Clinical trial results:
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.

Summary

EudraCT number	2015-003934-28
Trial protocol	GB SE
Global end of trial date	30 December 2019

Results information

Result version number	v1 (current)
This version publication date	01 January 2021
First version publication date	01 January 2021

Trial information

Trial identification

Sponsor protocol code	SPON1455-15

Additional study identifiers

ISRCTN number	ISRCTN16067611
ClinicalTrials.gov id (NCT number)	NCT02837094
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cardiff University
Sponsor organisation address	McKenzie House, 36 Newport Rd, Cardiff, United Kingdom, CF24 0DE
Public contact	Professor Colin Dayan, Cardiff University, +44 02920742182, dayancm@cardiff.ac.uk
Scientific contact	Professor Colin Dayan, Cardiff University, +44 02920742182, dayancm@cardiff.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	17 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 December 2019
Global end of trial reached?	Yes
Global end of trial date	30 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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.

Protection of trial subjects:

N/A

Background therapy:

All subjects were patients with type 1 diabetes who received s/c insulin treatment as per clinical indication.

Evidence for comparator:

N/A

Actual start date of recruitment	01 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 5
Worldwide total number of subjects	6
EEA total number of subjects	6

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	6
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

There were 2 recruiting sites: Cardiff, UK and Linkoping, Sweden. Between 30/10/2016 and 05/10/2018 , 109 potential participants were referred, 6 were enrolled and received the trial treatment. 103 were excluded.

Pre-assignment

Screening details:

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 be contacted to provide information to the study team if needed.

Pre-assignment period milestones

Number of subjects started	6
Number of subjects completed	6

Period 1

Period 1 title	Baseline period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open label uncontrolled early phase safety study, so no blinding or randomisation were performed. In keeping with standard phase 1 study designs, no placebo or control group were included as the primary aim was to establish whether there are any major unexpected safety issues in the use of the IMP for the first time in man.

Arms

Arm title	Treatment arm

Arm description:

IMP

Arm type	Interventional
Investigational medicinal product name	Investigative medicine product comprising proinsulin peptide C19-A3 linked to Gold Nanoparticles
Investigational medicinal product code	C19-A3 GNP
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

C19-A3 GNP was administered intradermally via CE marked Nanopass 600nm microneedles. 3 doses were given at 4 weekly intervals. The dose given was equivalent to 10ug of C19-A3 peptide.

Number of subjects in period 1	Treatment arm
Started	6
Completed	4
Not completed	2
Consent withdrawn by subject	1
Halt to dosing	1

Baseline characteristics

Reporting groups

Reporting group title	Baseline period

Reporting group description: -

Reporting group values	Baseline period	Total	
Number of subjects	6	6	
Age categorical			
Age at consent (years): 28.46 (8.06) Range: 18.29 – 37.34			
Units: Subjects			
Adults (18-64 years)	6	6	
Age continuous Units: years arithmetic mean standard deviation	 28.46 ± 8.06	 -	
Gender categorical			
Female (%): 33.3%			
Units: Subjects			
Female	2	2	
Male	4	4	
Ethnicity Units: Subjects			
White	6	6	
Age at diagnosis of type 1 diabetes			
26.16 (9.45) years			
Units: Years arithmetic mean standard deviation	 26.16 ± 9.45	 -	
Duration of diabetes Units: Months arithmetic mean standard deviation	 27 ± 31.47	 -	

Subject analysis sets

Subject analysis set title	Treatment group
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects are included in this group.

Subject analysis set title	Comparison group
Subject analysis set type	Safety analysis

Subject analysis set description:

There is no comparison group as this is open label and not a placebo controlled trial.

Reporting group values	Treatment group	Comparison group	
Number of subjects	6	6	
Age categorical			
Age at consent (years): 28.46 (8.06) Range: 18.29 – 37.34			
Units: Subjects			
Adults (18-64 years)	6		
Age continuous Units: years arithmetic mean standard deviation	±	±	
Gender categorical			
Female (%): 33.3%			
Units: Subjects			
Female Male			
Ethnicity Units: Subjects			
White			
Age at diagnosis of type 1 diabetes			
26.16 (9.45) years			
Units: Years arithmetic mean standard deviation	±	±	
Duration of diabetes Units: Months arithmetic mean standard deviation	±	±	

End points

End points reporting groups	
Reporting group title	Treatment arm
Reporting group description: IMP	
Subject analysis set title	Treatment group
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects are included in this group.	
Subject analysis set title	Comparison group
Subject analysis set type	Safety analysis
Subject analysis set description: There is no comparison group as this is open label and not a placebo controlled trial.	

Primary: Assessment of the safety of C19-A3 GNP	
End point title	Assessment of the safety of C19-A3 GNP
End point description: There were no significant safety concerns.	
End point type	Primary
End point timeframe: Treatment and follow-up period.	

