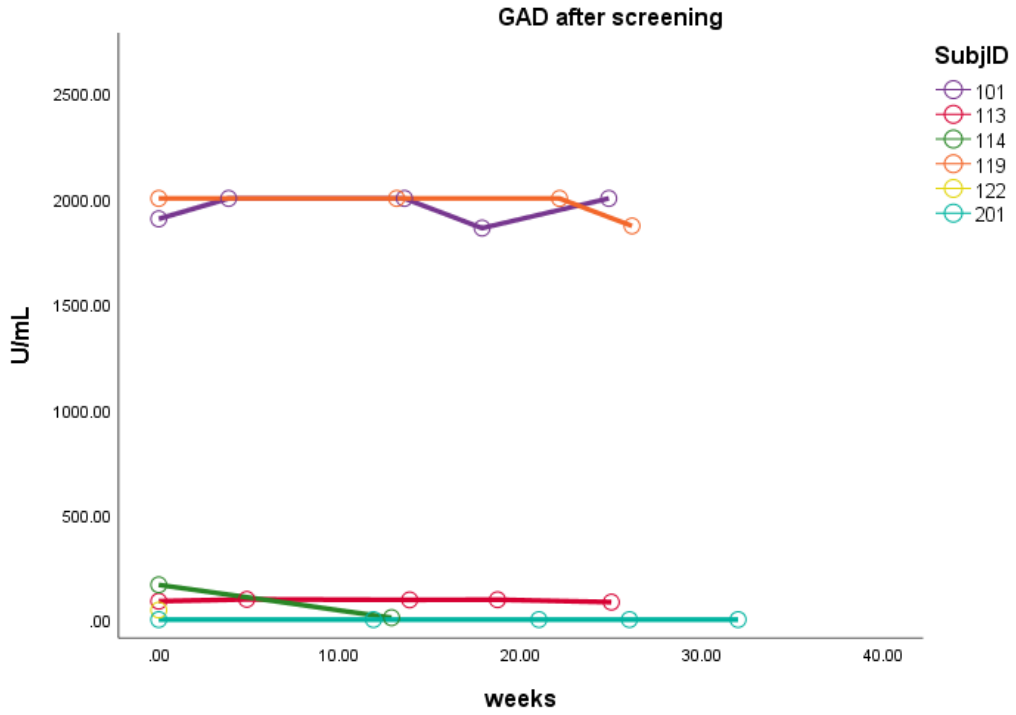


Fig 12

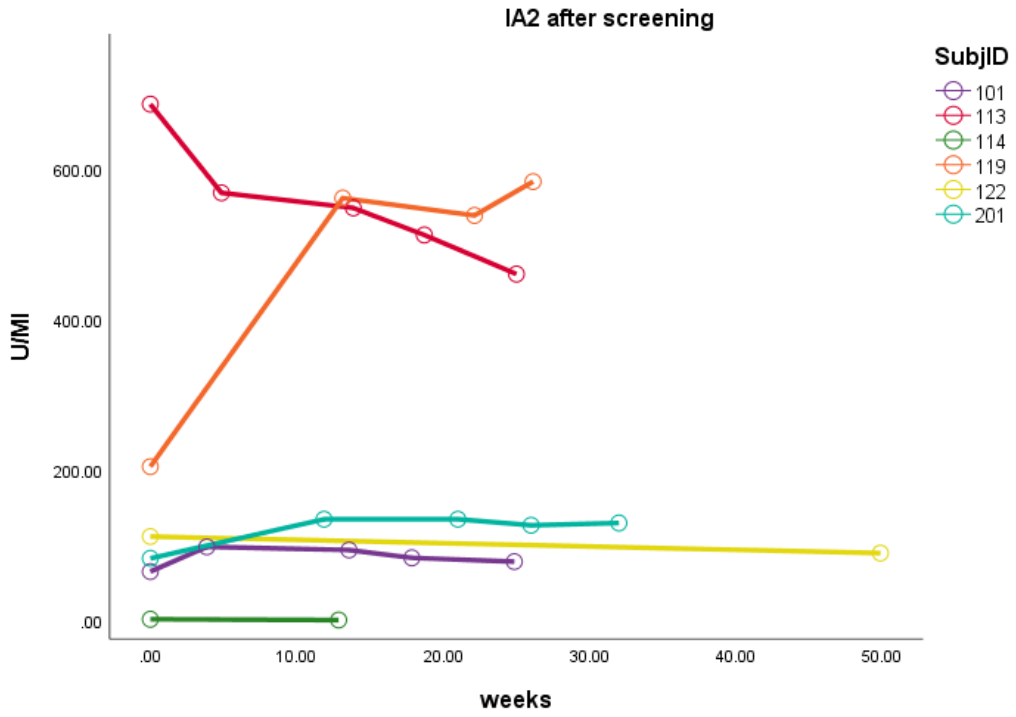
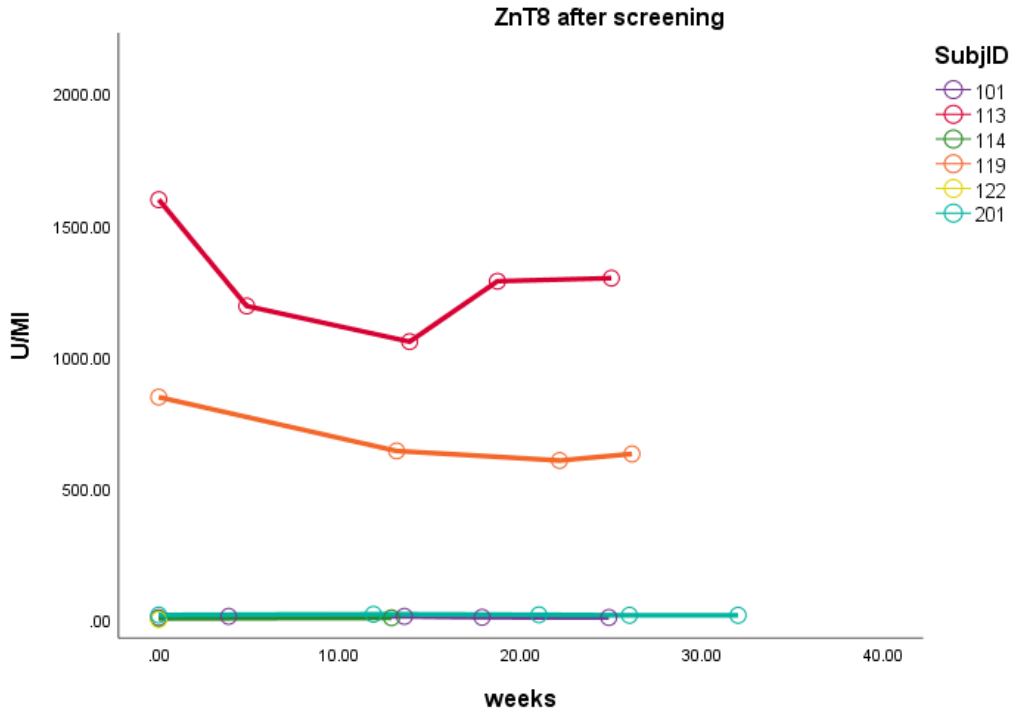

IA2 after screening
SubjID
101
113
114
119
122
201
U/Ml
600.00
400.00
200.00
.00
.00
10.00
20.00
30.00
40.00
50.00
weeks

Fig 13


ZnT8 after screening
SubjID
101
113
114
119
122
201
U/Ml
2000.00
1500.00
1000.00
500.00
.00
.00
10.00
20.00
30.00
40.00
weeks

7.7 Assessment of kidney health

Samples for measuring urine albumin to creatinine ratio (ACR), urine Cystatin C and serum Cystatin C were collected for every participant at Visit 1,2,5,6 and 7. Findings were shown in Fig 14, 15 and 16.

Fig 14

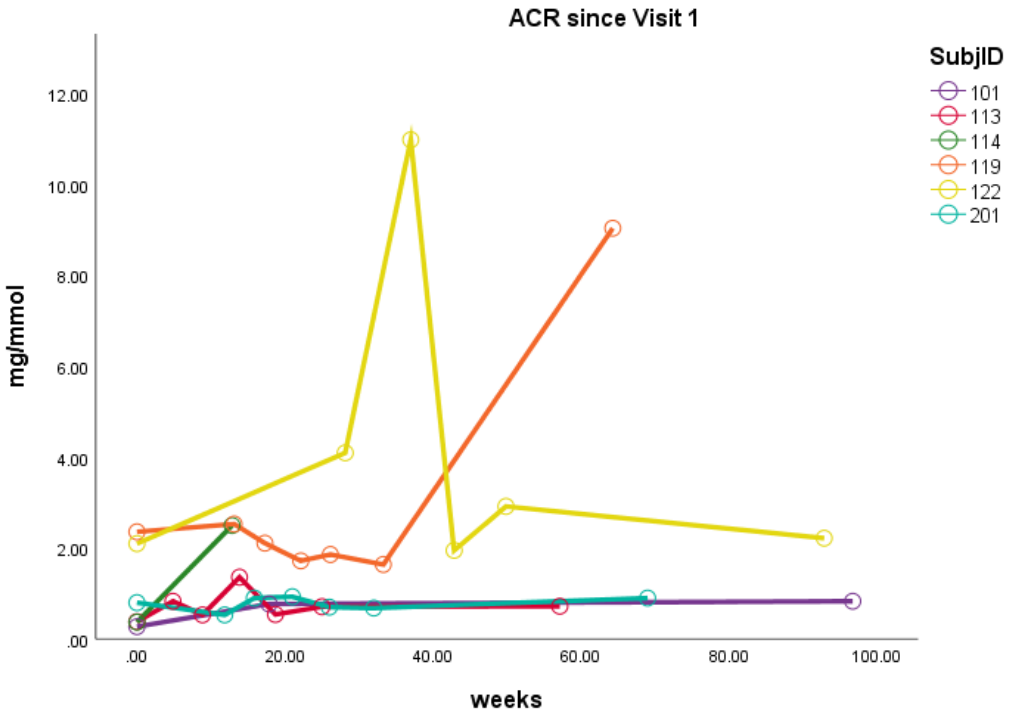


Fig 15

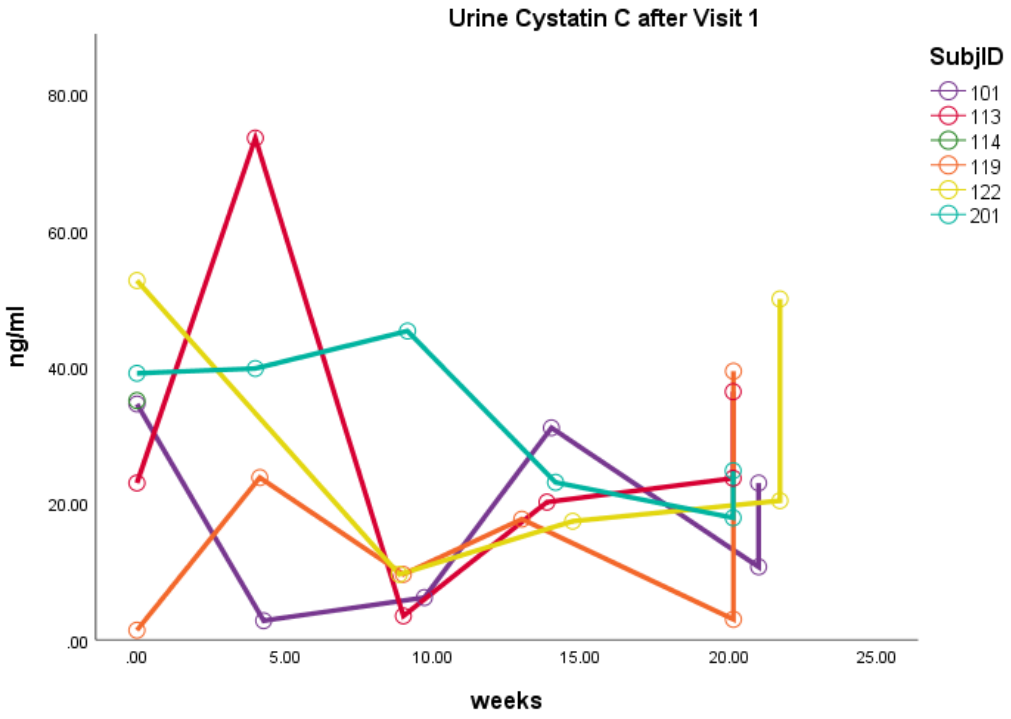
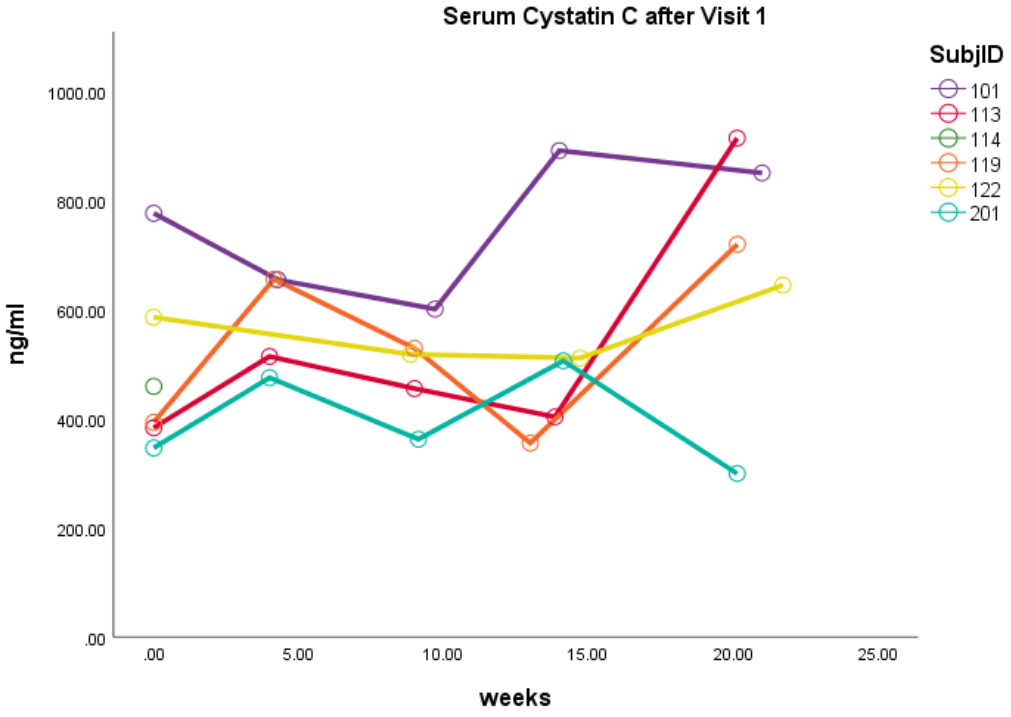

Urine Cystatin C after Visit 1
SubjID
101
113
114
119
122
201
80.00
60.00
40.00
20.00
.00
ng/ml
.00
5.00
10.00
15.00
20.00
25.00
weeks

Fig 16


Serum Cystatin C after Visit 1
SubjID
101
113
114
119
122
201
1000.00
800.00
600.00
400.00
200.00
.00
ng/ml
.00
5.00
10.00
15.00
20.00
25.00
weeks

7.8 Symptomatic hypoglycaemia

There were 17 episodes of symptomatic hypoglycaemic events, involving three participants (101, 113, 119). Most of the events (13/17) were mild, the others (4/17) were moderate in severity. All the moderate events were related to one participant (101). None of the symptomatic hypoglycaemic events caused hospital visits. Table 8 summarised the details of all symptomatic hypoglycaemic events.

