



## 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 Linköping, 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, Linköping 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.

| <b>Number of subjects in period 1</b> | 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)<br>Range: 18.29 – 37.34 |                 |       |  |
| Units: Subjects  |                 |       |  |
| Adults (18-64 years)   | 6               | 6     |  |
| Age continuous   |                 |       |  |
| Units: years   |                 |       |  |
| arithmetic mean  | 28.46           |       |  |
| standard deviation   | ± 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  | 26.16           |       |  |
| standard deviation   | ± 9.45          | -     |  |
| Duration of diabetes   |                 |       |  |
| Units: Months  |                 |       |  |
| arithmetic mean  | 27              |       |  |
| standard deviation   | ± 31.47         | -     |  |

### Subject analysis sets

|   |                  |
|---|------------------|
| Subject analysis set title  | Treatment group  |
| Subject analysis set type   | Safety analysis  |
| Subject analysis set description:<br>All subjects are included in this group.   |                  |
| Subject analysis set title  | Comparison group |
| Subject analysis set type   | Safety analysis  |
| Subject analysis set description:<br>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)<br>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:<br>IMP   |                  |
| Subject analysis set title  | Treatment group  |
| Subject analysis set type   | Safety analysis  |
| Subject analysis set description:<br>All subjects are included in this group.   |                  |
| Subject analysis set title  | Comparison group |
| Subject analysis set type   | Safety analysis  |
| Subject analysis set description:<br>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:<br>There were no significant safety concerns. |  |
| End point type   | Primary                                |
| End point timeframe:<br>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                    |  |  |

|                                   |  |
|-----------------------------------|--|
| <b>Attachments (see zip file)</b> | Data Review Report/Data Review Report v3 clean.pdf |
|-----------------------------------|--|

### Statistical analyses

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

|   |  |  |  |
|---|--|--|--|
| Hyperpigmentation deltoid.<br>subjects affected / exposed<br>occurrences (all)  | 3 / 6 (50.00%)<br>7  |  |  |
| Red skin discolouration / Red Skin<br>discolouration deltoid.<br>subjects affected / exposed<br>occurrences (all)                   | 2 / 6 (33.33%)<br>6  |  |  |
| Skin discoloration at injection site<br>subjects affected / exposed<br>occurrences (all)  | 2 / 6 (33.33%)<br>2  |  |  |
| Hyperpigmentation without redness.<br>subjects affected / exposed<br>occurrences (all)  | 1 / 6 (16.67%)<br>1  |  |  |
| Intermittent Pruritis at injection site.<br>subjects affected / exposed<br>occurrences (all)  | 1 / 6 (16.67%)<br>1  |  |  |
| Pain at injection site<br>subjects affected / exposed<br>occurrences (all)  | Additional description: Painful injection site.<br>1 / 6 (16.67%)<br>1 |  |  |
| Skin erythema at injection site.<br>subjects affected / exposed<br>occurrences (all)  | 1 / 6 (16.67%)<br>2  |  |  |
| Reaction at injection site: Red,<br>slightly swollen, itchy when touched.<br>subjects affected / exposed<br>occurrences (all)       | 1 / 6 (16.67%)<br>1  |  |  |
| Granuloma at injection site<br>subjects affected / exposed<br>occurrences (all)   | 1 / 6 (16.67%)<br>1  |  |  |
| Musculoskeletal and connective tissue<br>disorders<br>Pressure in neck and head<br>subjects affected / exposed<br>occurrences (all) | 1 / 6 (16.67%)<br>1  |  |  |
| Infections and infestations<br>Insect bite<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 6 (16.67%)<br>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:<br>2.1.S.5 Validation of Analytical Methods<br>2.1.P.5.5 Characterisation of Impurities<br>2.1.P.8.1 Stability Summary and Conclusion<br>2.1.P.8.2 Post Approval Stability Protocol<br>2.1.P.8.3 Stability Data   |
| 21 April 2016    | Change of overseeing trials unit.<br>Lengthening of follow up period and addition of follow-up phone call post IMP administration, following advice from competent authorities.<br>Additional exclusion criteria.<br>Reduction in blood draw volume at trial visits.<br>Clarification on "conditions for interruption of dosing to individuals."<br>Additional renal function tests for safety monitoring.<br>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<br>2.1.P.5.5 Characterisation of Impurities<br>2.1.P.8.1 Stability Summary and Conclusion<br>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 | <p>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.</p> <p>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.</p> <p>The 4 subjects who received all 3 doses had gold skin hypersensitivity testing and all 4 tested positive.</p> <p>Dermatologists advised that usually &lt;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.</p> <p>The temporary dosing halt was decided to allow time to gather further information and obtain expert advice following the gold hypersensitivity testing.</p> <p>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.</p> <p>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.</p> | -            |

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: