Clinical Protocol: CRC374/Ad4HIV

Statistical Analysis Plan

Role	Signature	Date
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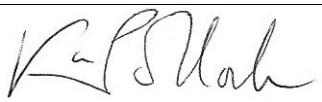
Dr Katrina Pollock Imperial College London Principal Investigator		27 July 2021
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Any other sponsor Representatives	N/A	N/A

Version Control Log

Version No.	Page No.	Section	Change Details
0.1	Various	Various	Initial version.
0.2	Various	Various	After initial review by other team members
0.3	Various	Various	After meeting with investigators, Primary endpoint was changed to nasal mucosal secretion

Table of Contents

1 Abbreviations

Ab	Antibodies
CTU	Clinical Trials Unit
ELISA	Enzyme Linked Immunosorbent Assay
HIV	Human immunodeficiency virus
IMP	Investigational Medical Product
LAP	Lab Analysis Plan

2 Study Rationale

This study aims to evaluate the use of new HIV-1 vaccine products in a phase I clinical trial by exploring the impact of different boosting options for MVA-C and CN54gp140 for oral Ad4 serotype 4 vector prime expressing HIV-1 CN54 (Ad4-EnvCN54) to optimise systemic and mucosal responses.

This regime will identify the most immunogenic strategy for the induction of durable mucosal and systemic protective antibody responses. This will facilitate up-selection of the most promising regime for accelerated development towards a phase II efficacy trial.

Part 1 is exploratory and designed to select conditions capable of promoting enhanced systemic and mucosal B cell responses in a limited number of participants.
Part 2 is dependent upon Part 1 and is designed to study groups selected on performance in part 1 in an expanded number of subjects. Data from both stages will be combined for safety and immunological analyses.

3 Study Design

To identify an effective Ad4 based oral vaccine that promotes systemic and mucosal responses to the HIV-1 envelope glycoprotein. This study will adopt a two-part adaptive clinical trial.

The study will assist in rapidly screening the impact of different routes, combination regimes and boosting options to Ad4-EnvCN54, MVA-CN54 and CN54gp140 / MPLA, to augment systemic and mucosal antibody responses following initial priming with Ad4.

This is a phase I trial in healthy male and female participants. The study will enrol 48 participants to Part 1 (6 in each group) and 12 participants in Part 2. Recruitment will select potential participants who are willing to undergo serial blood draws. Additional participants may be enrolled to replace any early withdrawals.

The clinical trial was conducted at the NIHR Imperial Clinical Research Facility (ICRF) at Hammersmith Hospital, London.

3.1 Part 1

In Part 1, n=6 participants per group will be randomised to groups A-H (Table 1). This design varies the number of Ad4 administrations, from 1 to 3, combined with either CN54gp140 protein boosts (A-D) or co-administration of gp140 with MVA (E-H).

Arm 1 (Groups A-D): Depending on the allocation of groups, participants will receive Ad4-EnvCN54 or placebo orally, CN54gp140/MPLA, and placebo I.M injections at month 0 (Week 0), 3 (Week 12) & 6 (Week 24).

Arm 2 (Groups E-H): Depending on the allocation of groups, participants will receive Ad4-EnvCN54 or placebo orally, CN54gp140/MPLA and MVA-CN54 I.M injections at month 0 (Week 0), 3 (Week 12) & 6 (Week 24).

Groups A (gp140 alone) and E (MVA-CN54/CN54gp140 alone) will serve as control groups to assess the added benefit of the Ad4 vector. Each vaccine group (A-H) will be assessed for number of mucosal responders (mucosal antibody (nasal/rectal/genital) as measured by ELISA), and titre (mucosal and systemic) of antigen specific binding antibody.

Enrolment through to completion of the primary immunological assessment for each group will be 7 months.

3.2 Part 2

The study will enrol an additional 6 participants to two groups in Part 2 (Table 2). The best regimes from groups A-D (Ad4-EnvCN54 /CN54 rgp140) and/or E-H (Ad4-EnvCN54/MVA-CN54/CN54 rgp140) (if meeting the pass criteria) will be expanded to n=12.