Table 8 Hypoglycaemic events

Details	**No of reports (n=17)**	**No of Participants involved (n=3)**
Symptoms		
Tremor	11	2
Hunger	9	3
Sweating	7	2
Weakness/Tiredness	4	1
Dizziness	4	2
Agitated	4	1
Severity		
mild	13	3
moderate	4	1
Cause		
Too much insulin	12	2
Excessive physical activity	4	2
Meal delayed or omitted	1	1
Counter Measure		
Oral carbohydrate	17	3
Blood Glucose		
Min - Max	2.1 - 3.9	3

8. Excretion of gold

At visits 1, 1b, 3b, 4, 5, 6 and 7 blood and urine samples were taken for gold concentrations to enable assessment of gold excretion. Number of aliquots analysed for each participant at each visit ranged from 1 to 7. Findings from the assessment across time are shown in the following charts (Fig 17, Fig 18).

Fig 17

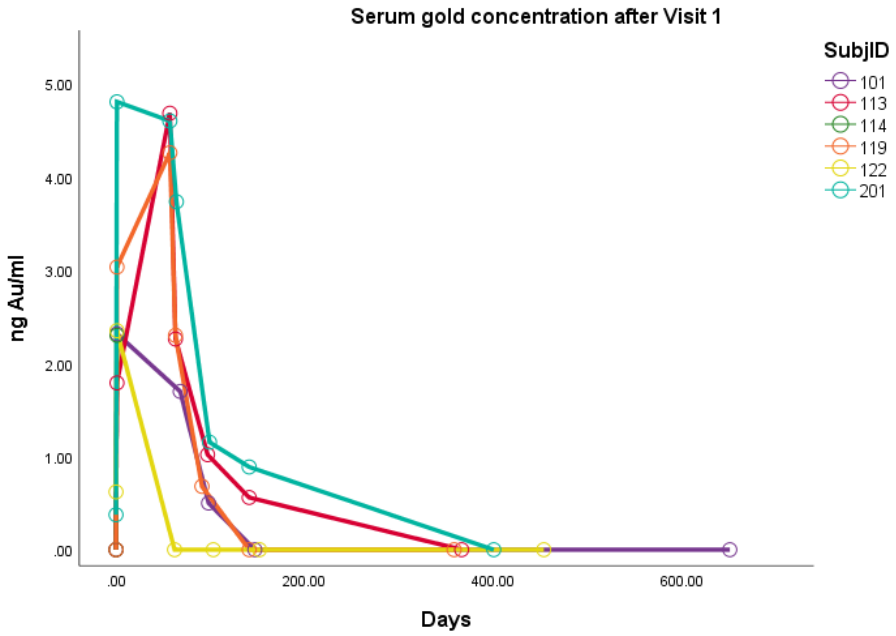
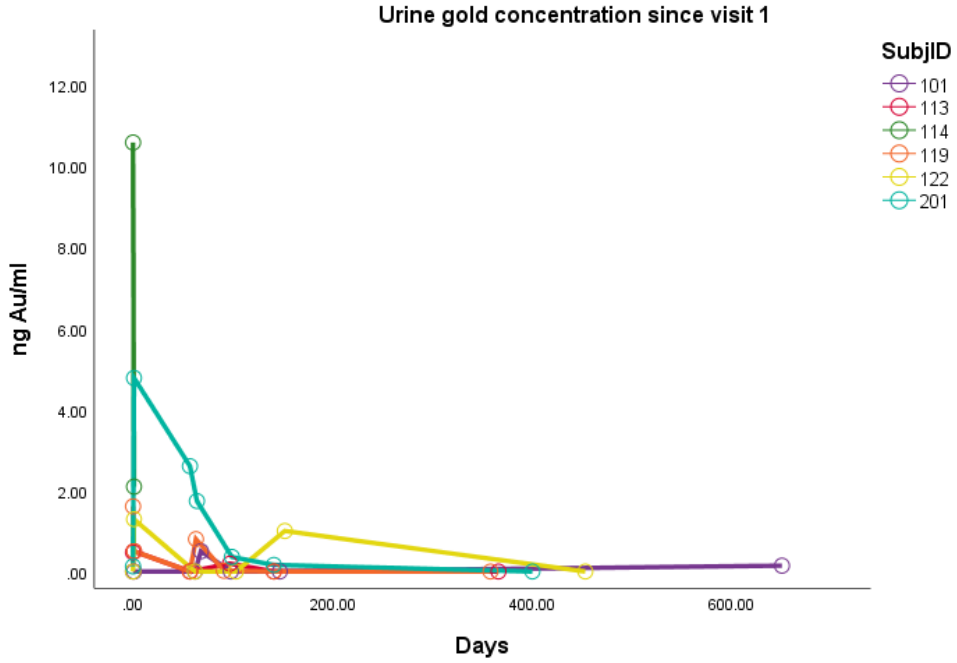


Fig 18



participant 114 had higher post injection 1 gold conc than before injection 1, Date of sample not verified.

9. Adverse Events

As at the report date, there were 48 adverse events (AE) reported for 6 participants. One has been reported as an SAE. Table 9a summarised of incidence of AEs , number of participants involved and whether they have been reported as Serious Adverse Events (SAE).

Table 9a Incidence of Adverse Events

Description of adverse event	No of people*	(%)**		Total no of events	Reported as SAE
Overall	6	100%		48	1
Compylobacter infection	1	16.67%		1	1
Positive result to gold sensitivity / Gold allergy / Positive gold allergy / Gold hypersensitivity	5	83.33%		5	0
Hyperpigmentation deltoid	3	50%		7	0
Red skin discolouration / Red Skin discolouration deltoid	2	33.3%		6	0
Skin discoloration / Skin discoloration at injection site	2	33.3%		2	0
Hyperpigmentation without redness	1	16.67%		1	0
Intermittent Pruritis at injection site	1	16.67%		1	0
Painful injection site	1	16.67%		1	0
Skin erythema at injection site	1	16.67%		2	0
Reaction at injection site: Red, slightly swollen, itchy when touched	1	16.67%		1	0
Granuloma	1	16.67%		1	0
Common cold	2	33.3%		3	0
Cold	1	16.67%		1	
Headcold	2	33.3%		3	0
Headache	1	16.67%		4	0
Coryza	1	16.67%		2	0
Upper respiratory infection	1	16.67%		1	
Sore throat	1	16.67%		1	0
Influenza	1	16.67%		1	0
Nausea	1	16.67%		1	0
Vomiting	1	16.67%		1	0
Pressure in neck and head	1	16.67%		1	0
Insect bite	1	16.67%		1	0

**Number of participants experiencing an AE (participant is to be counted only once for each adverse event)*

All six participants showed some skin reactions at the injection sites. Details would be shown separately.

Of the six participants, 2 (33.33%) participants experienced moderate AEs but the events were unrelated to the study. All six participants (100%) experienced mild AEs:- 5 very likely related to the trial; 1 possibly related; 3 unlikely to be related; 4 unrelated (Table 9b).

Table 9b AE experienced by participants by severity and relatedness to the trial.