End point values	Treatment group	Comparison group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6		
Units: Subjects	6	6		

Attachments (see zip file)	Data Review Report/Data Review Report v3 clean.pdf

Statistical analyses

Statistical analysis title	Statistical analysis pending
Comparison groups	Treatment group v Comparison group
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Pending
Parameter estimate	Pending

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from the time each participant received their first dose of IMP until one month after their last trial visit. At each visit, participants were assessed for AEs. Between 13/10/2016 and 17/04/2020, 48 AEs were reported for 6 participants.

Adverse event reporting additional description:

Each participant was given a patient diary and asked to record details of any new illnesses they experienced and any medication taken. The diary was reviewed at each trial visit. At each visit participants were assessed for AE's by the clinical staff and details recorded in the trial CRF.

Assessment type	Systematic

Dictionary used

Dictionary name	Dictionary not used.
Dictionary version	0

Reporting groups

Reporting group title	All trial participants

Reporting group description:

In total there were 48 adverse events reported for the 6 participants. One was reported as an SAE. 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. All six participants showed skin reactions at injection sites.

Serious adverse events	All trial participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Diarrhoea and vomiting	Additional description: Campylobacter infection.		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	All trial participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
Nervous system disorders			

Headache			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	4		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Common cold			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	3		
Cold			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Headcold			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	3		
Coryza			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Upper respiratory infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Sore throat			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Gold hypersensitivity	Additional description: Positive result to gold sensitivity / Gold allergy / Positive gold allergy / Gold hypersensitivity		
subjects affected / exposed	5 / 6 (83.33%)		
occurrences (all)	5		

Hyperpigmentation deltoid. subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 7		
Red skin discolouration / Red Skin discolouration deltoid. subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 6		
Skin discoloration at injection site subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2		
Hyperpigmentation without redness. subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Intermittent Pruritis at injection site. subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Pain at injection site subjects affected / exposed occurrences (all)	Additional description: Painful injection site. 1 / 6 (16.67%) 1		
Skin erythema at injection site. subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2		
Reaction at injection site: Red, slightly swollen, itchy when touched. subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Granuloma at injection site subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Musculoskeletal and connective tissue disorders Pressure in neck and head subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Infections and infestations Insect bite subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 April 2016	Amendment to trial protocol, PIS and ICF following review by REC, MHRA and MPA and update of IMPD sections: 2.1.S.5 Validation of Analytical Methods 2.1.P.5.5 Characterisation of Impurities 2.1.P.8.1 Stability Summary and Conclusion 2.1.P.8.2 Post Approval Stability Protocol 2.1.P.8.3 Stability Data
21 April 2016	Change of overseeing trials unit. Lengthening of follow up period and addition of follow-up phone call post IMP administration, following advice from competent authorities. Additional exclusion criteria. Reduction in blood draw volume at trial visits. Clarification on "conditions for interruption of dosing to individuals." Additional renal function tests for safety monitoring. Clarification of AE reporting responsibilities with the new trial unit.
23 June 2016	To update the protocol and patient information sheet to reflect changes to the trial.
24 October 2016	Update of IMPD sections 2.1.P.5.5 Characterisation of Impurities 2.1.P.8.1 Stability Summary and Conclusion 2.1.P.8.3 Stability Data
03 March 2017	Addition of information on skin reaction at injection site and addition of optional skin biopsy and blister sample.
16 May 2017	Addition of taking photographs of the injection sites and option of the injecting in the underside of the upper arm instead of the usual deltoid region.
17 October 2017	Addition of Patient Identification Centre (PIC).
07 November 2017	Request to extend IMP expiry date.
17 November 2017	Request to extend patient follow-up by adding an optional visit 12 months post first injection to gain more immunological information.
23 July 2018	Addition of optional patch skin test to assess gold hypersensitivity in participants.
26 November 2018	Halt to dosing and recruitment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
22 November 2018	Temporary halt of trial due to suspecting that the IMP induced gold hypersensitivity in trial subjects. Recruitment and dosing were halted and participants were followed up as per protocol. 6 subjects were treated with the IMP, 4 received all 3 doses, 1 had 1 dose and then withdrew and 1 had 1 dose and did not proceed to the second due to suspicion of inducing gold hypersensitivity. The 4 subjects who received all 3 doses had gold skin hypersensitivity testing and all 4 tested positive. Dermatologists advised that usually <10% of people have gold hypersensitivity and 4 from 4 testing positive is a higher rate than would be expected and was likely to be related to the IMP. The temporary dosing halt was decided to allow time to gather further information and obtain expert advice following the gold hypersensitivity testing. Following discussions with the DSMB and Trial Management Group, it was decided that the trial would not recruit or dose any further patients but follow-up visits would continue as per protocol. This decision was reached as the study had achieved its aim to assess safety and how well the IMP is tolerated. The timing of IMP expiry and scheduled end of recruitment (Jan 2019) along with the temporary halt in dosing led to the decision that no further IMP would be given and the study end date would be unaffected.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The planned number of subjects for this trial was 8 adults and no adolescents, not 6 and 1 as stated in the "Trial Information" section.

Notes: