Declaration of the End of Trial Form (cf. Section 4.2.1 of the *Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial*[1])

NOTIFICATION OF THE END OF A CLINICAL TRIAL OF A MEDICINE FOR HUMAN USE TO THE COMPETENT AUTHORITY AND THE ETHICS COMMITTEE

For official use

Date of receipt :	Competent authority registration number: 21439/0232/001 Ethics committee registration number: 10/H0604/75

To be filled in by the applicant

A MEMBER STATE IN WHICH THE DECLARATION IS BEING MADE :

B TRIAL IDENTIFICATION

B.1 EudraCT number :	2010-01-018596-24
B.2 Sponsor's protocol code number:	PID no. 10066
Full title of the trial :	Assessment of Salmonella Typhim Vi(TM) vaccine (Sanofi Pasteur MSD) for the investigation of selective Antibody deficiency to polysaccharide.

C APPLICANT IDENTIFICATION (please tick the appropriate box)

C.1	**DECLARATION FOR THE COMPETENT AUTHORITY**	☐
C.1.1	Sponsor	☐
C.1.2	Legal representative of the sponsor	☐
C.1.3	Person or organisation authorised by the sponsor to make the application.	X
C.1.4	**Complete below**:	
C.1.4.1	Organisation : *Oxford University Hospitals NHS Trust*	
	Name of person to contact : *Heather House*	
C.1.4.2	Address : l *Research and development Department, joint Research Office, Block 60, Churchill hospital Oxford*	
C.1.4.3	Telephone number :*01865572232*	
C.1.4.4	Fax number :*01865572242*	
C.1.4.5	E-mail:Heather.house*@ouh.nhs.uk*	

C.2	**DECLARATION FOR THE ETHICS COMMITTEE**	☐
C.2.1	Sponsor	☐
C.2.2	Legal representative of the sponsor	☐
C.2.3	Person or organisation authorised by the sponsor to make the application.	X
C.2.4	Investigator in charge of the application if applicable[2]:	
	• Co-ordinating investigator (for multicentre trial):	☐
	• Principal investigator (for single centre trial):	X
C.2.5	**Complete below** :	
C.2.1.1	Organisation: *Oxford University Hospitals NHS Trust*	
C.2.5.1	Name : *Professor B L Ferry*	
C.2.5.2	Address : *Clinical laboratory immunology , Churchill hospital, Oxford OX3* 7LA	
C.2.5.3	Telephone number :*01865225983*	
C.2.5.4	Fax number :*01865225990*	
C.2.5.5	E-mail :*Berne.Ferry@ouh.nhs.uk*	

D END OF TRIAL

D.1	**Date of the end of the complete trial in all countries concerned by the trial**?
D.1.1	(2015/04/14):

D.2	**Is it an early termination?**[3]	yesX no ☐

1 OJ, C82, 30.3.2010, p. 1; hereinafter referred to as 'detailed guidance CT-1'.
2 According to national legislation.
3 Cf. Section 4.2. of the detailed guidance CT-1.

D.2.1	If yes, give date (2015/04/14):
D.2.2	Briefly describe in an annex (free text): *attached*
D.2.2.1	The justification for early termination of the trial;
D.2.2.2	Number of patients still receiving treatment at time of early termination in the MS concerned by the declaration and their proposed management;
D.2.2.3	The consequences of early termination for the evaluation of the results and for overall risk benefit assessment of the investigational medicinal product.

E SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

E.1 I hereby confirm that/confirm on behalf of the sponsor that:

- The above information given on this declaration is correct; and
- That the clinical trial summary report will be submitted within the applicable deadlines in accordance with the applicable guidance by the Commission.[4]

E.2	**APPLICANT TO THE COMPETENT AUTHORITY** (as stated in C.1)	☐
E.2.1	Date :	
E.2.2	Signature :	
E.2.3	Print name:	

E.3	**APPLICANT TO THE ETHICS COMMITTEE** (as stated in C.2) **:**	☐
E.3.1	Date : 16/04/2015	
E.3.2	Signature :	
E.3.3	Print name: B L Ferry	

Reasons for Early Termination : See letter below

[4] Section 4.3. of the detailed guidance CT-1.

Oxford University Hospitals NHS
NHS Trust

April 16th 2015

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APPENDIX 1

Dear Colleague,

Assessment of Salmonella Typhim Vi(TM) vaccine (Sanofi Pasteur MSD) for the investigation of selective Antibody deficiency to polysaccharide.