Description of adverse event	Mild (n=6) n* (%)**	Moderate (n=2) n (%)	Severe (n=0) n (%)
Very likely related			
Positive result to gold sensitivity / Gold allergy / Positive gold allergy / Gold hypersensitivity	5 (83.33%)	0	0
Red skin discolouration / Red Skin discolouration deltoid	2 (33.33%)	0	0
Skin discoloration / Skin discoloration at injection site	2 (33.33%)	0	0
Hyperpigmentation deltoid	2 (33.33%)	0	0
Hyperpigmentation without redness	1 (16.67%)	0	0
Intermittent Pruritis at injection site	1 (16.67%)	0	0
Painful injection site	1 (16.67%)	0	0
Skin erythema at injection site	1 (16.67%)	0	0
Reaction at injection site: Red, slightly swollen, itchy when touched	1 (16.67%)	0	0
Granuloma	1 (16.67%)	0	0
Possibly			
Hyperpigmentation deltoid	1 (16.67%)	0	0
Red skin discolouration / Red Skin discolouration deltoid	1 (16.67%)	0	0
Unlikely	1 (16.67%)		
Cold	1 (16.67%)	0	0
Coryza	1 (16.67%)	0	0
Headache	1 (16.67%)	0	0
Headcold	1 (16.67%)	0	0
Pressure in neck and head	1 (16.67%)	0	0
Sore throat	1 (16.67%)	0	0
Not related			
Common cold	0	1 (50%)	0
Compylobacter infection	0	1 (50%)	0
Influenza	0	1 (50%)	0
Common cold	1 (16.67%)	0	0
Headcold	1 (16.67%)	0	0
Insect bite	1 (16.67%)	0	0
Nausea	1 (16.67%)	0	0
Upper respiratory infection	1 (16.67%)	0	0
Vomiting	1 (16.67%)	0	0

*.*Number of participants experiencing a certain severity of an adverse event where each participant is counted only once at highest level of severity.*

*** % of participants experiencing a certain severity of an adverse event*

All six participants showed skin reactions at injection sites. Further details reported separately.

10. Serious Adverse Events

One serious adverse event (SAE) was reported for one participant. The participant was treated in Southmead from 19/Mar/2019 - 20/Mar/2019 for diarrhoea and vomiting. She was found to have campylobacter infection and discharged home on oral antibiotics. Table 10 summarised details of the SAE.

Table 10 Details of SAE

Site	Cardiff
Participant ID	113
Description of SAE	Campylobacter infection
Onset Date	19/03/2019
Stop Date	20/03/2019
Seriousness	Hospitalisation
Action taken in relation to the IMP	Not applicable as participant already had the last dose of the IMP on 10/01/2018
Expected	No
Relationship to Intervention	Not related
Outcome	Resolved
Other information	Stool culture carried out and IV Teicoplanin, Oral Metronidazole and ciprofloxacin prescribed

11. Data Accrual

Table 11 summarised data accrual for key data items as of report date.

Table 11 Accrual of data for key data items

Key Data Items	N expected	N completed
Baseline demographics	6*	6*
Details of IMP received by participants (doses |persons)	14 doses |6 persons	14 doses |6 persons
Immediate post injection observations (hours|visits|persons)	36 hours|14 visits | 6 persons	36 hours|14 visits | 6 persons
24 hour report (sets | persons)	14 sets | 6 persons	13 sets | 6 persons
General laboratory assessments (sets | persons)	37 sets | 6 persons	37 sets | 6 persons[1]
MMTT performed (sets | persons)	16 sets |6 persons	15 sets [2] |6 persons
CGM downloads (sets |persons)	16 sets |6 persons	15 sets |6 persons
Samples for autoantibody tests	32 sets |6 persons	22 sets[2] | 6 persons
Excretion of Gold Serum Urine	 37 sets | 6 persons 37 sets | 6 persons	 35 sets | 6 persons 37 sets | 6 persons
Hypoglycaemia Assessment Logs	NA	17 episodes
AE log	NA	48 events
SAE log	NA	1 event

*One participant withdrew

[1] A complete set included all the tests listed in Section 6

[2]Un-analysed set(s) stored and to be analysed when laboratory facilities re-opened after COVID 19 lockdown eased off