Final Report for the Environmental Protection Agency

GMO Register Number:	G0536-01
GMO Notifier:	The GUIDE Department St James's Hospital Dublin 8
Address of Notifier:	Welcome Trust/HRB Clinical Research Facility St James's Hospital Dublin 8

General Information

On the 22nd July 2014, St James's Hospital received consent to release the GM vaccines AdCh3NSmut1 (SNIF Reference No: B/IE/14/01) and MVA-NSmut (SNIF Reference No: B/IE/14/02) at the Wellcome Trust-HRB Clinical Research Facility for the purposes of a clinical trial evaluating a Hepatitis C vaccine strategy. This trial looked to evaluate the safety and immunogenicity of a novel vaccine strategy in HIV-1 seropositive individuals.

Report Status

This the final report on the Hepatitis C vaccine trial. The report details an overview of the clinical trial, a protocol synopsis, ethical and regulatory approvals, description of the investigational products, the study population, characteristics of the release and the results of the clinical trial with respect to primary (safety) and secondary (immunogenicity) endpoints.

Overview

This study was a Phase I clinical trial to assess the safety / tolerability (primary study endpoint) and immunogenicity (secondary study endpoint) of a heterologous prime-boost HCV vaccine candidate regimen in HIV-1 seropositive, HCV-negative individuals (aged 18-60). 20 individuals were recruited to the study between 2 sites (St James's Hospital, Dublin, Ireland and Kantonsspital, St Gallen, Switzerland).

Protocol Synopsis

The study was a Phase I multicentre open label clinical trial. Follow up duration was 8 months with 12 study visits in total. The investigational products, AdCh3NSmut1 and MVA-NSmut, were administered in a prime-boost fashion, by intramuscular injection, 8 weeks apart. Safety and tolerability were assessed by including actively and passively collected data on adverse events.

Immunogenicity was assessed by the measurement of HCV immunogen- specific T cell responses by standardised IFN-γ ELISpot assays and by exploratory immunological studies.

Ethical, Regulatory Approval and Consent

The study protocol and related documents were reviewed and approved by the Irish and Swiss Ethical Committees: Tallaght University Hospital / St. James's Hospital Joint Research Ethics Committee and Ethikkommission Ostschweiz EKOS (formerly Ethikkommission St.Gallen), Switzerland. Full ethical approval for the trial was given on 8th July 2014 and 15th December 2014, respectively, and where appropriate, all subsequent substantial amendments were approved, prior to implementation, by these committees.

The study was performed in conformity with the declaration of Helsinki and in agreement with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP; CPMP/ICH/135/95) July 1996).

The study was performed in compliance with the requirements of current Irish, Swiss and EU legislation. The Competent Authorities were the Health Products Regulatory Authority (Ireland (formerly Irish Medicines Board)) and Swissmedic (Switzerland). The study's EudraCT number was: 2014-000731-16.

Notice of acceptance for clinical trial authorization was provided by the Health Products Regulatory Authority (CT Number: CT/900/552/1 – AdCh3NSmut1/MVA-NSmut) on 3rd December 2014 and Swissmedic on 16th January 2015. Where appropriate, all subsequent substantial amendments were submitted to the both authorities for approval prior to implementation.

The Patient Information Leaflet detailed the procedures involved in the study (aims, methodology, potential risks and anticipated benefits) and the Investigators explained these verbally to each patient prior to obtaining consent. The patient then signed and dated the informed consent form to indicate that they fully understood the information and were willing to participate in the study.

Patients were given copies of the signed consent form to keep for their records. The original consent forms are kept in confidential site-specific files at each site. All patients provided written informed consent to participate in the study prior to being screened.

Description of the Investigational Products

The investigational medicinal products used in this clinical trial were an adenoviral vectored vaccine based on AdCh3, and an MVA-vectored vaccine. Each of the two viral vectors encoded the same immunogen (NSmut).

NSmut Insert:

The Hepatitis C virus (HCV) non-structural region (NS) was used as the basis for the immunogen in these candidate vaccines. It is well conserved between all six HCV genotypes and several of the major subtypes (between 74 and 79% sequence identity at the amino acid level). The NS region encompasses approximately two thirds of the HCV genome (1985 amino-acids) and encodes five different proteins (NS3, NS4a, NS4b, NS5a and NS5b) that result from the proteolytic cleavage of the HCV polyprotein by the encoded NS3 protease.

For safety reasons, a mutation inactivating the enzymatic activity of the encoded polymerase gene was introduced. This replaced the original amino acid sequence GlyAspAsp at positions 1711 to 1713 in the catalytic site of the NS5b with the inactive AlaAlaGly.

AdCh3NSmut1:
AdCh3NSmut1 was derived from the original AdCh3NSmut by introduction of minor changes in the vector backbone; improved features were obtained in terms of production during the manufacturing process. AdCh3NSmut1 was manufactured in compliance with Good Manufacturing Practice by Advent SRL, Pomezia (Roma), Italy. AdCh3NSmut1 was released by Advent and it was labeled and released for the PEACHI-02 trial by the Qualified Person (QP) at the Clinical Biomanufacturing Facility (CBF), Jenner Institute, University of Oxford. AdCh3NSmut1 was supplied as a liquid at the concentration of $5.0x10^{10}$ vp/ml.

MVA-NSmut:
Modified Vaccinia Ankara (MVA), an attenuated orthopox vaccine vector, was chosen for heterologous boost. MVA-NSmut was manufactured in compliance with Good Manufacturing Practice by Impfstoffwerk Dessau-Tornau (IDT), Germany; it was labelled and released for the PEACHI-02 trial by the Qualified Person (QP) at CBF, Jenner Institute, University of Oxford. MVA- NSmut was supplied as liquid at the concentration of $9.0x10^{8}$ pfu/ml.

The investigational medicinal products were supplied as 0.65 ml sterile aliquots in glass vials. The vials were stored between -70°C and -90°C, in locked freezers at the Wellcome-HRB Clinical Research Facility at St James's Hospital or the Clinical Trials Unit (CTU) of the Kantonsspital St.Gallen, Switzerland, respectively, and managed by the respective CTU's. All movements of the study vaccines between CBF and the trial suite representatives in charge of storage, and between the locked freezer and the clinic room were documented.

Study Population

The number of HIV-1 seropositive volunteers screened was 25. All screened participants were on antiretroviral therapy with a suppressed HIV viral load (<40 copies/ml) for >6 months prior to screening and with a CD4 cell count >350 cells/µL at screening. Of the 25 screened HIV-1 seropositive patients, 20 were enrolled and all 20 participants completed all study procedures and follow-up visits. None of the participants withdrew consent or had to be excluded.

Characteristics of the Release

Thirty vaccine vials were received at the clinical research facility, from the Clinical BioManufacturing Facility in Oxford, United Kingdom, for conduct of the clinical trial on 10th June 2015. The clinical trial commenced on the 15th June 2015 with the screening of the first participant at St James's Hospital. Between 30th June 2015 and 2nd August 2016, 12 participants received both vaccines at St James's Hospital. The vaccines were administered by intramuscular injection, in a prime-boost fashion, 8 weeks apart. All GMO material and potentially contaminated material was autoclaved prior to disposal. The remaining unused 6 vaccine vials were returned to ReiThera Srl in Naples, Italy on 30th August 2016.

All patients who participated in the clinical trial completed the full 8 months of follow-up. The last follow-up visit took place on the 26th January 2017.

The Results of the Deliberate Release

The results of the Hepatitis C vaccine trial with respect to safety and immunogenicity are summarised below.

The vaccines were well tolerated. No serious adverse events (SAEs) or suspected unexpected serious adverse reactions (SUSARs) occurred. Adverse events (AEs) reported did not differ significantly between trial sites. There was no observed impact of vaccination on parameters of HIV control (CD4 cell count, plasma viral load). Safety reports were submitted and reviewed by the trial's Drug Safety Monitoring Board as specified in the protocol.
AEs were typically short-lived and self-limited. AEs after MVA-booster vaccination were reported to be more severe. The most common AEs were local pain and fatigue, followed by myalgia.

The secondary study endpoint of the vaccine study was the immunogenicity of AdCh3NSmut1 prime and MVA-NSmut boost vaccinations. The primary assay to monitor T cell responses to Hepatitis C Virus NS antigens was an Interferon gamma (IFN-γ) ELISpot on freshly isolated Peripheral Blood Mononuclear Cells (PBMCs) at pre-defined time points (weeks 0, 2, 4, 8, 9, 12, 14, and 34). Peptides 15 amino acids (a.a.) long and overlapping by 11 a.a., spanning the whole HCV genotype 1b NS3-5b region, and arranged in six peptide pools were used as re-stimulation antigens in the IFN-γ ELISpot.

T cell responses were induced in all HIV-1 seropositive individuals. Priming with AdCh3NSmut induced T cell responses after 2 to 4 weeks (mean 477 ±584 SFU/10^6PBMC) that were markedly enhanced following MVA boost (mean 3094 ±2376 SFU/10^6PBMC).

Summary

The primary objective of the study was to demonstrate the safety of the heterologous AdCh3NSmut1 and MVA-NSmut prime-boost regimen in HIV-1 seropositive individuals.

The vaccines were generally well tolerated. The majority of the local and systemic adverse events were graded mild or moderate, and typically resolved spontaneously within 24 to 48 hours. There were no serious adverse events related to vaccination. The reactogenicity profile of the vaccines was similar to that observed in healthy individuals without HIV infection, indicating the vaccines are associated with predictable adverse reactions that are self-limiting in nature.

All vaccines were administered by intramuscular injection, in a prime-boost fashion, 8 weeks apart. The vaccines were administered and disposed of in accordance with detailed standardised operating procedures. All GMO material and potentially contaminated material was autoclaved prior to disposal. As outlined in the Environmental Risk Assessments, given the attenuated nature of the vaccines and their lack of replicative capacity in mammalian

cells, it was felt that the issue of a significant release to the wider environment was negligible.

In conclusion, we have shown that a T cell-inducing Hepatitis C vaccine candidate is safe in HIV-1 seropositive individuals with suppressed viraemia and a robust CD4 count and able to induce antigen-specific T cell responses. Overall, the reactogenicity and immunogenicity profile was comparable to healthy volunteers.