This is a single centre study which was designed to assess patient and control groups response to polysaccharide vaccination. specifically, Typhim Vi vaccination in comparison to Pneumovax vaccination. The study was expected to last three years from recruitment of first patient.(July 2011) or until the last patient had been enrolled.

We would like to terminate this study early for the following reasons.

PATIENTS in Immunology Clinics

1. CVID is a very rare disease, (1 in 50,000 to 1 in 75,000 prevalence)
2 CVID is a diagnosis of exclusion and over the last 10 years, a large number of new single gene disorders have been identified that patients who previously would have been identified as having CVID have not been diagnosed as having. New genetic assays have identified these patients as having another disease entity other than CVI. It is a fact that over the time period of this trial, patients who would previously have been diagnosed with CVID actually were shown to have CD40 Ligand deficiency, X-Linked lymphoproliferative disease, DOCK 8 deficiency and XMEN syndrome, amongst other diagnoses. While this is excellent for the patients..
3 This has resulted in a much slower uptake of patients newly diagnosed as CVID.
4 Since the beginning of this trial, use of the vaccine has become part of normal clinical care, as an element in the diagnostic toolkit to assess the immune status of patients. The data from 6 of these patients has been used in the analysis of the trial (appendix 2) without specific consent. As all of these patients have a chronic illness and are cared for by the immunology care team, it should be possible to obtain retrospective consent from the remaining 6 patients. We would like permission to use the data under these conditions
5 The recruitment rate of patients has virtually stopped in the last 6 months.
6 The licenced Salmonella vaccine is already used in suspected CVID patients as a diagnostic tool. During the course of this trial, despite the evidence not being available, there is now a move to use the vaccine as a standard of care diagnostic tool because of the complex immune status of the potential participants
7 The numbers of new CVID patients we have been able to study however have provided us with pilot data which does back the original aim of the trial and we have published an abstract of this work which accompanies this declaration.
8 We intend to publish the summary report as a peer reviewed paper within 12 months.

NORMAL Controls

9 These were recruited from the Travel clinic at the University of Oxford and the trial was being coordinated and run by an experienced nurse.
10 The retirement of this nurse in Autumn 2014 led to decreased nursing time at the clinic and despite many helpful discussions, it has been very difficult to continue this part of recruitment for the trial and we have been unable to recruit any further volunteers.

For the reasons given above, we feel that it is proving extremely difficult to continue with this study. We are satisfied that the data we have collected to date- and which we have presented at an International conference in October 2014 to very interested colleagues- while being preliminary is also sufficient for clinicians in this field to make an informed clinical decision as to whether they wish to switch to using anti-Salmonella vaccine.

We have reason to believe that the data we have collected to date from this trial will be clinically useful in our field.

We include the poster we presented at ESID 2014 as Appendix 2

We hope to publish the pilot data in a peer reviewed paper within 12 months of the close of this trial

We hope that the reasons given above are clear and we would be happy to provide any further information required

Yours Sincerely

B L Ferry

APPENDIX 2

Oxford University Hospitals NHS
NHS Trust

Salmonella typhim Vi® vaccine (Sanofi Pasteur MSD) for the investigation of antibody deficiency to polysaccharide: preliminary results of UK study

C.S. Evans[1], A.C. Cullinane[1], E.A.L. Bateman[1], J.Miller[2], F. Dhalla[2], D. Arnold[2], R. Jain[2], S.Y. Patel[2], S.A. Misbah[2], B.L. Ferry[1]
[1]*Department of Clinical Laboratory Immunology, Churchill Hospital, Oxford, UK,*
and [2]*Clinical Immunology, John Radcliffe Hospital, Oxford, UK*

Introduction

Evaluation of antigen-specific antibody responses is important in diagnosing suspected antibody deficiency. It has been suggested that the licensed polysaccharide vaccine *Salmonella Typhim Vi®* may be an appropriate substitute for the current *Pneumovax* test vaccine. This may be of particular utility following the introduction of the conjugate pneumococcal vaccine, *Prevnar*, into the childhood vaccination schedule, since this prior conjugate vaccine exposure may complicate interpretation of polysaccharide test vaccination with *Pneumovax*.

Limited data exist defining vaccine response ranges to *Salmonella Typhim Vi®*. We compared responses to *Salmonella Typhim Vi®* vaccine in suspected antibody deficient patients with those of healthy controls, and also with their responses to the *Pneumovax* vaccine.

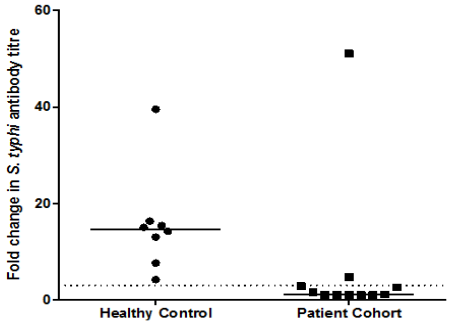

Figure 1. Fold change in *S. typhi* antibody titre in healthy controls and antibody deficient patients following vaccination with *Salmonella Typhim Vi™*

Results

3/11 healthy controls had pre-vaccination Salmonella antibody titres >120U/ml, likely due to prior exposure not identified during recruitment. These participants were excluded from data analysis. None of the patient cohort had Salmonella antibodies prior to vaccination.

Based on previous work [1], we defined a vaccine response as a 3-fold increase in antibody titre. Using this cut-off all 8 healthy controls responded to the vaccine, with a median fold increase of 14.6 (range 4.2-39.5). However, only 2/11 patients demonstrated a response, with median fold increase of 1.0 (range 1.0-51.0)(**Figure 1**).

These results were very similar to the *Pneumovax* responses, which showed a median fold increase of 1.9 in the patient cohort. The patients who responded to the Salmonella vaccine also responded to pneumococcal (**Fig. 2**); the large difference in fold change demonstrated by patient 7 is due to the greater analytical range of the VaccZyme Anti-*S typhi* Vi IgG ELISA Kit compared to the pneumococcal ELISA.

Patient 9 was the only patient to demonstrate a response to *Pneumovax* (7.4 fold increase) but not to Salmonella (1.6 fold increase).

Table 1. Healthy control and patient cohorts

	Healthy controls (n=11)	Patients (n=11)
Sex M:F (% male)	7:4 (64%)	5:6 (45%)
Median age (range)	24 (23-47)	58 (28-74)

Method

11 patients with diagnosed or suspected antibody deficiencies from Clinical Immunology at the John Radcliffe Hospital, Oxford and 11 healthy controls from the Oxford University Travel Clinic were recruited under the ethical approval of the Oxfordshire Research Ethics Committee (10/H0604/75).

The VaccZyme Anti-*S typhi* Vi IgG ELISA Kit (The Binding Site Group Ltd.) and an in-house ELISA were used to quantify antibody levels to salmonella and pneumococcal respectively, prior to vaccination with *Salmonella Typhim Vi®* (Sanofi Pasteur MSD) and *Pneumovax,* and 3-4 weeks post-vaccination.

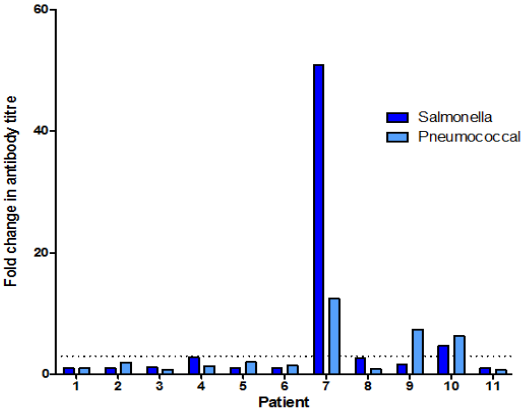

Figure 2. Vaccine responses to Salmonella Typhim Vi vs Pneumovax in antibody deficient patients

Conclusions

We have compared the *Salmonella Typhim Vi®* vaccine with *Pneumovax* for the evaluation of polysaccharide responses in antibody-deficient patients. Our data suggest *Salmonella Typhim Vi®* may be an acceptable substitute for *Pneumovax* for use as a polysaccharide test vaccine in the workup of suspected antibody deficiencies, and that a 3-fold increase in antibody titre is an appropriate cut-off to define a response.

This is an on-going study and we hope to further corroborate these findings through recruitment of additional patients and healthy controls.

Reference: [1] Ferry BL, Misbah SA, Stephens P, Sherrell Z, Lythgoe H, Bateman E, Banner C, Jones J, Groome N, Chapel HM. Development of an anti-Salmonella typhi Vi ELISA: assessment of immunocompetence in healthy donors. Clinical & Experimental Immunology 2004; **136**:297-303.