Trial Title: A phase I/IIa, single centre, dose-escalation study to assess the safety and immunogenicity of the recombinant adenovirus Meningococcal B vaccine candidate ChAdOx1 MenB.1

Internal Reference Number / Short title: 2017, 04 Investigating a new Vaccine Against Meningitis B (in Oxford) - VAMBOX

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Sponsor:	University of Oxford
Funder:	Medical Research Council / National Institute of Healthcare Research, British Research Council

Investigator Agreement

"I have read this protocol and agree to abide by all provisions set forth therein. I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice. We declare no financial conflict of interest in this study."

Chief Investigator Signature:

Principal Investigator Signature:

Statistician Signature:

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

Contents

1. KEY TRIAL CONTACTS

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2. SYNOPSIS

Trial Title	**A phase I/IIa, single centre, dose-escalation study to assess the safety and immunogenicity of the recombinant adenovirus Meningococcal B vaccine candidate ChAdOx1 MenB.1**	
Internal ref. no. (or short title)	2017,04 Investigating a new Vaccine Against Meningitis B (in Oxford)- VAMBOX	
Clinical Phase	Phase I/IIa	
Trial Design	Single centre dose escalation safety and immunogenicity interventional study.	
Trial Participants	Healthy adults aged 18 to 50 years, inclusive	
Planned Sample Size	79-90 participants	
Treatment duration	Single dose +/- booster dose at 1 month or 6 months	
Follow up duration	1 year (52 weeks)	
Planned Trial Period	December 2017 (start of recruitment) – 30/06/2022 (End Of Study Date).	
	Objectives	Outcome Measures
Primary	To investigate safety and tolerability of 2.5 x 10^{10} viral particles (VP) or 5x10^{10} VP of the proposed ChAdOx1 MenB.1 vaccine against meningococcus capsular group B in healthy adults aged 18 to 50 years of age, when given one dose +/- one booster dose; and when given as a booster following primary Bexsero vaccination, in	The recording and assessment of local and systemic adverse events following administration of each vaccine dose: 1. Tenderness and pain at the injection site 2. Induration 3. Redness 4. Swelling

	comparison to standard two dose Bexsero vaccination (the current standard of care) or two dose Trumenba vaccination.	5. Headache 6. Malaise 7. Myalgia 8. Nausea and/or vomiting 9. Anorexia 10. Fever 11. Arthralgia 12. Blood parameters Any unsolicited symptom(s) not listed above
Secondary	To determine the immunogenicity of 2.5 x 10^{10} VP or 5x10^{10} VP of the proposed ChAdOx1 MenB.1 vaccine against meningococcus capsular group B in healthy adults aged 18 to 50 years of age when given one dose +/- one booster dose; and when given as a booster following primary Bexsero vaccination in comparison to standard two dose Bexsero vaccination (the current standard of care) or two dose Trumenba vaccination.	Use of the Serum bactericidal antibody (SBA) assay against homologous strains.
Tertiary	A) To utilize exploratory immunogenicity assays to determine the immunogenicity of 2.5 x 10^{10} VP or 5x10^{10} VP of the proposed ChAdOx1 MenB.1 vaccine against meningococcus capsular group B in healthy adults aged 18 to 50 years of age when given one dose +/- one booster dose; and when given as a booster following primary Bexsero vaccination; in comparison to standard two dose Bexsero vaccination (the current standard of care) or two dose Trumenba vaccination.	A) Immunological assays to study the immune responses to vaccines potentially including: 1. Serum bactericidal antibody (SBA) titre against a panel of strains and at other times points to secondary outcome. 2. Antibody concentration against vaccine antigens before and after each dose. 3. Quantification of circulating vaccine-induced B-cell responses specific for vaccine

		antigens before and after each dose. 4. Quantification of vaccine-induced, antigen specific T-cell responses and associated cytokine production before and after each dose. 5. Serum opsonophagocytic activity against a panel of isogenic strains before and after each dose. Gene expression profile after immunisation and DNA storage for investigation of the genetic associations with the immune response. 6. Innate immune activation
	B) To make two new reference serums against the two meningococcal vaccines developed to target serogroup B disease, Bexsero and Trumenba.	B) Development of International Standards to be considered for use in SBA and opsonophagocytic assays.
Investigational Medicinal Product #1	Vaccine ChAdOx1 MenB.1	
Formulation	The ChAdOx1 MenB.1 vaccine is formulated in 10 mM Histidine, 35 mM NaCl, 1 mM $MgCl_2$, 0.1 mM EDTA, 0.5 % (v/v) ethanol, 7.5 % (w/v) sucrose, 0.1 % (w/v) PS80, in Water for Injection (WFI) at pH 6.6, sterile-filtered. The vaccine is stored frozen (-80°C nominal) in Type 1 glass, particle free (as per USP or Ph. Eur. Method), sterile and depyrogenated vials each containing 0.45mL.	
Dose	2.5 x 10^{10} (low dose) or 5x10^{10} (high dose) viral particles (VP)	
Route of administration	Intramuscular	
Vaccine Schedule	4 different schedules for arms receiving the IMP #1: 1. Single low dose vaccine at D0 (Group 1 in Fig 5, p21) 2. Single high dose vaccine at D0 (Group 2 in Fig 5, p21) 3. Single high dose vaccine at D0, with further booster high dose vaccine at 6 months (Group 3 in Fig 5, p21)	

	4. Single Bexsero vaccine at D0 followed by a high dose IMP vaccine at 6 months (Group 4 in Fig 5, p21)
Investigational Medicinal Product #2	Bexsero
Formulation	Each dose of vaccine contains recombinant *Neisseria meningitidis* group B NHBA fusion protein (50 micrograms); recombinant *Neisseria meningitidis* group B NadA protein (50 micrograms); recombinant *Neisseria meningitidis* group B FHbp fusion protein (50 micrograms) and Outer membrane vesicles (OMV) from *Neisseria meningitidis* group B strain NZ98/254 (25 micrograms measured as amount of total protein containing the PorA P1.4)
Dose	0.5ml per dose
Route of administration	Intramuscular
Vaccine Schedule	3 different schedules for arms receiving the IMP #2: 1. Two doses at day 0 and day 28 (Group 5 in Fig 5, p21) 2. Two doses at day 0 and day 180 (Group 6 in Fig 5, p21) 3. Single dose at day 0 before administration of IMP #1 at day 180 (group 4 in Fig 5, p21)
Investigational Medicinal Product #3	Trumenba
Formulation	Sterile suspension of two recombinant lipidated factor H binding protein (fHBP) variants. Each dose of Trumenba is formulated to contain 60 micrograms of each fHBP variant subtype (120 micrograms total protein), 0.018 mg of polysorbate 80, and 0.25 mg of Al3+ as AlPO4 in 10 mM histidine buffered saline at pH 6.0.
Dose	0.5ml per dose
Route of administration	Intramuscular
Vaccine Schedule	Two doses at day 0 and day 180

3. ABBREVIATIONS

4CMenB	4 Component Meningococcal B vaccine (i.e. Bexsero)
AE	Adverse event

ANOVA	Analysis of Variance
AR	Adverse reaction
ASC	Antibody Secreting Cell
CBF	Clinical BioManufacturing Facility
CCVTM	Centre for Clinical Vaccinology & Tropical Medicine
CFU	Colony Forming Units
CI	Chief Investigator
CRF	Case Report Form
CSM	Centre for Statistics in Medicine, University of Oxford
CTRG	Clinical Trials & Research Governance, University of Oxford
DSUR	Development Safety Update Reports
DSMC	Data Safety Monitoring Committee
ELISA	Enzyme Linked Immunosorbent Assay
EMEA	European Medicines Agency
EU-IBIS	Invasive Bacterial Infections Surveillance in European Union
fHbp	Factor H binding protein
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
GP	General Practitioner
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
MHRA	Medicines and Healthcare products Regulatory Agency
MLST	Multi-Locus Sequence Typing

NadA	Neisseria adhesion A
NHBA	Neisseria Heparin Binding Antigen
NIBSC	National Institute for Biological Standards and Control
OMP	Outer Membrane Protein
OMV	Outer Membrane Vesicle
OVC	Oxford Vaccine Centre
OVG	Oxford Vaccine Group
PBMC	Peripheral Blood Mononuclear Cell
PRN	Pro Re Nata (as required)
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SBA	Serum Bactericidal Antibody
SOP	Standard Operating Procedure
ST	Sequence Type
SUSAR	Suspected Unexpected Serious Adverse Reactions
TDS	Ter Die Sumendum (three times per day)
TOPS	The Over volunteering Prevention System (http://www.tops.org.uk)
TMF	Trial Master File
ULN	Upper Limit of Normal
QDS	Quaque Die Sumendum (four times per day)
VP	Viral Particle
WFI	Water For Injection

4. BACKGROUND AND RATIONALE

4.1. Meningococcal disease and vaccine prevention

Neisseria meningitidis (also called meningococcus or *N. meningitidis)* is a gram-negative bacteria that is an important cause of meningitis and septicaemia, particularly in infant, child and young adult populations, with mortality as high as 8-10%. *N. meningitidis* exists as several capsular groupss based on the capsular polysaccharides, with groups A, B, C, W, X and Y accounting for almost all human meningococcal disease. In the UK in 2015/16, the capsular group B accounted for 444 (55.2%) of the 805 reported and confirmed cases of invasive meningococcal disease (1).