The pass criteria for mucosal responders will be analysed in the first 32 participants (first four participants from each dosing group) at week 26 (the primary immunogenicity endpoint). The primary pass criteria will assess IgA responses in rectal mucosal samples, whereby a group will be considered to have met the pass criteria if there is a mucosal IgA titre greater than 100 ng/mL in the rectal secretions of ≥2 participants within a group at week 26.

However, if none of the groups meet this criterion, the selection will be expanded to include IgA responses from other mucosal secretions (nasal, cervico-vaginal (female participants) and semen (male participants)).

In the event that none/more than one of the groups meet this criterion, the selection will be based on week 26 median serum IgG titres. Statistical analysis comparing across groups A-D and E-H will be performed using the Kruskal-Wallis Test with Dunn's correction for multiple comparisons.

In the event that there is no statistical significance observed, the vaccination groups with the least and greatest exposure to the vaccine products (A and D) will be expanded into part 2 to allow for greater assessment of safety data.

4 Vaccination Schedule – Part 1 & Part 2

The doses, methods and schedule of immunisation are described below.

Table 1: Schedule of Doses and Method of Vaccinations

PART I							PART II	
	Group	N	Month 0	Month 3	Month 6		N	Vaccinations 1,2,&3
ARM 1	A	6	Oral placebo	CN54gp140 + Oral placebo +I.M placebo	CN54gp140 + Oral placebo +I.M placebo		12	Selected dosage from Part I
	B	6	Ad4-EnvCN54	CN54gp140 + Oral placebo +I.M placebo	CN54gp140 + Oral placebo +I.M placebo			
	C	6	Ad4-EnvCN54	CN54gp140 + Ad4-EnvCN54 +I.M placebo	CN54gp140 + Oral placebo +I.M placebo			
	D	6	Ad4-EnvCN54	CN54gp140 + Ad4-EnvCN54 +I.M placebo	CN54gp140 + Ad4-EnvCN54 +I.M placebo			
ARM 2	E	6	Oral placebo	CN54gp140 + MVA-CN54 + Oral placebo	CN54gp140 + MVA-CN54 + Oral placebo			
	F	6	Ad4-EnvCN54	CN54gp140 + MVA-CN54 + Oral placebo	CN54gp140 + MVA-CN54 + Oral placebo			
	G	6	Ad4-EnvCN54	CN54gp140 + MVA-CN54 + Ad4-EnvCN54	CN54gp140 + MVA-CN54 + Oral placebo			
	H	6	Ad4-EnvCN54	CN54gp140 + MVA-CN54 + Ad4-EnvCN54	CN54gp140 + MVA-CN54 + Ad4-EnvCN54			
		48					max 12	

5 Randomisation

5.1 Part 1

The study will use sentinel dosing as a safety precaution. The first 6 participants successfully enrolled into the trial will be sequentially pre-allocated to treatment groups B, C, D, F, G and H. The first participant will be enrolled to group B. The safety data for this participant will be reviewed at day 7 before enrolling the next participant to group C. This process will be repeated for the other groups. This will ensure an escalation of the number of Ad4-EnvCN54 administrations combined with either CN54gp140 protein boosts (B-D) or co-administered CN54gp140 and MVA-CN54 (F-H).

After the accumulated safety data (up to day 7) for the 6th participant has been reviewed, on their first day of dosing the remaining participants will be block randomised into groups as follows:

- Block 1 (n=10): A, A, B, C, D, E, E, F, G, H
- Blocks 2-5 (n=8/block): A, B, C, D, E, F, G, H

5.2 Part 2

Participants will be randomised to the groups chosen for expansion. Participants will be blind to the vaccine regime group to which they have been assigned. The laboratory undertaking immunological analysis will also be blinded to group and dosing regimen to prevent bias in analysis.

Six additional healthy participants per group will be recruited and randomised to the best two regimes from A-D (Ad4-EnvCN54/CN54gp140) and E-H (Ad4-EnvCN54/MVACN54/CN54gp140).

The visits schedule for participants in Part 2 will be the same as that for participants in Part 1.

6 Blinding

This is a single-blind, randomised trial with placebo controls. Participants will be block-randomised centrally, using the randomisation schedule produced by the statisticians at the Surrey CTU, to the study groups shown in Table 1, using a computer-generated algorithm with a back-up manual procedure. Randomisation will be stratified on the basis of gender.

All participants in Part 1 and Part 2 will be blinded to the vaccine regime group to which they have been assigned. The laboratory teams undertaking immunological analysis will also be blinded to group and dosing regimen to prevent bias in analysis. The clinical team will remain unblinded to the vaccine regime of trial participants throughout.

7 Replacing Withdrawals

As the number of participants per group is small and hence each participant is essential to the study, those who withdraw from the study will be replaced before completion of the week 26 visit.

8 Study hypothesis

The study hypothesis is that priming with an orally delivered mucosal replicating vector (Ad4) will significantly enhance the magnitude and durability of mucosal and systemic antibody responses to HIV-1 gp140 on boosting with recombinant protein, with or without co-administration of a non-replicating pox vector (MVA-C).

9 Study Populations

Four different study populations have been defined and listed according to their importance.

1. **Safety population**

Those participants who received at least one dose of experimental vaccine will be included in the safety population

2. **Per-protocol (PP) population:**

PP includes all participants randomised and immunised with all scheduled vaccinations, and who completed the trial with no major protocol deviations

3. **Intention-to-treat (ITT) population:**

ITT population includes all participants randomised and given at least one vaccination in the trial

4. **Modified-Intention-to-treat (mITT):**

mITT population includes all participants randomised and given at least one immunisation in the trial (including those participants whose sample collection
occurred outside the allowed windows)

10 Study Endpoints

10.1 Primary Endpoints Measure(s) - Part 1 & Part 2

10.1.1 Immunogenicity

Antigen specific mucosal (nasal and rectal for all, cervico-vaginal for women, and semen for men,) antibody (ng/ml) responses two weeks after the final immunisation. Out of these, nasal is considered to be the site with primary importance.

10.1.2 Safety and Tolerability

- Proportion of participants with severe or greater (Grades 3-4) adverse

reactions during the study
- Proportion of participants with vaccine-related serious adverse events (SAEs) throughout the study period

10.2 Secondary Endpoints Measure(s) – Part 1 & Part 2

10.2.1 Immunogenicity:

To assess the kinetics of immune responses elicited by each of the vaccine regimens:

Frequency of serum and mucosal binding antibodies to HIV CN54gp140 antigen measured by binding ELISA.

10.3 Exploratory Endpoints Measure(s) - Part 1 & Part 2

The following endpoints are measured as part of the exploratory analysis.

- Frequency and magnitude of HIV-gp140 specific B-cell-mediated responses in the systemic compartment measured by B-cell ELISPOT.
- Frequency, titre and avidity of serum binding antibodies to other HIV Env antigens (alternative clades) by ELISA or other assays.
- Frequency and titre of serum neutralising antibodies to homologous virus, and, if warranted a wider a panel of viruses representing different clades.
- Longevity of serum and mucosal responses at 12 months following final immunization
- Frequency and magnitude of HIV-specific T-cell mediated responses measured by T-cell and ICS (Intracellular Cytokine Staining).
- PBMC ex-vivo HIV susceptibility assay
- Measurement of CN54gp140 serum IgA responses over time
- Frequency and magnitude of T-cell chemokine and cytokine release following ex-vivo antigen stimulation quantified by Luminex.
- Epitope mapping of B- and T-cell responses
- Serum antibody responses to Ad4-EnvCN54 and MVA-CN54 as a marker of anti-vector immunity and vaccine “take”
- Ex vivo analysis of colorectal biopsies for activation markers by ICS (Part 2 only)
- Susceptibility of rectal biopsies to HIV-infection – infection assays

Durability of responses will also be determined by measurement of response at weeks 26 (visit 9) and 48 (visit 11) of the trial schedule

11 Data Transfers

Most of the data is held in Promasys® database maintained by the section of data management at the Surrey CTU except the results of various laboratory results which are collated and held by the laboratory manager at Imperial College London.

Laboratory manager at ICL will send the laboratory data held in spreadsheets to the data management team at Surrey CTU.

Once the SAP is finalised and signed off, SAS datasets held in Promasys database and spreadsheets received from Imperial laboratory will be transferred into a folder that is only accessible by the statisticians and a data transfer form is signed by the both the data manager and the statistician to confirm the data transfer has been successfully undertaken.

12 Statistical Analysis

12.1 Responders

All mucosal and serum samples will be screened for antigen specific antibodies (IgG and IgA). The absolute levels of antibody in samples that are found to be positive will be determined using a standardised and quantitative ELISA developed in Robin Shattock's laboratory at Imperial College London. In this sandwich capture ELISA, the Ab of interest is captured by the relevant target antigen and then detected using a labelled isotype specific secondary Ab. An estimate of the concentration of Ab in the sample is calculated by interpolation relative to a standard curve based on titration of purified human standards IgG or IgA captured by anti-human kappa/lambda-specific antibodies.

The number of 'responders' in each assay will be presented by time-point and group as a proportion with 95% confidence interval. A 'responder' will be defined as a participant in whom a response was detected in the immunogenicity sample taken two weeks after the final vaccination. A positive result will be defined relative to a pre-defined cut-off threshold value and assays will be validated using predefined thresholds based on the responses to positive and negative control stimuli. More information on the assay and definition of positive results will be supplied in the LAP. Titres of antigen specific antibodies will be described by time-point and group and compared using rank tests where appropriate.

12.2 Primary Endpoint Analysis

12.2.1 Assessing Immunogenicity

The immunogenicity assessment involves collecting mucosal antibody responses including nasal, rectal, cervico-vaginal, semen, secretion samples at weeks 0, 4, 12, 16, 24, 26 and 48.

Nasal secretions will be considered the most important of all.

Separately for each mucosal response, the proportion of responders and its 95% confidence interval will be reported at each time point for each group.

Separately for each mucosal response and type of antibody (IgG and IgA), the null hypothesis of no association between responders and vaccination group is tested using the Fisher's exact test implemented using the FISHER option in the TABLES statement of the procedure PROC FREQ in SAS systems.

The above method is used in both part 1 and part 2. Part-specific methods are specified in sections 12.2.1.1 and 12.2.1.2.

12.2.1.1 Part 1

The primary endpoint involves statistically contrasting the number of responses with regards to each of the mucosal antibody responses collected in week 26 between the vaccination groups.

In part 1, due to the small number of subjects in each group (n=6) it is unlikely that the data will follow the assumptions required in parametric tests such as Analysis of Variance. Non-parametric methods based on ranks will therefore be adopted.

SAS procedure PROC NPAR1WAY with option WILCOXON is used to invoke the Kruskal-Wallis test, a non-parametric test based on ranks, to statistically contrast vaccination groups, separately, with respect to each mucosal antibody response.
This analysis is performed separately for IgG and IgA antibodies.

If any one group is significantly different from the rest of the groups, i.e. a significant p-value is obtained from the main analysis, Dwass, Steel, Critchlow-Fligner multiple comparison post-hoc tests will be carried out to identify the differences between groups, implemented using the DSCF option in NPAR1WAY procedure in SAS.

An excerpt of the SAS code that will be used in the primary endpoint analysis is as below.

```
proc npar1way data=data wilcoxon DSCF;
class group;
run;
```

12.2.1.2 Part 2

As 12 participants per group, i.e. 6 each from part 1 and 2 and 24 in total are involved in part 2, the statistical analysis could be based on parametric methods such as a General Linear Mixed Model, if the data from individual group are not severely skewed.

A General Linear Mixed Model is employed using PROC MIXED statistical procedure in SAS systems, separately, considering each mucosal response variable as outcome variable, the arm (arm1 and arm2) as a fixed effect and gender (female and male) as a covariate. The participant will be used as a random effect. The denominator degrees of freedom are adjusted using the Kenward-Roger approximation.

An excerpt of the SAS code that will be used in part 2 is given below.

```
proc mixed data=data;
class group gender;
model response=arm gender/ddfm=kr;
random participant;
run;
```

If data are found to be severely skewed, the non-parametric methods as described in section 12.2.1.1 in part 1 will be used to contrast response variables between arms (arm 1 and arm 2). In this case, gender cannot be included in the analysis.

12.2.2 Safety and Tolerability

Safety data analysis will be based on the safety population and procedure described in here is applicable for both part 1 and part 2.

The following table illustrates the schedule used in capturing and monitoring adverse events.

Visit		1	2	3	4	5	6	7	8	9	10	11
Study Month		M0			M3			M6				M12
Study Week		W0	W1	W4	W12	W13	W16	W24	W25	W26	W28	W48
Study Day		D0	D7	D28	D84	D91	D112	D168	D175	D182	D196	D336
Visit Windows (Days)	-90		±1	±2	[1] -7/+14	±1	±2	[1] -7/±14	±1	±2	±2	±14
Solicited Adverse Events		X[6]	X		X[6]	X		X[6]	X			
Review Solicited AE on diary card			X			X			X			
Unsolicited Adverse events		X[6]	X	X	X[6]	X	X	X[6]	X	X	X	
Serious adverse events		X	X	X	X	X	X	X	X	X	X	X

Information on three different types of adverse events/reactions were collected at various timepoints, particularly pre- and post- vaccination on the day, throughout the study namely the serious, solicited, unsolicited adverse events. Adverse events/reactions are categorised both in terms of the severity (graded 1-4) and relatedness to the IMP (unrelated, unlikely, possible, probable, and definitely related).

As part of the safety and tolerability aspect of the primary endpoint reporting, the following will be reported,

- The frequency and percentage of participants with vaccine-related serious adverse events (SAEs) throughout the study period

- The frequencies and percentages of participants with severe or greater (Grades 3-4) adverse reactions at each time point during the study will be reported.

In addition to that, the frequencies and percentages of all adverse events/reactions separately for solicited, unsolicited and in combination will be reported and grouped by time point (separately for each time points and for all time points combined), severity

(graded 1-4) and relatedness (unrelated, unlikely, possible, probable, and definitely related). Whenever possible results will be split between arm 1 and arm 2 in part 1.

12.3 Secondary Endpoint Analysis

The secondary endpoints are related to the systemic responses which are based on serum antibody levels as specified in section 10.2. They will be analysed in the same way as the primary endpoint described in section 12.2.1 and 12.2.2. The same approach is used in both part 1 and part 2.

12.4 Exploratory Endpoint Analysis

The exploratory analyses entail a wide range of laboratory analysis and procedures including ELISA, ICS, ELISPOT, Luminex and the likes, resulting with either a continuous outcome or binary outcome variable. The same approach is used in both part 1 and part 2.

All exploratory endpoints specified in section 10.3 will be analysed as per the primary endpoint as described in section 12.2.1 and 12.2.2.

13 Summary Statistics

Summary statistics of responses measured at multiple time points will be reported by each time point separately as well as all time points combined. These summaries will be classified by group and by gender within each group.

- Mucosal CN54gp140-specific antibody responses (IgA & IgG)
- Systemic CN54gp140-specific antibody responses (IgA & IgG)
- HIV-gp140 specific B-cell-mediated responses
- Serum binding antibodies to other HIV Env antigens
- Serum neutralising antibodies to homologous virus
- HIV-specific T-cell mediated responses
- T-cell chemokine and cytokine release
- Colorectal biopsies (Part 2 only)

and other responses related to exploratory outcomes

The frequencies and percentages of each of the responses listed above will also be reported.

Summary statistics of variables taken the screening will be reported separately by group, and by groups combined.

- Demographic information such as age and ethnic origin
- The general physical examination measured weight (kg), height (cm), BMI, temperature, blood pressure and heart rate (vital signs), inspection of the skin and respiratory, cardio-vascular, abdominal, and neurological systems

Continuous variables are summarised by a measure of central tendency (mean/median) and a measure of spread (standard deviation / range /Inter Quartile Range) depending on the skewness of the data.

Categorical variables are summarised by frequencies and percentages.

For each variable analysed, a boxplot will be produced to graphically illustrate the differences between groups, in terms of the medians, range, interquartile range. Boxplots will also highlight the outliers.

14 Multiplicity

The results presented will not be adjusted for multiplicity accounting for comparison of multiple outcomes. However, multi-group comparisons in part 1 will be adjusted for pairwise comparisons following a significant omnibus test.

15 Missing data

Missing data will not be imputed. Where they occur, in the parametric analysis, they will be assumed to be missing at random, so that likelihood-based analyses (GLMM) will be considered robust. Case deletion will be automatic for non-parametric methods.

16 Interim analysis

No interim analyses are planned for this study.

17 Statistical software

Both SAS® version 9.4 and STATA IC version 16 will be used in the analysis and quality checking processes.

18 List of Tables

Table 1.1 – Part 1 - Primary Endpoint – Immunogenicity
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Table 3.1 – Part 1 – Secondary Endpoints
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Summary Statistics 1.1 – Part 1 – Mucosal Response
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Summary Statistics 3.1 – Part 1 – Exploratory Endpoints
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Summary Statistics 4.1 – Part 1 - Demographics
Summary Statistics 4.2 – Part 2 - Demographics

Summary Statistics 5.1 – Part 1 - Vital Signs
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Summary Statistics 6.1 – Part 1 - Medical History
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Summary Statistics 7.1 – Part 1 - Lab Parameters
Summary Statistics 7.2 – Part 2 - Lab Parameters

Example tables

Table 1.1a – Primary endpoint - Part 1 – Immunogenicity - Mucosal antibody responses at 26 weeks (numerical)

		Arm 1				Arm 2				Kruskal-Wallis test p-value
	Group	A	B	C	D	E	F	G	H	
		IgG								
	N									
Nasal (ng/ml)	Median (IQR)									
Rectal (ng/ml)	Median (IQR)									
Cervico-vaginal (ng/ml)	Median (IQR))									
Semen (ng/ml)	Median (IQR)									
		IgA								
	N									
Nasal (ng/ml)	Median (IQR)									
Rectal (ng/ml)	Median (IQR))									
Cervico-vaginal (ng/ml)	Median (IQR)									
Semen (ng/ml)	Median (IQR)									

Table 1.1b – Primary endpoint - Part 1 – Immunogenicity –Multiple comparison post-hoc tests following Kruskal-Wallis test*

	IgG					IgA			
Comparison	**Nasal**	**Rectal**	**Cervico-vaginal**	**Semen**		**Nasal**	**Rectal**	**Cervico-vaginal**	**Semen**
	p-value	**p-value**	**p-value**	**p-value**		**p-value**	**p-value**	**p-value**	**p-value**
A vs B									
A vs C									
A vs D									
B vs C									
B vs D									
C vs D									
E vs F									
E vs G									
E vs H									
F vs G									
F vs H									
G vs H									
A vs E									
A vs F									
A vs G									
A vs H									
B vs E									
B vs F									
B vs G									
C vs D									
C vs E									
C vs F									
C vs G									
C vs H									

	IgG					IgA			
Comparison	**Nasal**	**Rectal**	**Cervico-vaginal**	**Semen**		**Nasal**	**Rectal**	**Cervico-vaginal**	**Semen**
D vs E									
D vs F									
D vs G									
D vs H									
Arm 1 vs Arm 2 (A-D) vs (E-H)									

***Dwass, Steel, Critchlow-Fligner multiple comparison post-hoc tests**

Table 1.2 – Primary endpoint - Part 2 – Immunogenicity - Mucosal antibody responses at 26 weeks

				Kruskal-Wallis test p-value	Group effect* (95% CI) (Arm 2 vs Arm 1)	P value
		Arm 1 group	**Arm 2 group**			
		IgG				
	N					
Nasal (ng/ml)	Mean (SD)					
Rectal (ng/ml)	Mean (SD)					
Cervico-vaginal (ng/ml)	Mean (SD)					
Semen (ng/ml)	Mean (SD)					
		IgA				
	N					
Nasal (ng/ml)	Mean (SD)					
Rectal (ng/ml)	Mean (SD)					
Cervico-vaginal (ng/ml)	Mean (SD)					
Semen (ng/ml)	Mean (SD)					

*Fixed effects group coefficient, adjusted for gender.

Summary Statistics 1.1 – Part 1 - Mucosal antibody responses - IgG

		Arm 1												Arm 2											
Group		A			B			C			D			E			F			G			H		
		M	F	All	M	F	All	M	F	All	M	F	All	M	F	All	M	F	All	M	F	All	M	F	All
n				6			6			6			6			6			6			6			6
		IgA																							
		Week 0																							
Nasal (ng/ml)	Mean (SD)																								
Rectal (ng/ml)	Mean (SD)																								
Cervico-vaginal (ng/ml)	Mean (SD)																								
Semen (ng/ml)	Mean (SD)																								
		Week 4																							
Nasal (ng/ml)	Mean (SD)																								
Rectal (ng/ml)	Mean SD																								
Cervico-vaginal (ng/ml)	Mean (SD)																								
Semen (ng/ml)	Mean (SD)																								
		Week 12																							
Nasal (ng/ml)	Mean (SD)																								
Rectal (ng/ml)	Mean (SD)																								
Cervico-vaginal (ng/ml)	Mean (SD)																								
Semen (ng/ml)	Mean																								

		Arm 1												Arm 2											
Group		A			B			C			D			E			F			G			H		
		M	F	All	M	F	All	M	F	All	M	F	All	M	F	All	M	F	All	M	F	All	M	F	All
n				6			6			6			6			6			6			6			6
	(SD)																								
		Week 16																							
Nasal (ng/ml)	Mean (SD)																								
Rectal (ng/ml)	Mean (SD)																								
Cervico-vaginal (ng/ml)	Mean (SD)																								
Semen (ng/ml)	Mean (SD)																								
		Week 24																							
Nasal (ng/ml)	Mean (SD)																								
Rectal (ng/ml)	Mean (SD)																								
Cervico-vaginal (ng/ml)	Mean (SD)																								
Semen (ng/ml)	Mean (SD)																								
		Week 25																							
Nasal (ng/ml)	Mean (SD)																								
Rectal (ng/ml)	Mean (SD)																								
Cervico-vaginal (ng/ml)	Mean (SD)																								
Semen (ng/ml)	Mean (SD)																								
		Week 26																							

		Arm 1												Arm 2											
Group		A			B			C			D			E			F			G			H		
		M	F	All	M	F	All	M	F	All	M	F	All	M	F	All	M	F	All	M	F	All	M	F	All
n				6			6			6			6			6			6			6			6
Nasal (ng/ml)	Mean (SD)																								
Rectal (ng/ml)	Mean (SD)																								
Cervico-vaginal (ng/ml)	Mean (SD)																								
Semen (ng/ml)	Mean (SD)																								
		Week 28																							
Nasal (ng/ml)	Mean (SD)																								
Rectal (ng/ml)	Mean (SD)																								
Cervico-vaginal (ng/ml)	Mean (SD)																								
Semen (ng/ml)	Mean (SD)																								
		Week 48																							
Nasal (ng/ml)	Mean (SD)																								
Rectal (ng/ml)	Mean (SD)																								
Cervico-vaginal (ng/ml)	Mean (SD)																								
Semen (ng/ml)	Mean (SD)																								