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HA-1

# Clinical Trial Summary Report

## A phase I clinical trial of the vaccination of healthy human volunteers against the minor histocompatibility antigen (mHAg) HA-1 using a DNA and MVA 'prime/boost' regimen

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| Sponsor: | University of Birmingham |
| Sponsor reference number: | RG_08-080 |
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## CLINICAL TRIAL SUMMARY REPORT

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| Acronym: | HA-1 |
| Title: | A phase I clinical trial of the vaccination of healthy human volunteers against the minor histocompatibility antigen (mHAg) HA-1 using a DNA and MVA 'prime/boost' regimen |
| Sponsor: | University of Birmingham |
| Sponsor Reference Number: | RG_08-080 |
| EudraCT Number: | 2011-001773-99 |
| REC Reference Number: | GTAC180 |
| Details of Investigational Medicinal Product(s): | pDOM-HA-1 (DNA fusion Vaccine) Primer<br>pDOM-HA-1 DNA solution comprises pDOM-HA-1 DNA formulated in phosphate buffered saline. The pDOM-HA-1 DNA solution was provided at a concentration of 1.0 mg/mL, as a clear, colourless, sterile liquid for intra-muscular injection. The drug product wass presented in Type I glass vials, with butyl rubber stoppers and aluminium crimps. A 1.3 mL fill was provided so that 1.0 mL could be withdrawn for injection.<br>pDOM-HA-1 was supplied by Bristol Institute for Transfusion Sciences (BITS) Clinical Biotechnology Centre, Bristol at a concentration of 1mg/ml per vial.<br>Therapeutic class: Vaccine<br>MVA-HA-1 (DNA Vaccine) Booster<br>MVA-HA-1 is a Tris-buffered aqueous formulation of MVA-HA-1, which was provided at a concentration of 1 x 108 plaque forming units/mL (pfu/mL) for intramuscular injection. The drug product was presented as a cloudy white suspension; in Type I glass vials, with a butyl rubber stopper and aluminium crimp seal.<br>MVA-HA-1 was provided at a concentration of 1 x 108 plaque forming units/mL (pfu/mL) for intramuscular injection.<br>MVA-HA-1 was supplied by Impfstoffwerk Dessau-Tornau (IDT), Germany and final QP release performed by Biotec Services International, Bridgend UK.<br>Therapeutic class: Vaccine |
| *Details of Trial Arms:* | Cohort A – 1mg pDOM-HA-1 x 2 cycles plus MVA boost (108 pfu)<br>Cohort B – 1mg pDOM-HA-1 x 3 cycles plus MVA boost (108 pfu)<br>Cohort C – 2mg pDOM-HA-1 x 2 cycles plus MVA boost (108 pfu)<br>Cohort D – 2mg pDOM-HA-1 x 3 cycles plus MVA boost (108 pfu)<br>For each cohort, if 1 out of 3 participants experienced a DLT then another 3 participants were recruited to receive the same dose. If 2 out of three participants in a cohort experienced a DLT, the dose below were defined as the MTD. If participants are already receiving the lowest dose, the study would be stopped. |
| Start Date:<br>*Date trial opened to recruitment* | 13-Dec-2012 |
| End of Trial:<br>*Date of declaration of the end of the trial* | 28-Jul-2020 |

This report was prepared by the Chief Investigator and the Cancer Research UK Clinical Trials Unit (CRCTU) on behalf of the Sponsor.

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| Signature: |  | Date: | 28th October 2021 |

## GENERAL INFORMATION

**Trial Design (consider using diagrams)**

This was a phase I, single-centre, dose-escalating trial in healthy male adult volunteers.

**Scientific Background**

Allogeneic blood stem cell transplants are known to have the potential to cure haematological malignancies and a major component of this effect is mediated through the donor immune system. Whilst graft-versus-host-disease(GvHD) is a common feature of allogeneic haematopoietic stem cell transplants (HSCT), patients developing GvHD also experience an increased graft-versus-leukaemia (GvL) effect. A major challenge in improving treatment outcomes is the prevention of GvHD while maintaining GvL. Both effects are mediated by alloreactive T-cells and it is known that lymphocyte infusions from the stem cell donor (termed donor lymphocyte infusion-DLI) can cure patients with relapsed haematological malignancy following an allogeneic HSCT. The DLI mediates a graft-versus-leukaemia (GvL) effect which is most active against leukaemic cells in patients with relapsed chronic myeloid leukaemia (CML), where around 80% of patients achieve durable complete remission (CR). However, only around 20% of patients with relapsed acute myeloid leukaemia (AML) or myeloma, and many fewer with acute lymphocytic leukaemia (ALL), show responses to DLI.

In addition, complications of unselected DLI, such as severe GvHD in 14% and marrow aplasia in a smaller number of patients, are significant causes of mortality.

GvL is thought to be mediated largely by alloreactive T cells which recognise minor histocompatibility antigens – short peptides which are presented by HLA molecules. HA-1 is a potent and immunodominant minor histocompatibility antigen (mHAg) which is expressed selectively by haematopoietic cells. T cells against HA-1 are believed to be of importance in the generation of GvL, and the emergence of donor HA-1-specific T cells in peripheral blood has been shown to be closely associated with disease remission in HA-1+ patients who receive DLI following HSCT.

To improve the GvL effect, immunisation of HA-1- stem cell donors with an HA-1 vaccine prior to lymphocyte donation could potentially generate HA-1-specific cytotoxic T lymphocytes (CTL), which after adoptive transfer to the relapsed recipient, may provide a potent anti-leukaemia effect in HA-1+ leukaemia patients. Further, such 'vaccine-augmented DLI' may potentially allow HA-1-specific T cells to be selected and purified for targeted immunotherapy in those patients at high risk of severe GvHD who would normally not be eligible for standard, unselected DLI.

**Trial Rationale**

HA-1 is an ideal target for therapeutic strategies to enhance GvL effects. Studies have shown that the presence of HA-1-specific CTLs in patients following DLI for relapsed disease is associated with disease remission, and that these cells kill the allogeneic HA-1 expressing tumours in vitro. Participants will vaccinate HA-1- donors against HA-1 using the heterologous prime / boost strategy (DNA/MVA) which has been used to vaccinate against infectious diseases such as HIV and malaria , as well as cancers such as melanoma. In many of these trials a cellular immune response has been induced in the vaccinees. The HLA-A2-restricted CTL-epitope was chosen, VLHDDLLEA (VLH) from HA-1 as the antigen. We have previously shown that vaccination of HLA-A2 transgenic mice with the DNA construct "pDOM", encoding the VLH epitope from HA-1 at the C-terminal end, induces a functional T cell response to HA-1. We propose to use the pDOM-HA-1 DNA vaccine to prime HA-1- donors and to boost the response with a modified vaccinia Ankara virus (MVA) encoding the same CTL epitope from HA-1 (MVA-HA-1).

**Objectives**

Primary Objective

- To demonstrate the safety of pDOM-HA-1 and MVA-HA-1 vaccines administered in man and to establish a safe dose for phase II evaluation

Secondary Objective

- To establish if these vaccines induce a CTL immune response to HA-1 in HA-1- immunocompetent subjects
- To define the kinetics of the anti-HA-1 cellular T cell response in order to determine the optimal timing for harvesting DLI

**Outcome Measures**

Primary

- To assess the safety and toxicity (graded according to Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials)
- To establish the Maximum Tolerated Dose (MTD) of the heterologous prime-boost vaccine against HA-1 in normal immunocompetent HA-1 negative volunteers

Secondary

- To assess timing and magnitude of peak HA-1 specific CTL response.

**Statistical Considerations**

The sample size was based on a conventional dose escalation study with a maximum of 3 + 3 participants per dosing schedule thus potentially a minimum of 12 and a maximum of 24 participants.

Descriptive statistics were used to assess the safety and toxicity of the heterologous prime-boost vaccine. Proportions and counts were calculated for categorical data and measures of central tendency and spread for continuous data.

All participants were assessed for toxicity. Safety variables will be summarised by descriptive statistics. AEs were reported for each dose level, summarised by incidence rates and classified by the worst observed severity grade. Laboratory data were presented by dose level at each observation time. Values outside normal limits were identified and summarised by frequency distribution. Laboratory variables were described using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.

**Trial Population**

The Trial Population for the trial was Healthy male adult volunteers who have a HLA-A2:0201 positive (HLA-A2+) and HA-1- genotype. In total, nine patients were recruited to the HA-1 trial over a period of 48 months. Seven of these patients were aged between 18-64 years old and the remaining two patients were aged between 65-84 years old.

## SUBJECT DISPOSITION

**Eligibility Criteria**

Inclusion Criteria

- HLA-A2+ and HA-1- genotype
- ≥ 18 years of age
- Healthy male adult volunteers
- Written informed consent given
- WHO performance status 0-1
- Haematological and biochemical values within normal laboratory range, or, if abnormal, not considered to be clinically significant by the Principal Investigator to prevent participation in the trial

Exclusion Criteria

- Females
- Donors with previous adverse effects to vaccination
- Donors on treatment with steroids/immunosuppressive drugs
- Participants who are not willing to use an adequate method of barrier contraception for the duration of the trial treatment if engaged in sexual activity with a female of childbearing potential and for at least 28 days following the last vaccination

- History of severe allergy
- Participants known to be serologically positive for Hepatitis B, C or HIV
- Previous participation in a vaccine clinical trial or participation in any clinical research in the 6 weeks prior to registration
- Planned or possible foreign travel requiring vaccination until 28 days after the last planned study vaccination
- Any vaccination (including the flu vaccine) 6 weeks before trial entry
- Any planned vaccine during and 6 weeks after receiving the study vaccine
- Any other medical condition which in the Investigator's opinion would make the participant unsuitable for participation in this study

**Recruitment**

In total, nine patients were recruited to the HA-1 trial over a period of 48 months. There were 6 participants recruited to Cohort A; 3 participants initially and a further 3 participants when the cohort was expanded due to safety concerns. 3 participants were also recruited to Cohort B. Cohorts C and D: Abandoned due to recruitment difficulties and expiration of pDOM and MVA vaccines in April and July 2017 respectively.

**Withdrawals**

None

## PATIENT CHARACTERISTICS

**Patient Characteristics**

Table 3: Patient characteristics

| Patient No. | Age | Cohort | DLT observed | No. of adverse events observed (n=238) | No. considered vaccine related N (%) |
|---|---|---|---|---|---|
| 01 | 69 | A | - | 19 | 8 (42) |
| 02 | 65 | A | - | 35 | 10 (29) |
| 03 | 45 | A | Myalgia (g2), Headache (g2) | 40 | 6 (15) |
| 04 | 50 | A (expanded) | - | 31 | 8 (26) |
| 05 | 44 | A (expanded) | - | 28 | 10 (36) |
| 06 | 43 | A (expanded) | - | 22 | 4 (18) |
| 07 | 39 | B | - | 22 | 16 (73) |
| 08 | 50 | B | - | 17 | 9 (53) |
| 09 | 27 | B | - | 24 | 3 (13) |

## ENDPOINTS

**Definitions**

The primary outcome measure was to assess safety and toxicity and to establish the maximum tolerated dose of the heterologous prime-boost vaccine against HA-1 in normal immunocompetent HA-1 negative volunteers. The secondary outcome measure was to assess timing and magnitude of peak HA-1 specific CTL response. Peak HA-1 specific CTL response would be assessed by graphical illustration.

**Statistical Analysis**

Descriptive statistics were used to assess the safety and toxicity of the heterologous prime-boost vaccine. Proportions and counts were calculated for categorical data and measures of central tendency and spread for continuous data. All participants were assessed for toxicity. Safety variables were summarised by descriptive statistics. AEs were reported for each dose level, summarised by incidence rates and classified by the worst observed severity grade.

## ADVERSE EVENTS

**Adverse Events**

Table 4. Adverse Events

| | **Grade 1-2** | **Grade 3-4** | **All grades** |
|---|---|---|---|
| ***Non-haematological*** | N (%) | | |
| Hypertension | 39 (16) | 15 (6) | 54 (23) |
| Hypermagnesemia | 22 (9) | - | 2 (22) |
| Injection site reactions (includes pain, tenderness, bruising and swelling) | 20 (8) | - | 20 (8) |
| ***Haematological*** | | | |
| Increased monocytes | 7 (3) | - | 7 (3) |
| Neutropenia | 6 (3) | - | 6 (3) |
| Leukopenia | 3 (1) | - | 3 (1) |

**Serious Adverse Events**

Table 5: List of Serious Adverse Events during the trial

| **Serious Adverse Events** | Vaccinated Patients |
|---|---|
| Total subjects affected by serious adverse events | |
| subjects affected / exposed | 0/9 (0.00%) |
| number of deaths (all causes) | 0 |
| number of deaths resulting from adverse events | 0 |

## MORE INFORMATION

**Substantial Amendments**

| Amendment number | Date of amendment | Protocol version number | Type of amendment | Summary of amendment |
|---|---|---|---|---|
| 1 | 15-Feb-2012 | 3 | Substantial | Clarification of primary outcome measures, Committee membership, end of trial definition |
| 2 | 31-Oct-2012 | 4 | Substantial | Clarification of SAE reporting period and length of participant monitoring, removal of collection of concomitant medications, removal of pregnancy test at screening, clarification of inclusion and exclusion criteria, correction of route of MVA-HA-1 vaccine, correction of contact details |
| 3 | 20-Mar-2014 | 5 | Substantial | Change to inclusion criteria, definition of dose-limiting-toxicity, additional safety wording added |
| 4 | 24-Oct-2014 | 6 | Substantial | Change to cohort scheduling, addition of nursing staff able to obtain screening consent, change to period of monitoring post-vaccination |
| 5 | 14-Oct-2016 | 7 | Substantial | Update to pre-clinical activity, change to dose-limiting-toxicity definition, change to vaccine dose escalation scheme, change to end of trial definition |

Limitations and Caveats

Cohorts C and D were abandoned due to recruitment difficulties and expiration of pDOM and MVA vaccines in April and July 2017 respectively.

## CONCLUSIONS

A heterologous prime-boost DNA-MVA vaccination strategy in HA-1− healthy volunteers is tolerable, safe and elicits a detectable and sustained HA-1-specific CD8+ T-cell response. 3 doses of 1mg pDOM-HA-1 with 1 dose of MVA-HA-1 boost should be used in future Phase II studies. This work provides the basis for trials to investigate the adoptive transfer of HA-1-specific CD8+ T-cells to recipients of allo-SCT as “vaccine-augmented DLI”.

## DISSEMINATION

Eldershaw SA, Pearce H, Inman CF, Piper KP, Abbotts B, Stephens C, Nicol S, Croft W, Powell R, Begum J, Taylor G, Nunnick J, Walsh D, Sirovica M, Saddique S, Nagra S, Ferguson P, Moss P, Malladi R.

DNA and modified vaccinia Ankara prime-boost vaccination generates strong CD8+ T cell responses against minor histocompatibility antigen HA-1.

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