Effective conjugate vaccines against the A, C, W and Y polysaccharide subtypes have been produced (2) and are currently an established part of the UK vaccine schedule, with dramatic reductions in the incidence of these subtypes. Creation of a vaccine against the capsular group B has proven more difficult due to the poor immunogenicity of the B polysaccharide due to its similarity to human antigen(3).

In 2013, the first effective vaccine against Group B meningococcus (Men B) was licensed in the UK by Novartis (subsequently GSK); Bexsero ®. This vaccine utilises four non-polysaccharide components of the Men B – a recombinant Factor H binding protein (FHbp); Neisseria Heparin Binding Antigen (NHBA) fusion protein; recombinant Neisseria adhesion A (NadA) protein; and Outer Membrane Vesicles from *Neisseria meningitidis* group B strain NZ98/254 containing PorA P1.4. As it utilises four components, the vaccine is known as the 4 Component Meningococcal B, or 4CMenB, vaccine.

The 4CMenB/Bexsero vaccine is thought to provide protection against 88% of meningococcus B strains(4). It, however, only has borderline cost-effectiveness and requires three administrated doses in infants/young children in the UK vaccine schedule, and may require up to four to achieve protective immunity. Additionally, the vaccine has high rates of fever after administration.

Trumenba vaccine was authorised for UK use in May 2017. It is a vaccine composed of 2 recombinant lipidated factor H binding protein (fHbp) variants. fHbp variants segregate into 2 immunologically distinct subfamilies, A and B, and over 96% of meningococcal serogroup B isolates in Europe express fHbp variants from either subfamily on the bacterial surface.

The efficacy of Trumenba has not been evaluated through clinical trials. Vaccine efficacy has been inferred by demonstrating the induction of serum bactericidal antibody responses to 4 meningococcal serogroup B test strains. A two or three-dose schedule is recommended for this vaccine. Safety and efficacy of Trumenba in children below 10 years of age have not been established. No data are available.

There is, a need for an alternative vaccine with less side-effects, lower manufacturing and delivery costs, particularly in the era of increased pressure to control healthcare costs.

This study provides an opportunity to compare the safety profile of the study vaccine, Bexsero and Trumenba side by side.

4.2. The outer membrane protein fHbp as vaccine antigen

Factor H binding protein (fHbp) is an important virulence factor expressed on the surface of *N. meningitidis*. The function of fHbp is to bind human complement factor H (fH), an important down-regulator of the host alternative complement pathway. Binding of human fH to the bacterial surface via fHbp interferes with complement-mediated lysis of the bacteria and is an important immune evasion strategy of *N. meningitidis*. Strains in which fHbp has been deleted have reduced binding to fH and reduced survival in human complement mediated bacterial killing assay compared to wild type strains. The discovery of meningococcal fHbp has led to the development of the two recombinant meningococcal group B vaccines that incorporate fHbp (4CMenB or Bexsero® by Novartis/GSK and a vaccine composed of two fHbp variants manufactured by Pfizer Inc.). Following vaccination, fHbp incorporated in the vaccine is expected to form a complex with human fH, and this interaction between fH and fHbp adversely affected the immunogenicity of the 4CMenB vaccine in transgenic mice expressing human fH. In mice immunised with 4CMenB, the ability of anti-fHbp antibodies to inhibit binding of fHbp to fH appears to be crucial to the breadth of bactericidal activity(5)(6). While serum anti-fHbp antibodies elicited by wild type fHbp in wild type mice inhibited binding of fH to fHbp, the corresponding antibodies elicited in human fH

transgenic mice enhanced fH binding(7). These results suggested that a wild type fHbp is not the ideal antigen for a vaccine composition to be used in humans. Several groups, therefore, engineered fHbp mutants to eliminate fH binding, and showed that some mutants have enhanced protective antibody responses in the presence of human fH (8)(9). Therefore the use of a mutated fHbp antigen seems a viable candidate for a Men B vaccine.

4.3. Adenovirus based immunization strategies

Adenoviruses have been investigated as vaccine delivery platform since the 1970s. Vaccination of 2 million US military personnel using orally administered live human adenovirus serotype 4 and 7 have shown good safety and efficacy data(10). Adenoviruses can infect several cell types but no evidence of insertional mutagenesis has been observed. The adenoviral genome is well characterized and easy to manipulate. Adenoviruses cause mild disease but deletion of key genes (E1 which is required for viral replication) renders them replication-defective. Replication-deficient adenoviruses can be propagated in cell lines approved by regulatory agencies for human product development (human embryonic kidney cells 293) and following Good Manufacturing Practice. Recombinant Adenoviral vectors expressing antigens from HIV-1, TB, malaria, influenza, RSV and hepatitis C virus, are in phase I/II clinical trials, and elicit strong antibody responses in humans with an excellent safety record. Recently, excellent safety and immunogenicity was observed in a phase I trial for malaria in 10 week-old Gambian infants(11).

Pre-existing immunity against highly prevalent human serotypes, present in up to 80% of individuals, may render certain serotype such as human serotype 5 vectors partially ineffective. Therefore other adenoviruses based on simian serotypes have now been developed, including Ox1, developed by Oxford University. Such vectors have hexon structures homologous to human serotype 4, but do not circulate at detectable levels in human populations and neutralizing antibody prevalence is very low in humans on all continents(12). These vectors are highly immunogenic: the most developed, based on ChAd63 serotype, has showed very good safety and exceptional immunogenicity in 14 human clinical trials involving 682 volunteers. Chimpanzee adenovirus Ox1 was developed in Oxford University from the group E chimpanzee adenovirus Y258(13). The immunogenicity of recombinant E1- E3- deleted vector ChAdOx1 is comparable to that of other species E derived chimpanzee adenovirus vectors including ChAd63, and the prevalence of ChAdOx1 virus neutralizing antibodies in adults was lower than for ChAd63 in British and Gambian infants. In a UK cohort of 100 people, no individual possessed a neutralisation titre above 200 (the threshold for a positive titre during routine pre-vaccination screening). The low seroprevalence of ChAdOx1 in humans suggests that this new vector could be particularly efficacious in a clinical setting. Therefore ChAdOx1 now offers an attractive option for vaccine development against Men B and we elected to employ this novel replication-deficient viral vector to develop an adenovirus-vectored vaccine expressing a mutated fHbp with reduced binding to human fH in order to induce protective antibody responses to Men B.

4.4. The investigational product ChAdOx1 MenB.1

4.4.1 Description of ChAdOx1 MenB.1

The vaccine consists of the replication-deficient (E1 and E3 deleted) simian adenovirus vector ChAdOx1, containing a genetic cassette encoding for the meningococcal capsular group B antigen fHbp variant 1.1 with a point mutation to prevent binding to the natural human ligand, fH (S223R), codon optimized for mammalian expression, under the control of the strong cytomegalovirus (CMV) immediate early promoter.

4.4.2 Generation of ChAdOx1 MenB.1 adenovirus vector

The vaccine construct was generated at the Oxford Vaccine Group, University of Oxford. Manufacture of the vaccine was carried out in accordance with the requirements of GMP by:

Clinical BioManufacturing Facility (CBF)

Old Road, Headington

Oxford OX3 7JT, UK

MIA (IMP) 21584

Full technical details of the assembly process can be found in the Investigator's Brochure (IB)

4.4.3 ChAdOx1 vector

The ChAdOx1 vector is replication-deficient as the E1 gene region, essential for viral replication, has been deleted. The virus will not replicate in cells within the human body. In addition the E3 locus, which promotes viral particle release and inhibits the host's antiviral response, is also deleted. ChAdOx1 propagates only in cells expressing E1, such as HEK293 cells and their derivatives or similar cell lines such as Per.C6 (Crucell).

4.4.4 Rationale for ChAdOx1 MenB.1 as a trial intervention

The ChAdOx1 vector has been used in at least 129 participants from phase 1 clinical trials in Oxford to date (Clinicaltrial.gov numbers NCT01818362, NCT01829490 and NCT01623518). The experience with these adenovirus vaccine vectors demonstrate that they appear to be well tolerated with minimal side effects, especially in comparison to the reactogenic 4CMenB vaccine or other viral vectored vaccines such as Modified Vaccinia Ankara (MVA). Additionally, the results from pre-clinical studies (see below) suggest that it produces bactericidal antibodies comparable to 4CMenB after only one dose and these persist for longer.

Therefore this new vaccine candidate has potentially less side effects and longer-lasting immune response from fewer doses than 4CMenB. We are therefore testing it in a first-in-man Phase I/IIa clinical setting, primarily for safety, but also to obtain descriptive immunogenicity data. The doses chosen {$2.5x10^{10}$ and $5x10^{10}$ viral particles (VP)} are based on unpublished data and experience from a recent University of Oxford trial involving the ChAdOx1 vaccine vector (TB034, ClinicalTrial.gov reference NCT01829490).

4.5. 4CMenB/Bexsero

4.5.1 Rationale for use as a control vaccine

Given that 4CMenB/Bexsero is the current standard of care for vaccination against Men B and therefore represents the benchmark for the acceptability of side-effects for a Men B vaccine, a control arm will be included in this study to compare reactogenicity. Additionally, the inclusion of a 4CMenB control arm will allow descriptive comparisons of immunogenicity to inform further trials with ChAdOx1 MenB.1.

