END OF TRIAL REPORT

Trial Information	
Title	**CAMVAC** / A study of the immune response to vaccination in Multiple Sclerosis patients treated with Alemtuzumab
Chief Investigator:	Dr Alasdair Coles
EudraCT no.:	2009-011523-31
REC Ref no.:	09/H0720/64
R&D no.:	A091598
Sponsor:	Cambridge University Hospitals NHS Foundation Trust
Sponsor's Address:	Research and Development Department Box 277 Addenbrooke's Hospital Hills Road Cambridge CB2 0QQ
Investigational Medicinal Products:	**Revaxis** Manufacturer: Sanofi Pasteur MSD Limited, MA no.: PL06745/0123 **Pneumovax II** Manufacturer: Sanofi Pasteur MSD Limited, MA no.: PL06745/0103 **Menitorix** Manufacturer: GlaxoSmithKline UK, MA no.: PL10592/0217
Date of End of Trial:	02-Aug-2011 (End of Trial Declaration dated 28-Jul-11)
Final Analysis carried out by:	Dr Claire McCarthy

Trial Objectives and Main Findings	
Study Design:	A phase IV, non-blinded single-arm trial of the safety and efficacy of vaccines in multiple sclerosis patients treated with alemtuzumab. Enrolled patients received one or all of 3 vaccines: These vaccines were Pneumovax II (T-cell independent recall antigen), Revaxis (combined tetanus toxoid, diphtheria toxoid and inactivated polio viruses types 1, 2 and 3 acting as T-cell dependent recall antigens vaccine); and Menitorix (conjugated *Haemophilus influenzae* type b and *Neisseria meningitidis* group C polysaccharides, a T-cell dependent neo-antigen). IgG levels were measured before and 4 weeks after vaccination. Control rates of seroprotection and seroconversion were taken from historical data on the efficacy of these vaccines in healthy people.
No. of participants:	It was planned to recruit 60 patients to the study. The trial terminated early after 24 patients completed the study as per protocol. Pt 14 PD was entered into the trial on the 24th November 2009, after having received routine vaccination from his GP, and received follow-up serology testing as per protocol. The early termination of the trial was justified after a preliminary analysis of data demonstrated that the scientific objectives of the study, including

	assessment of the risk benefit analysis of the IMPs, could be achieved with fewer-than-planned participants.
Statistical Methods:	Serum IgG levels were measured before and 4 weeks after vaccination. "Seroprotection" was defined as obtaining the accepted minimum antibody level that is considered protective against the disease. "Seroconversion" indicates a four-fold rise in antibody level for Revaxis and Menitorix. The results from our patients were compared to those for published healthy controls, however, there was only good age-matched control data for Revaxis seroprotection. No Revaxis seroconversion data could be found, however, one paper detailed geometric mean titres (GMT) and geometric mean titre ratios (GMTR) for healthy controls. No healthy adult control data could be found for Menitorix, therefore Haemophilus *influenzae* b (Hib) and meningococcal C responses were compared to healthy adult responses to other Hib and meningococcal C conjugate vaccines. There is wide variation in anti-pneumococcal antibody responses in healthy subjects and a normal response to pneumococcal polysaccharide vaccine is not well defined, not all healthy subjects make a 2-fold response. There were no published seroprotection rates available for Pneumovax II and seroconversion data was only available for 2 polysaccharides, therefore seroconversion rates from pooled pneumococcal polysaccharide vaccine studies were used. Lymphocyte cell counts were measured by flow cytometry prior to vaccination. In addition, stored serum samples from before, 1 month and 9-12 months after the patient's' treatment with alemtuzumab, were analysed for antibodies to: measles, mumps, rubella, VZV and EBV.
Results:	All of the 22 alemtuzumab patients given Revaxis had seroprotective levels of antibodies to tetanus and diphtheria both before and after vaccination. One person was not protected against polio viruses 2 and 3 before and after vaccination and also had no increase in their pre-vaccination polio virus 1 titre. Seven other patients had no rise in one or more of their polio virus antibody titres. GMTRs for polio viruses 1, 2 and 3 in post-alemtuzumab patients vs. healthy controls were: 3.5 vs. 7.3, 5 vs. 10 and 16.5 vs. 17 respectively. There was no difference in GMTR for diphtheria in post-alemtuzumab patients compared to healthy controls. GMTR could not be calculated for tetanus as the majority of patients had post-Revaxis antibody levels above the upper detection limit of the assay, therefore, an accurate ratio could not be calculated. Meningococcal C was designed to be a novel antigen to our patients' immune systems and this is reflected in the low pre-vaccination seroprotective levels (13%). Following Menitorix responses to Hib were normal and meningococcal C seroprotection rose to 91% which is in keeping with the 90% seroprotection rate seen in 136 healthy adults given the meningococcal C conjugate vaccine Menjugate (meningococcal C conjugated to diphtheria protein) but is lower than 100% seroprotection achieved in healthy adults given Meningitec (meningococcal C conjugated to mutant diphtheria toxin). Four out of 23

	patients (83%) failed to seroconvert to meningococcal C compared to 98-100% of healthy controls. Patients were classified as either 'responders' or 'non-responders' to Revaxis and Menitorix. Revaxis response was defined as having seroprotection to diphtheria, tetanus and all 3 polio viruses. Menitorix response was defined as having both seroprotection and seroconversion to meningococcal C and Hib. The patients were then split in to 2 groups: those who were within 6 months of alemtuzumab treatment and those who were more than 6 months post-alemtuzumab. There was no significant difference in the proportion of non-responders to each individual vaccine, however, 14 out of 16 (88%) of patients who were over 6 months post-alemtuzumab responded to both Revaxis and Menitorix vaccines compared to 2 out of 5 (40%) of patients who were within 6 months of alemtuzumab (p=0.03). Serum antibodies to common viruses were tested in 20 patients. Prior to alemtuzumab treatment a 100% of patients had positive IgG antibodies to rubella, VZV, EBV (VCA and EBNA) and measles and 85% were positive to mumps. At 1 month and 9-11 months after treatment all patients with pre-existing antibodies remained antibody positive to all of the viruses.
Conclusion:	We conclude, from this preliminary study, that patients treated using alemtuzumab retain antibodies protective against common viruses, 1 month and 12 months after alemtuzumab; and that they respond normally to a range of vaccines if given 6 months or greater after alemtuzumab. Earlier vaccinations may fail to generate appropriate immunity.

Dissemination of Research Findings and Publications	
To participants:	A letter summarising a participant's individual results has been sent to each participant. A letter sent to all patients treated with Alemtuzumab for multiple sclerosis in Addenbrookes Hospital, by Dr. Alasdair Coles in April 2012 has included a summary of the findings of this study.
Publications:	A paper summarising the study and it's findings has been drafted by Dr. Claire McCarthy and submitted for publication.

Chief Investigator's Signature	
Dr Alasdair Coles	Signature: A C P Date: 19/04/2012