In addition, this control vaccine will be used a prime dose in one arm (group 4, see 'trial design' below) and boosted by the IMP. This is to investigate the IMP's tolerability and immunogenicity in this context, which may be the IMP's eventual use, that is, as a booster to Bexsero to reduce the number of doses and/or improve the immunogenic response of the course.

A group with Bexsero given with a further booster at 1 month (group 5 in the trial design) will allow comparison of primary and secondary outcomes with the single dose ChAdOx1 MenB.1. This is because Bexsero requires 2 doses to be efficacious and would never be given as a single dose in real life.

A further group will be given a booster at 6 months (group 6 in the trial design). This is to allow a comparator for the primary and secondary outcomes to the groups where ChAdOx1 MenB.1 boosters are also given at six months (groups 3 & 4 in the study design).

4.6. Trumenba

Trumenba is of interest as a comparator vaccine due to the fact that it is now licensed in the UK.

This vaccine will be used to allow comparison of safety data between the study vaccine, Bexsero, and Trumenba.

In group 8, 20 individuals will receive an initial Trumenba vaccination, followed by booster vaccination at 6 months. This follows the recommended dosing schedule for this vaccine.

4.7. Serum Standard

Reference human serum containing antibodies against vaccine antigens for infectious agents, for use in biological assays, provide a means to standardise results across laboratories worldwide. Biological assays which inform the potency and or efficacy of vaccines take a range of formats including those which provide a functional read such as neutralization, opsonophagotic or bactericidal. These assays provide readouts which correlate with protection in humans, commonly known as correlates of protection. The other type of commonly used assays tests the immunogenicity of a vaccine, to see if it evokes an antibody dependant immune response against a vaccine. In some cases, namely the glycoconjugate vaccines, the amount of antibody in the blood directed against the polysaccharide antigen indicates if a person is protected against a vaccine. Measuring the antibodies in human serum provides invaluable data for sero-prevelance studies to determine how well a vaccine is working in an immunised population; to highlight vaccine failures; and to provide epidemiological data on the target organism and whether escape mutants are arising following vaccination.

Our proposal is to make two new reference serums against the two meningococcal vaccines developed to target serogroup B disease, Bexsero and Trumenba. Adult volunteers will be immunised with the Bexsero or Trumenba vaccines following the recommended schedule of 0 and 6 months. This should allow the two serums to be comparable without compromising the response to Bexsero despite a different time gap between doses than that recommended (14).

4.8. Findings from non-clinical studies with the ChAdOx1 MenB.1 vaccine

Three types of non-clinical studies have been performed with ChAdOx1 MenB.1:

1. **Expression of the antigen in mammalian cells upon infection with ChAdOx1 MenB.1, and capacity to bind human fH.**

Mammalian cells infected with ChAdOx1 MenB.1 express fHbp on the cell surface (data not shown). A wild type version of fHbp then binds its natural ligand human fH, as seen with HuAd5 fHbp1.1 (Fig.1). However, binding of human fH on the mutated fHbp1.1 S223R (whether expressed from HuAd5 or ChAdOx1 adenoviral backbones) was significantly less (Fig 1)

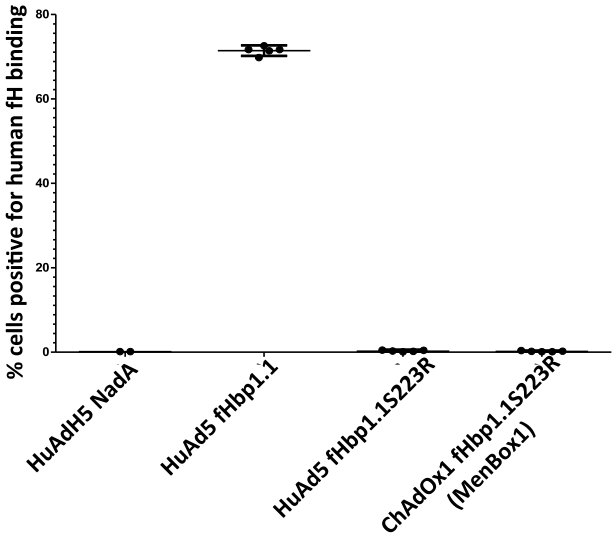

Figure 1. Binding of human fH on mammalian cells infected with different adenovirus vectors. HuAd5 is an alternative adenovirus vector; fHbp 1.1 is the wildtype fHbp; fHbp1.1S223R is the mutated version.

2. Immunology and biological activity studies of ChAdOx1 MenB.1 performed in mouse models (outbred, inbred and transgenic for human fH).

When immunised with ChAdOx1 MenB.1, transgenic mice expressing human fH (and thus representing a more accurate model of the human situation than wild type mice) have produced anti-fHbp antibodies with a robust SBA two and six weeks after vaccination (Fig. 2).

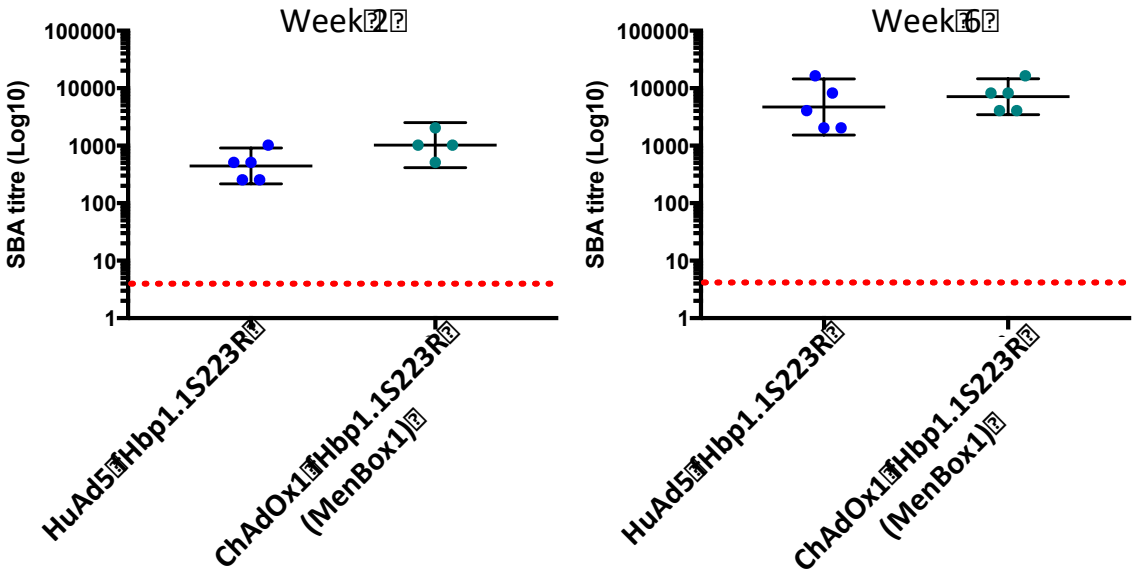

Figure 2: The Serum Bactericidal Assay titres against infectious Men B in samples from fH-transgenic mice immunized with two adenovirus vectors (HuAd5 and ChAdOx1) encoding the mutated fHbp1.1S223R.

A longer term immunogenicity study in transgenic mice showed a persistent bactericidal antibody response in mice vaccinated with ChAdOx1 vector with the mutated fHbp1.1S223R compared to those vaccinated with 4CMenB (See fig 3).

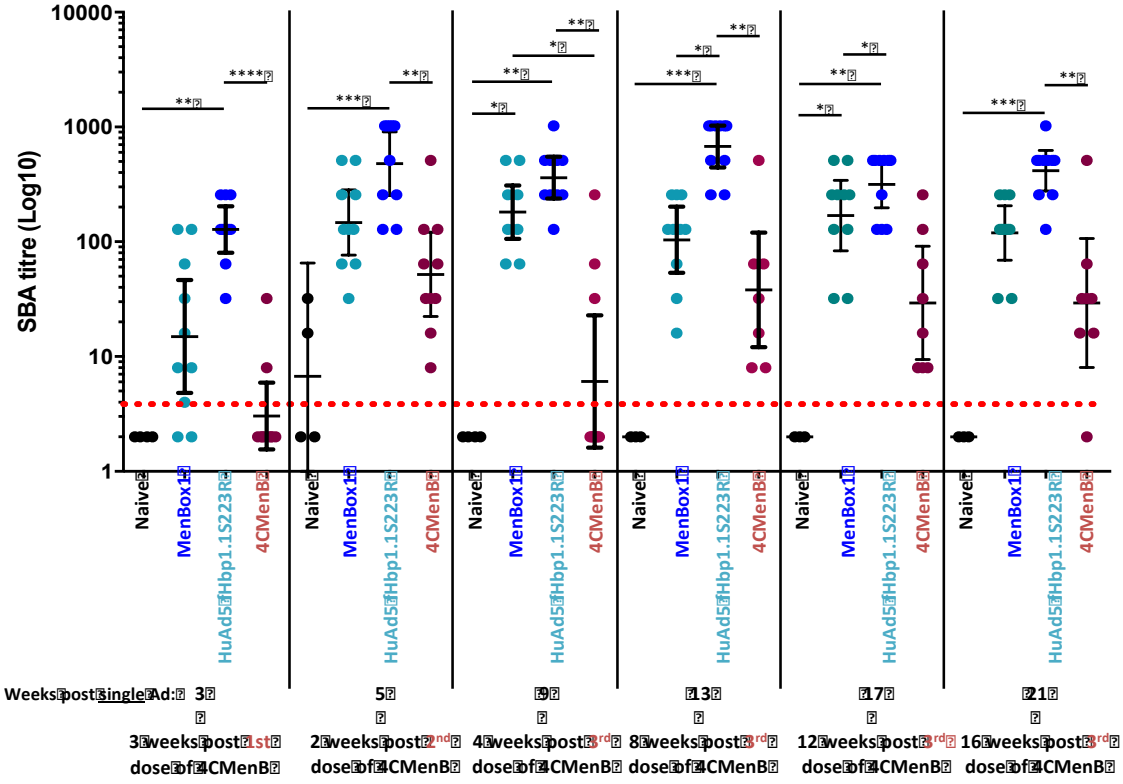

Figure 3 - Immunogenicity of ChAdOx1 MenB.1 in human fH transgenic mice at several time points (indicated below the X axis) post a single adenovirus injection (dark blue for ChAdOx1 MenB.1 and light blue for the HuAd5 counterpart), compared to mice immunized once, two or three times with 4CMenB (in red). Each mouse is represented by a dot and the geometric mean with 95% confidence interval of the group are displayed (horizontal lines). The red horizontal dashed line represent the threshold for protection (titre of 1:4). Statistical comparison of the SBA titres was performed by ANOVA at each time point, * $p<0.05$, ** $p<0.01$, *** $p<0.001$ and **** $p<0.0001$.

3. Toxicity studies of ChAdOx1 MenB.1 administered in mice (Envigo)

A toxicology study was performed by injecting mice with high doses (25µl) of either phosphate-buffered solution or ChAdOx1 MenB.1 and comparing the two groups. There was no difference in clinical features between the two groups, with minor haematological/biochemical differences at D28. A post-mortem examination revealed single enlarged lumbar lymph nodes in 2/20 mice injected with ChAdOx1 MenB.1, compared to none in the control arm. In conclusion, treatment with the vaccine ChAdOx1 menB.1 was well tolerated and was not associated with any adverse effects.

Full details of these studies can be found in the IB.

5. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To investigate safety and tolerability of 2.5 x 10^{10} VP or 5x10^{10} VP of the proposed ChAdOx1 MenB.1 vaccine against meningococcus capsular group B in healthy adults aged 18 to 50 years of age when given one dose +/- one booster dose; and when given as a booster following primary Bexsero vaccination in comparison to standard two dose Bexsero vaccination (the current standard of care); or two dose Trumenba vaccination.	The recording and assessment of local and systemic adverse events following administration of each vaccine dose; Tenderness and pain at the injection site 1. Induration 2. Redness 3. Swelling 4. Headache 5. Malaise 6. Myalgia 7. Nausea and/or vomiting 8. Anorexia 9. Arthralgia 10. Fever 11. Blood parameters 12. Any unsolicited symptom(s) not listed above	eDiary records from Day 0 (day of vaccination) to Day 6 for solicited symptoms (plus later if any persisting symptoms). Unsolicited adverse events up until and including 28 days following the last vaccine. Serious adverse events (SAEs) during the entire study. Safety blood tests at Day 0, and D1 and D7 following vaccination
Secondary Objectives To determine the immunogenicity of 2.5 x 10^{10} VP or 5x10^{10} VP of the proposed ChAdOx1 MenB.1 vaccine against meningococcus capsular group B in healthy adults aged 18 to 50 years of age when given one dose +/- one booster dose; and when given as a booster following primary Bexsero vaccination in comparison to standard two dose Bexsero vaccination (the current	Serum bactericidal antibody (SBA) assay against homologous strains before and after each dose.	Blood samples after both initial immunisation and booster 6 months later.

standard of care) or two dose Trumenba vaccination.		
Tertiary Objectives A) To determine the immunogenicity of 2.5 x 10^{10} VP or 5x10^{10} VP of the proposed ChAdOx1 MenB.1 vaccine against meningococcus capsular group B in healthy adults aged 18 to 50 years of age when given one dose +/- one booster dose; and when given as a booster following primary Bexsero vaccination, in comparison to standard two dose Bexsero vaccination (the current standard of care); or two dose Trumenba vaccination using exploratory immunological techniques	A) Immunological assays to study immune responses to vaccines, potentially including: 1. Serum bactericidal antibody (SBA) titre against a panel of strains and at other time points to secondary outcome 2. Quantification of circulating vaccine-induced B-cell responses specific for vaccine antigens before and after each dose. 3. Quantification of vaccine-induced, antigen specific T-cell responses and associated cytokine production before and after each dose. 4. Serum opsonophagocytic activity against a panel of isogenic strains before and after each dose. 5. Gene expression profile after immunization and DNA storage for investigation of the genetic associations with the immune response. 6. Innate immune activation	A) Blood samples from study visits.
B) To make two new reference serums against the two meningococcal vaccines developed to target serogroup B disease, Bexsero and Trumenba.	B) Development of International Standard to be considered for use in SBA and opsonophagocytic assays.	B) Serum sample at day 28 following second immunisation

6. TRIAL DESIGN

6.1. Overview of Trial Design

The study is a phase I/IIa, single centre, dose-escalation study to assess the safety and immunogenicity of a single dose +/- booster dose of the recombinant adenovirus Meningococcal B vaccine candidate ChAdOx1 MenB.1 in healthy adults. The participants will be divided into 8 subgroups as described below. The total number of participants required to reach the primary endpoint will be 67-70 depending on safety outcomes in group 1, see below. The serum standard arms will comprise 32-40 individuals depending on consent. The total number of individuals in the trial will be 79-90.

1. **Group 1 - Low dose arm** – This group will consist of 3-6 individuals who will receive a single dose of 2.5 x10^{10} VP of ChAdOx1 MenB.1 according to a 3+3 study plan outlined in section 6.2. A

favourable DSMC review of the safety data from this arm will be required before commencement of group 2.

2. **Group 2 - High dose arm** – This group will only proceed after DSMC review of Group 1 and approval. This group will consist of 10 participants assigned to receive a single dose of the higher dose $5x10^{10}$ VP of ChAdOx1 MenB.1. See section 6.2 for further details regarding safety and dose escalation. A favourable DSMC review of the safety data from this arm will be required before the commencement of group 3
3. **Group 3 - High dose ChAdOx1 MenB.1 plus booster arm** – this group will consist of 8 participants who will receive the high dose $5x10^{10}$ VP of ChAdOx1 MenB.1, with a repeat booster dose at 6 months. Administration of the booster dose will be subject to favourable interim review of the safety data of group 2 by the DSMC.
4. **Group 4 - Bexsero with high dose ChAdOx1 MenB.1 booster arm** – this group will consist of 8 participants who will receive a dose of Bexsero at Day 0 with a booster high dose of ChAdOx1 MenB.1 at 6 months.
5. **Group 5 - Bexsero Control arm** – This group will consist of 10 individuals who will receive two doses of Bexsero at Day 0 and Day 28 as per adult licensing. This group will act as a control to groups 1 and 2.
6. **Group 6 - Bexsero 6 month boost control arm** – This group consist of 8 individuals who will receive Bexsero doses at Day 0 and 6 months. This group will act as a control for groups 3 and 4. These individuals will also contribute to the development of the serum standard.
7. **Group 7 – Bexsero 6 month boost serum standard arm** – This group will consist of 12-20 individuals who will receive Bexsero doses at Day 0 and 6 months. Numbers may vary due to the possibility that individuals from group 6 may not consent to giving a larger blood volume, in which case a maximum of 20 individuals will be recruited into group 7.
8. **Group 8 – Trumenba 6 month boost serum standard arm** – This group will consist of 20 individuals who will receive Trumenba doses at Day 0 and 6 months. All 20 individuals will have safety visits at D0, D1 and D7 after vaccination. A subset of 10 individuals will have extra samples taken (see Table 9).

A schematic of the vaccination arms and when they receive which vaccine is seen in figure 5. Aside from vaccination, these participants are followed up according to the schedules detailed in tables 1-6.

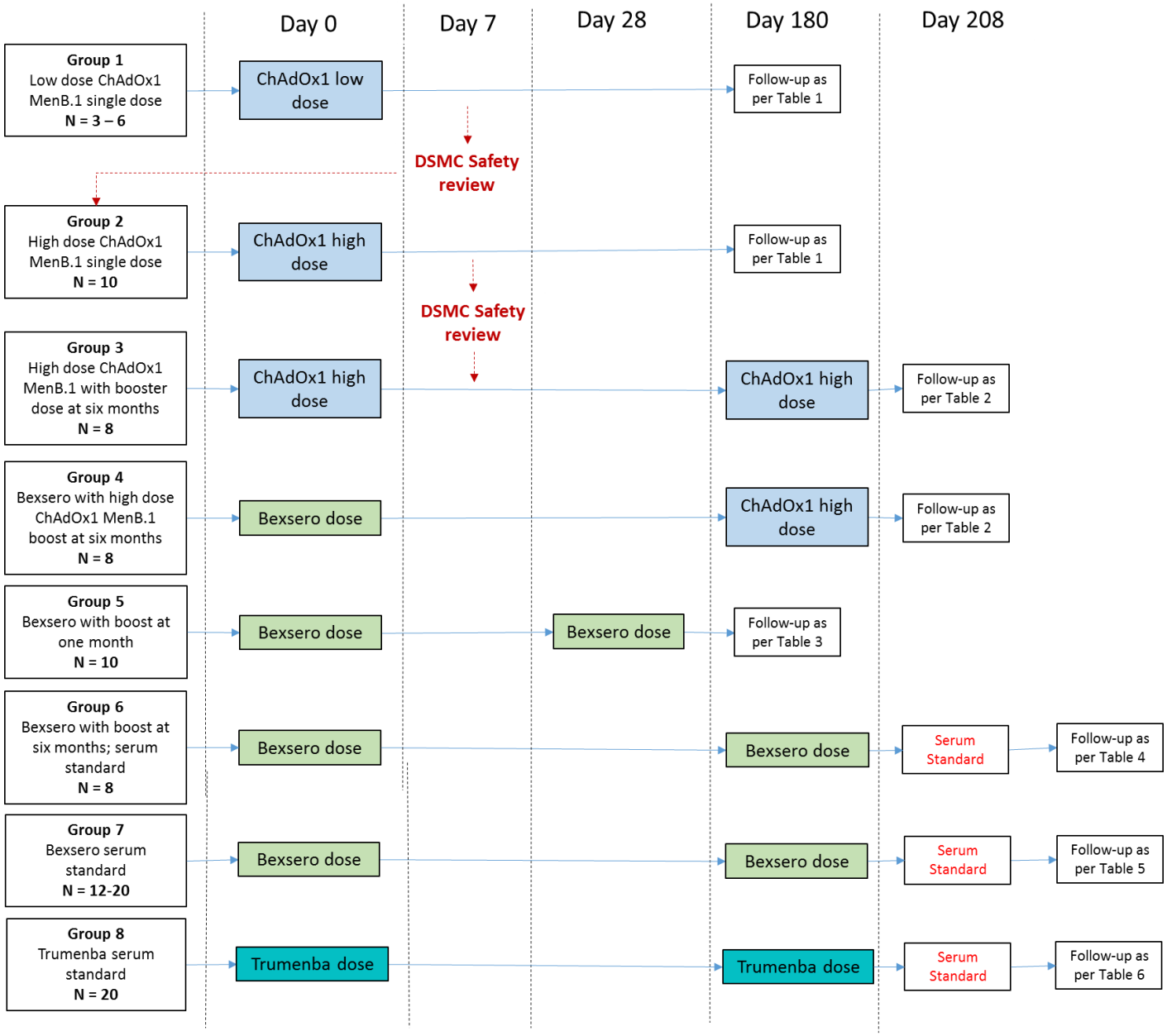

Figure 5. Schematic of trial design. Boxes in blue represent ChAdOx1 MenB.1; green Bexsero; turquoise Trumenba

Table 1. Scheduled visits per participant and procedures performed at each visit (**for Groups 1-2**).

Visit Number	**Screening (V0)**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V12**	**V13**
Indicative Study Day		1	2	7	14	28	56	84 (12w)	180 (6m)	208 (7m)	365
Day post last vaccine		0	1	7	14	28	56	84	180	208	365
Visit Window (days)		N/A	0	+/- 1	+/- 2	+/- 4	+/- 4	+/- 4	+ 14 (i.e. 180 – 194)	+/- 4	+/- 28
Informed consent	x										
Confirmation of consent		x									
Obtain 24 hr contact details		x									
Medical history (including demographics and medication)	x										
Interim medical history (including concurrent medication)		x	x	x	x	x	x	x	x	x	x
Physical examination	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test	x	x									
Urine sample	x										
Blood sample	x	x	x	x	x	x	x	x	x	x	x
12 lead ECG	x										
Vaccination		x									
e-Diary entries		x	x	x	x	x					
Intervention arm allocation		x									

Table 2. Scheduled visits per participant and procedures performed at each visit (**for Groups 3-4)**

Visit Number	**Screening (V0)**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**
Indicative Study Day		1	2	7	14	28	56	84 (12w)	180 (6m)	V8 + 1d	V8 + 7d	V8 + 14d	208 (7m)	365
Day post last vaccine		0	1	7	14	28	56	84	180	1	7	14	28	169
Visit Window (days)		N/A	0	+/- 1	+/- 2	+/- 4	+/- 4	+/- 4	+ 14 (i.e. 180 – 194)	0	+/- 1	+/- 2	+/- 4	+/- 28
Informed consent	x													
Confirmation of consent		x												
Obtain 24 hr contact details		x												
Medical history (including demographics and medication)	x													
Interim medical history (including concurrent medication)		x	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination	x													
Vital signs	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test	x	x							x					
Urine sample	x													
Blood sample	x	x	x	x	x	x	x	x	x	x	x	x	x	x
12 lead ECG	x													
Vaccination		x							x					
e-Diary entries		x	x	x	x	x			x	x	x	x	x	
Intervention arm allocation		x												

Table 3. Scheduled visits per participant and procedures performed at each visit (**for Group 5**)

Visit Number	**Screening (V0)**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V12**	**V13**
Indicative Study Day		1	2	7	14	28	56	84 (12w)	180 (6m)	208 (7m)	365
Day post last vaccine		0	1	7	14	28	28	56	158	208	337†
Visit Window (days)		N/A	0	+/- 1	+/- 2	+/- 4	+/- 4	+/- 4	+ 14 (i.e. 180 – 194)	+/- 4	+/- 28
Informed consent	x										
Confirmation of consent		x									
Obtain 24 hr contact details		x									
Medical history (including demographics and medication)	x										
Interim medical history (including concurrent medication)		x	x	x	x	x	x	x	x	x	x
Physical examination	x										
Vital signs	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test	x	x				x					
Urine sample	x										
Blood sample	x	x	x	x	x	x	x	x	x	x	x
12 lead ECG	x										
Vaccination		x				x					
e-Diary entries		x	x	x	x	x	x				
Intervention arm allocation		x									

Table 4. Scheduled visits per participant and procedures performed at each visit (**for Group 6)**

Visit Number	**Screening (V0)**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**
Indicative Study Day		1	2	7	14	28	56	84 (12w)	180 (6m)	V8 + 1d	V8 + 7d	V8 + 14d	208 (7m)	365
Day post last vaccine		0	1	7	14	28	56	84	180	1	7	14	28	169
Visit Window (days)		N/A	0	+/- 1	+/- 2	+/- 4	+/- 4	+/- 4	+ 14 (i.e. 180 – 194)	0	+/- 1	+/- 2	+/- 4	+/- 28
Informed consent	x													
Confirmation of consent	`	x												
Obtain 24 hr contact details		x												
Medical history (including demographics and medication)	x													
Interim medical history (including concurrent medication)		x	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination	x													
Vital signs	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test	x	x							x					
Urine sample	x													
Haemoglobin check													x	
Blood sample	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum Standard													x	
12 lead ECG	x													
Vaccination		x							x					
e-Diary entries		x	x	x	x	x			x	x	x	x	x	
Intervention arm allocation		x												

Table 5. Scheduled visits per participant and procedures performed at each visit (**for Group 7**)

Visit Number	Screening (V0)	V1	V8	V12
Indicative Study Day		1	180 (6m)	208
Day post last vaccine		0	180	28
Visit Window (days)		N/A	+ 14 (i.e. 180 – 194)	+14 (i.e. 208-222)
Informed consent	x			
Confirmation of consent		x		
Medical history (including demographics and medication)	x			
Interim medical history (including concurrent medication)		x	x	x
Vital signs	x	x	x	x
Urine pregnancy test	x	x	x	
Haemoglobin check				x
Blood sample	x	x	x	x
Serum standard				x
12 Lead ECG	x			
Vaccination		x	x	
e-Diary entries		x	x	
Intervention arm allocation		x		

Table 6. Scheduled visits per participant and procedures performed at each visit (**for Group 8**)

*10 individuals as a subset of group 8

Visit Number	Screening (V0)	V1	V2	V3	V5*	V8	V9	V10	V12	V13*
Indicative Study Day		1	2	7	28	180 (6m)	V8 + 1d	V8 + 7d	208	365
Day post last vaccine		0	1	7	28	180	1	7	28	185
Visit Window (days)		N/A	0	+/- 1	+/- 4	+ 14 (i.e. 180 – 194)	0	+/- 1	+14 (i.e. 208-222)	+/- 28
Informed consent	x									
Confirmation of consent		x								
Medical history (including demographics and medication)	x		x	x			x	x		
Interim medical history (including concurrent medication)		x			x*	x			x	x*
Vital signs	x	x	x	x	x*	x	x	x	x	x*
Urine pregnancy test	x	x				x				
Haemoglobin check									x	
Blood sample	x	x	x	x	x*	x	x	x	x	x*
Serum standard									x	
12 Lead ECG	x									
Vaccination		x				x				
e-Diary entries		x	x	x		x	x	x		
Intervention arm allocation		x								

6.2. Dose escalation

As this is a first in man trial, we will operate a dose escalation policy in groups 1-3 between the three doses represented by each group:

1. Single dose 2.5 x 10^{10} VP ('low dose' – group 1)
2. Single dose 5 x 10^{10} VP ('high dose' – group 2)
3. Single dose of 5 x 10^{10} VP followed by a booster at 6 months ('High dose' with booster – group 3)

The rationale for these doses is based on experience from previous ChAdOx1 phase 1 trials (see section 4.4.4 for more details). Escalation between these doses will be dependent on a favourable safety review by the DSMC

6.2.1 Dose Escalation process

Volunteers will be enrolled and doses escalated according to a 3+3 study plan as follows.

Group 1

The first volunteer will be vaccinated with 2.5 x 10^{10} VP of ChAdOx1 MenB.1**.** No other volunteers will be vaccinated until at least 48 hours has elapsed following this first vaccination. The chief or principal investigator will be asked to provide the decision on whether to proceed after the safety review (these reviews will include the results of safety blood tests) of the first volunteer. If there are no safety concerns then a further two volunteers will be vaccinated with the 2.5 x 10^{10} VP dose (therefore bringing the total number of volunteers receiving that dose to 3). These two volunteers will be vaccinated at least one hour apart.

If none of these three volunteers experience an unacceptable adverse reaction on review of the safety data (in the 7 days following vaccination), the next group will be enrolled (higher dose). An unacceptable adverse reaction is defined by a severe adverse event which lasts more than 48 hours and/or the occurrence of a serious adverse event.

If one of the low-dose volunteers experiences an unacceptable adverse reaction, a further three volunteers will be vaccinated at the same dose, with at least an hour between vaccinations (hence 3+3 design). If there are no further unacceptable adverse reactions in those three volunteers in the seven days following vaccination, recruitment to the high dose group will proceed as outlined below. If two or more of the three low-dose volunteers, or two or more of the six, develop an unacceptable adverse reaction, the study will be paused pending DSMC review.

Group 2

In the high dose (5 x 10^{10} VP) group, the first volunteer will be vaccinated ahead of the other volunteers. The safety profile in the ensuing 48 hours will be examined. If the safety profile is acceptable, a further two volunteers will be vaccinated at that dose, at least one hour apart. If none of these three volunteers experience an unacceptable adverse reaction on review of the safety data (in the 7 days following vaccination, as approved by the chief investigator), the rest of group 2 will be enrolled up to 10 participants. Once all these participants have reached 7 days post vaccination, the DSMC will then be asked to provide a safety review of the clinical data and safety blood tests of these participants.

If 1/3 of the high-dose volunteers experience an unacceptable adverse reaction, a further three volunteers will be vaccinated at the same dose, with at least an hour between vaccinations (again, 3+3 design). If there are no further unacceptable adverse reactions in those three volunteers in the seven days following vaccination, recruitment of the remaining participants to group 3 will proceed.

If 2 or more volunteers (≥2/3 or ≥2/6) experience unacceptable adverse reactions at this 'high dose', then the remaining numbers in the group will be vaccinated at 2.5 x 10^{10} VP dose (the 'low dose' used in Group 1). With the approval of the DSMC, the 'low dose' will be used instead of the high dose as detailed below in groups 3 and 4.

6.2.2 DSMC reviews

Between groups 1 and 2, and groups 2 and 3, a DSMC will need to review the safety data and give a favourable opinion of the results of the former groups in order to allow recruitment to the latter. If a favourable opinion is found of group 1, but not of group 2, then the DSMC will allow the 'low dose' to be used in group 3 and 4 instead of the high dose. Further full details of what these safety rules entail and the stopping rules therein, please see sections 10.7 – 10.9.

6.3. Group Allocation

Allocation to each arm will be decided by order of enrolment into the trial. Groups 1-3 will be preferentially recruited to ensure study progress as per the dose escalation process above. Recruitment to group 4 will be recruited to once group 3 has completed recruitment. Groups 5 and 6, as control arms, can be recruited at any time once progression from group 1 has occurred, although clear preference will be given to groups 2-4. The same will apply to groups 7 and 8.

Participants in Group 6 must first consent to the main study using the main VAMBOX Informed Consent Form (ICF) at their first visit. In their next visit, they would then be invited to participate in the Serum Standard part of the study, and we would consent them using the Serum Standard ICF.

6.4. Safety Monitoring

Throughout the study, the safety outcomes of the participants will be monitored. This will be done by monitoring of symptoms at visits and through the eDiary system, and through the monitoring of safety blood tests performed at each visit(see tables 4to 6).

Full details about the reporting of any adverse events or serious adverse events, and the role of the DSMC beyond the dose escalation reviews is discussed in section 10 of the protocol.

7. PARTICIPANT IDENTIFICATION

7.1. Trial Participants

Male or female participants aged 18-50 years inclusive who are in good health (as determined by a study doctor, medical investigation and in consultation with their general practitioner) and who are able to provide written informed consent, will be eligible for inclusion in this study.

A total of 67 participants meeting the primary endpoint are required. 32-40 participants will be recruited to the serum standard arms, depending on consent from those in group 6 to provide a serum standard.

7.2. Inclusion criteria

Participants must satisfy all of the following criteria to be considered eligible for the study:

- Willing and able to give written informed consent for participation in the study
- Aged between 18 and 50 years inclusive at the time of first vaccination

- In good health as determined by
    - Medical history
    - Physical examination
    - Clinical judgment of the investigators
- (Females of childbearing potential) Willing to use effective contraception (such as the oral contraceptive pill, contraceptive implant, barrier methods or complete abstinence from heterosexual sexual intercourse) from one month prior to first vaccination and for three months following last vaccine
- Able to attend the scheduled visits and to comply with all study procedures, including internet access for the recording of diary cards
- Willing to allow his or her General Practitioner to be notified of participation in the study
- Confirmation from the participants GP that they are satisfied from their knowledge of the volunteer that they are suitable to enrol and/or the provision of a detailed medical summary is provided to the study team to assess participant eligibility
- Agrees to refrain from donating blood for the duration of the trial
- Agree to be registered on the Trial Over-Volunteering Prevention Service (TOPS) and agree to provide their National Insurance number or passport number (if not a British citizen) for the purposes of registration
- Agree to provide National Insurance number and Bank details for reimbursement purposes

7.3. Exclusion Criteria

The participant may not enter the study if any of the following apply:

- History of significant organ/system disease that could interfere with trial conduct or completion. This includes any history of significant disease in the following;
    - Cardiovascular disease including congenital heart disease, previous myocardial infarction, valvular heart disease (or history of rheumatic fever), previous bacterial endocarditis, history of cardiac surgery (including pacemaker insertion), personal or family history of cardiomyopathy or sudden adult death
    - Respiratory disease such as uncontrolled asthma and chronic obstructive pulmonary disease
    - Endocrine disorders such as diabetes mellitus and Addison's disease
    - Significant renal or bladder disease, including history of renal calculi
    - Biliary tract disease
    - Gastro-intestinal disease such as inflammatory bowel disease, abdominal surgery within the last two years, coeliac disease and liver disease (including hepatitis B or C infection)
    - Neurological disease such as seizures and myasthenia gravis
    - Haematological problems such as anaemia or coagulation problems
    - Metabolic disease such as glucose-6-phosphate dehydrogenase deficiency
    - Psychiatric illness requiring hospitalisation or depression whose severity is deemed clinically significant by the study Investigators and/or GP
    - Known or suspected drug and/or alcohol misuse (alcohol misuse defined as an intake exceeding 42 units per week)
    - Non-benign cancer, except squamous cell or basal cell carcinoma of the skin and cervical carcinoma in situ
- History of allergy or anaphylaxis to a vaccine or any component within the vaccines used in this study
- Have any known or suspected impairment or alteration of immune function, resulting from, for example:

  - Congenital or acquired immunodeficiency
  - Human Immunodeficiency Virus infection or symptoms/signs suggestive of an HIV-associated condition
  - Autoimmune disease
  - Receipt of immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within the preceding 12 months or long-term systemic corticosteroid therapy
- Study significant abnormalities on screening investigations at the discretion of an Investigator
- Weight <50 kg
- Donation of blood within the last 3 (male) or 4 (female) months or plans on giving blood within the next year
- Receipt of a live vaccine within 4 weeks prior to vaccination, an inactivated influenza vaccine within 14 days of vaccination or another inactivated vaccine within 7 days prior to vaccination
- Plan to receive any vaccine other than the study vaccine within 4 weeks following vaccination
- Scheduled procedures requiring general anaesthesia during the study
- Receipt of immunoglobulin or any blood product transfusion within 3 months of study start
- Current active participation in another research study involving an investigational product or where involvement in this study could impact the results
- Previously having received a meningococcal B vaccine of any kind
- Previously having received a meningococcal ACWY vaccine in the last 10 years (groups 7 and 8)
- Previously having received a meningococcal C vaccine in the last 10 years (groups 7 and 8)
- Previously received any adenovirus based vaccine of any kind (usually as part of a trial) (Groups 1, 2, 3 and 4 only)
- Previous occurrence of disease caused by *N. meningitidis*
- Inability, in the opinion of the Investigator, to comply with all study requirements
- Female participants who are pregnant, lactating or planning pregnancy during the course of the study
- Participant unwilling to allow contact with their GP, is not registered with a GP, or GP not contactable.
- Any other significant disease or disorder which, in the opinion of the Investigator, may
  - Put the participants at risk because of participation in the study;
  - Influence the result of the study; and/or
  - Impair the participant's ability to participate in the study

7.4. Temporary exclusion criteria

The following applies to both initial enrolment and subsequent vaccination visits. If the temporary exclusion resolves within the time constraints of the trial, they can be enrolled and/or progression in the trial can continue.

- Receipt of immunosuppressive treatment/therapy such as chemo- or radiotherapy within the preceding 6 months or long-term systemic corticosteroid therapy (10mg daily or higher) or any systemic corticosteroid (or equivalent) treatment within 14 days prior to vaccination, or for more than 7 days consecutively within the previous 3 months. Febrile illness (oral temperature ≥37.5°C) or systemically unwell on the day of vaccination
- If a participant is taking systemic antibiotics then the vaccination is postponed until 7 days after the last dose. This does not apply to topical antibiotic preparations

- Use of antipyretics in the 4 hours prior to vaccination
- A laboratory AE considered, in the opinion of the Investigator, requiring of further time and/or investigation to resolve or stabilise prior to another dose of vaccine being administered

8. TRIAL PROCEDURES

8.1. Recruitment

Identification of study participants

In order to recruit the required cohort of participants, several strategies may be employed, including:

- Poster advertising: Display of posters advertising the study throughout local hospitals and doctor's surgeries, tertiary education institutions and other public places with the permission of the owner/ proprietor.
- Direct mail-out: This would involve direct mailing of the study information sheet to adults whose names and addresses have been obtained via the Electoral register or Open Exeter database. Those people who have indicated they do not wish to receive postal mail−shots would have their names removed prior to the Investigators being given the names and addresses. The company providing this service is registered under the Data Protection Act 1998.
- Email campaign and communication: We will contact representatives of local tertiary education establishments and local employers and ask them to circulate posters and link to study website by email or hard copy.
- Oxford Vaccine Centre (OVC) database for healthy volunteers: Direct email and link to members of the public who have registered their interest in potentially volunteering for clinical trials conducted by OVC. This secure database is maintain by OVC and members of the public registered here have given consent to have their details recorded and be contacted expressly for this purpose of being notified when a trial opens for recruitment. They understand this is not a commitment to volunteering for any trial they are contacted about.
- Media advertising: Local media, newspaper, radio and website advertisement placed in locations relevant for the target age group with brief details of the study and contact details for further information.
- Website advertising: Description of the study and copy of information booklet on the OVG website (with self-screening questions) and other websites (such as OUH intranet, Daily Info etc.).
- Exhibitions: Advertising material and/or persons providing information relating to the study will exhibit using stalls or stands at exhibitions, festivals and/or fairs, such as University Fresher's Fairs.
- Social Media advertising: Advertising posts/digital banners on social media sites such as Facebook and Twitter
- Royal Mail Leaflet: Royal Mail door-to-door service with delivery of invitation letters to the occupier in OVG envelopes to every household within certain postcode areas.

Recruitment, approach and initial eligibility assessment of potential study participants

Potential participants who are interested in study participation will be able to contact the OVG by telephone or email for further information. Once an expression of interest has been received by OVG, an information sheet will be sent via mail or email to the potential participants to read at their leisure. A brief screening exercise will be performed either via telephone or email with the participant by appropriately

trained members of the research team (usually a study nurse or doctor), or via the participant completing a self-assessment questionnaire. If the participants pass this assessment and are willing to proceed they are invited for a screening and consent visit, where their eligibility will be fully assessed by member of the clinical research team at the Oxford Vaccine Group.

8.2. Screening and Eligibility Assessment

Once informed written consent is obtained, the following baseline assessments and information is collected by an appropriately trained member of the study team (usually a nurse or doctor) as part of the assessment of inclusion/exclusion criteria:

- Participant demographics; age, sex and ethnicity
- Medical history
- Contraception use; female participants are asked if they are willing to use effective contraceptive measures one month prior to vaccination and for three months post final vaccination
- Use of concomitant medication (including over the counter medications, vitamins, illicit drug use and herbal supplements)
- History of alcohol and smoking use
- History of prior vaccination with any group B meningococcal vaccine or Adenovirus based vaccine
- Recording of resting pulse and blood pressure
- 12 lead ECG
- BMI (height and weight)
- Physical examination; cardiovascular, respiratory, abdominal and gross neurological examination
- Urine dipstick (and laboratory analysis if appropriate) and urine pregnancy test
- Blood samples for: haemoglobin count, white cell indices, platelet count, serum sodium, serum potassium, serum urea, serum creatinine, liver function tests, C-reactive protein, HIV, and Hepatitis B and C
- Point-of-care testing: measurement of blood glucose

The medical history, vaccination history and prescribed medication lists are based primarily on participant recall. With prior participant approval, the GP surgery will be asked to return a medical summary confirming the participants medical and immunisation history, which will be used with other screening information to determine eligibility.

8.3. Trial Over-volunteering Prevention System (TOPS)

Consent will be taken to register the participant onto The Over-volunteering Prevention System (TOPS) database to guard against the potential for harm that can result from excessive volunteering in clinical trials involving IMPs and blood donations. This will be done using the participants National Insurance number or passport number (if not a British citizen).

8.4. Informed Consent

The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed. Consent will be sought as described in relevant SOPs.

Written and verbal versions of the participant information booklet and informed consent form will be presented to the participant, detailing no less than:

- the exact nature of and the rationale for performing the study

- implications and constraints of the protocol
- the risks and benefits involved in taking part

It will be clearly stated that the participant is free to withdraw from the study at any time, for any reason and that they are under no obligation to give the reason for withdrawal. The participant will be allowed at least 24 hours to consider the information from when they receive it, and the opportunity to question the researcher, their GP or other independent parties to decide whether they will participate in the study. Written informed consent will be obtained by means of a dated signature of the participant and a signature of the study staff member who presented informed consent. A copy of the signed informed consent will be given to the participant and the original signed form will be retained at the study site. The informed consent discussion will be conducted by a nurse or doctor at the Oxford Vaccine Group who has been trained in the consent process.

8.5. Vaccination Visit

Vaccination visits (V1 +/- V5 +/- V8; – see tables 1-6) are held at the CCVTM. The visit procedure for the vaccination visits will be as follows:

- Ensure that participant consent remains valid and, at V1, ensure they are still happy to continue with the study
- Obtain and document interim medical history since the last visit and check eligibility criteria (specifically temporary exclusion to vaccination)
- Review electronic diary entries (V5 and V8 only)
- Review laboratory AE profile (V5 and V8 only)
- Record oral temperature, pulse and blood pressure
- Perform urinary pregnancy test for females
- Perform blood draw as per Tables 7-9
- Administer vaccine by IM injection
- Observe for immediate adverse events for 60 minutes (following ChAdOx1 MenB.1) or 15 minutes (following Bexsero or Trumenba). Provide participant with a Medic Alert Contact Card with 24 hour telephone number to reach a study doctor (V1 only – check at other vaccination visits)
- Obtain 24 hour contact details. The study team will obtain the name and number of a close friend, relative or housemate who will be kept informed of the study participant's whereabouts in the 2 weeks following vaccination. This person may be contacted if study staff are unable to contact the participant in the case of an emergency (Groups 1-4 only).
- Remind participants to contact the study team if they have any concerns regarding their wellbeing, symptoms and/or admission to hospital.
- Participants will be provided with eDiary log-on details and training on how to complete Additional paper backup copies of the eDiary will also be provided.
- Schedule next visit and re-iterate participant requirements such as completion of the electronic diary entries

8.6. Subsequent Visits

Other visits (as detailed in Table 1-6) will require the following procedures:

- Perform blood draw as per Tables 7-9
- Review electronic diary entries, laboratory tests, any adverse events and use of any concomitant medication since the last visit
- Record oral temperature, pulse and blood pressure
- Schedule next visit and re-iterate participant requirements such as return of the Diary Card entries

- Remind participants to contact the study team if they have any concerns regarding their wellbeing, symptoms and/or admission to hospital.

8.7. Unscheduled Visits

In the event of an unexpected or serious adverse event, a participant may need to have unscheduled clinic visits. These visits would have the same format as "subsequent visits" in section 8.6. Safety bloods might be sent at these visits, at the discretion of the investigator.

8.8. eDiary Monitoring

Throughout the study period, participants will have access to an eDiary system (internally created and managed by OVG). Participants will be asked to record their temperature, rate a list of solicited symptoms, and recorded any other unsolicited symptoms for seven days after vaccination. They will also be asked to record any new concurrent medications taken during the trial and any symptoms beyond the 7 day monitoring period.

Each participant will be given unique log-in details associated with their study number. Training for this will be given at the first visit as described above. A paper copy of the diary will be provided to allow for completion in the event of inability to access the online version for whatever reason.

8.9. Sample Handling

8.9.1 Blood testing schedule

Table 7. Details of which blood tests are performed on each visit for groups 1-6. These will be taken by an appropriately trained member of the research team (normally a nurse or doctor). The total volume of blood obtained per participant is up to approximately 1307ml from screening to the 52 weeks completion of all subsequent visits. Cells shaded in pink are for the six month boosted groups only (i.e. groups 3, 4 &6).

Visit	Week of Study visit	Day of visit	Antibodies/SBA (ml)	PBMCs (ml)	Cytokines (ml)	Functional genomics (ml)	Full blood count (ml)	LFTs, U&Es &CRP (ml)	HIV/Hep B/C (ml)	Serum standard	Visit volume (ml)
V0	Pre-study	Screening visit					2	2	2		6
V1	Week 0	D0	30	75	2	3	2	2			114
V2	D1	D1			2	3	2	2			9
V3	Week 1	D7	30	75	2	3	2	2			114
V4	Week 2	D14	30	50	2		2	2			86
V5	Week 4	D28	30	75	2		2	2			111
V6	Week 8	D56	30	50	2		2	2			86
V7	Week 12	D84	30	50	2		2	2			86

V8	Week 28	D180	30	50	2	3**	2	2			86-89
V9**	Week 28	V8 + 1d		20*	2	3	2	2			9-29
V10**	Week 29	V8 + 7d	30	75	2	3	2	2			114
V11**	Week 30	V8 + 14d	30	50	2		2	2			86
V12	Week 32	D208	30	75	2		2	2		201***	114-315
V13	Week 48-52	D365	30	50	2						82
							Total				894-1307

*Group 3 and 4 only

** Groups 3, 4, & 6 only

*** Group 6 only. Serum standard of 200ml, and Hb check (1ml)

Total blood volume/ml: Groups 1, 2 & 5 894
Group 3 & 4 1126
Group 6 1307

Table 8. Details of which blood tests are performed on each visit for group 7

Visit Designation	Week of Study visit	Day of visit	Serum (ml)	Full blood count (ml)	LFTs, U&Es &CRP (ml)	Serum for HIV/Hep B/C (ml)	Visit volume (ml)
V0	Pre-study	Screening visit		2	2	2	6
V1	Week 0	D0		2	2		4
V8	Week 28	D180		2	2		4
V12	Week 32	D208-222	200	2 1*	2		205
					Total		219

* 1ml required for haemoglobin check

Table 9. Details of which blood tests are performed on each visit for group 8

A subset of group 8 (*) will have extra blood tests taken. The total volume of blood obtained per participant is between 365ml and 649ml from screening to the 52 weeks completion of all subsequent visits.

Visit Designation	Week of Study visit	Day of visit	Serum (ml)*	PBMCs (ml)*	Functional Genomics*	Full blood count (ml)	LFTs, U&Es &CRP (ml)	Serum for HIV/Hep B/C (ml)	Visit volume (ml)
V0	Pre-study	Screening visit				2	2	2	6
V1	Week 0	D0	16*	40*	3*	2	2		4 or 63*

V2	Week 0	D1			3*	2	2		4 or 7*
V3	Week 1	D7	16*	40*	3*	2	2		4 or 63*
V5*	Week 4	D28	16*	40*		2*	2*		60*
V8	Week 28	D180	16*	40*	3*	2	2		4 or 63*
V9	Week 28	V8 + 1d			3*	2	2		4 or 7*
V10	Week 29	V8 + 7d	16*	40*	3*	2	2		4 or 63*
V12	Week 32	D208	200 or 216*	40*		2 1**	2		205 or 261*
V13*	Week 48-52	D365	16*	40*					56*
							Total		235 or 649*

*subset of 10 participants from group 8

** 1ml required for haemoglobin check

8.9.2 Safety and Screening Blood and Urine tests

The safety and screening blood tests (full blood count, U&Es, LFTs, CRP, HIV, and Hepatitis B/C) will be sent to the Oxford University Hospitals pathology laboratories (haematology, biochemistry or microbiology labs) for processing as per their standard SOPs. These labels will be labelled with the participants study number and initials, but no other identifying details. The urine tests (either urine dip or pregnancy test) will be performed by a trained member of the research team (usually a nurse or doctor) in real time during the appropriate study visit. If the urine dip reveals abnormalities suggestive of infection (i.e. presence of protein, leukocytes or nitrites) the urine sample will be sent to the OUH microbiology laboratory for culture.

Haemoglobin check prior to a ≥200ml large blood draw at V12 will be performed using a point-of-care test.

8.9.3 Laboratory immunology

In addition to blood samples needed for the safe conduct of the trial and assessment of the primary endpoint, blood samples from the participants will also be subjected to laboratory analyses in order to assess the objective defined in the secondary endpoint, and potentially for the exploratory objectives. These samples will be relabelled to a laboratory number upon processing in the OVG laboratory, which is linked to the original participant number. The plan for analysis is outlined below, and will be further detailed in a specific lab analysis plan:

a. Analysis of bactericidal activity

The ability of the antibodies in participants' serum samples to mediate killing of homologous meningococci in the presence of complement (serum bactericidal activity (SBA)), will be quantified. The target strain in

the SBA assay will be a strain carrying a homologous fHbp to the one present in the vaccines composition (fHbp variant 1.1). The SBA titre will be calculated as the lowest concentration of the serum dilution giving a 50% reduction of colony forming units (CFUs) of a specified inoculum of bacteria after incubation with participant serum in presence of complement.

b. Exploratory Analysis of immune responses elicited by the vaccines

Exploratory assays of particular scientific interest may include the quantification of the relative concentration of serum antibodies against vaccine antigens (fHbp and its natural ligand factor H, adenovirus structural proteins) by enzyme linked immunosorbent assay (ELISA).

Cellular responses to quantify the B- and T-cell responses specific to the vaccine components will be performed when feasible using peripheral blood mononuclear cells (PBMCs) derived from study participants sampled before, and at several time points after each dose, using memory B cells, plasma cells and cytokine ELISPOT and flow cytometric assay (phenotyping, intracellular cytokine staining).

The ability of serum antibodies to mediate an opsonophagocytic effect may differ in the new vaccine as compared to the licensed comparator and may be assessed by an assay tailored for use with a set of target strains as used in the serum bactericidal assay.

Innate immune activation may also be assessed.

Analysis of gene expression may be performed using peripheral blood. This analysis may highlight differences in gene expression induced by vaccination and provide insight into the immunobiology of vaccine responses. In addition, DNA samples obtained from peripheral blood will contribute to a Biobank of samples from multiple different Oxford Vaccine Group studies. These DNA samples will be used to analyse the genetic factors influencing vaccine responses (immunogenicity and reactogenicity). DNA extraction and storage will only occur with the specific consent of participants, and DNA will not be analysed for any other purpose than to assess factors influencing vaccine responses.

8.10. Discontinuation/Withdrawal of Participants from Trial Treatment

Each participant can exercise their right to withdraw from the study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including, though not exclusive to, the following:

- Pregnancy
- Ineligibility (either arising during the study or in the form of new information not declared or detected at screening)
- Significant protocol deviation
- Significant non-compliance with study requirements
- An adverse event which requires discontinuation of the study vaccinations, puts the participants health or wellbeing at undue risk or results in an inability to continue to comply with study procedures
- Consent withdrawn
- Lost to follow up

Withdrawal from the study will not result in exclusion of the data generated by that participant from analysis. The reason for withdrawal, if given, will be recorded in the CRF. All data and participant samples obtained up to the point of withdrawal will be used in the analysis. Any withdrawn participant will be offered further non-scheduled follow-up if there are participant safety concerns.

A participant who is withdrawn from the study can be replaced if the individual has not reached the Day 28; or serum standard donation for groups 7 and 8.

8.11. Definition of End of Trial

The end-of-study is completion of the last laboratory assay on the last participant sample. At this point, all samples will be destroyed, unless transferred to the Biobank with participant consent.

9. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

9.1. IMP Description

9.1.1 ChAdOx1 MenB.1

The vaccine product ChAdOx1 MenB.1 is formulated in 10 mM Histidine, 35 mM NaCl, 1 mM $MgCl_2$, 0.1 mM EDTA, 0.5 % (v/v) ethanol, 7.5 % (w/v) sucrose, 0.1 % (w/v) PS80, in Water for Injection, at pH 6.6, sterile-filtered. The vaccine is stored frozen (-80°C nominal) in Type 1 glass, particle free (as per USP or Ph. Eur. Method), sterile and depyrogenated vials. Each vial contains 450µl at 1.6x10e11 vp/ml. The product is manufactured, tested and labelled according to current EMEA guidelines in keeping with Good Manufacturing Practice (GMP). See the IB and IMPD for detailed descriptions of the final drug product.

9.1.2 Bexsero

The vaccine product Bexsero is a licenced vaccine against Meningococcal B disease. Each dose of vaccine contains recombinant Neisseria meningitidis group B NHBA fusion protein (50 micrograms); recombinant Neisseria meningitidis group B NadA protein (50 micrograms); recombinant Neisseria meningitidis group B FHbp fusion protein (50 micrograms) and Outer membrane vesicles (OMV) from Neisseria meningitidis group B strain NZ98/254 (25 micrograms measured as amount of total protein containing the PorA P1.4). Each individual dose is 0.5ml. See product SPC for full detailed description.

9.1.3 Trumenba

The vaccine product Trumenba is a licenced vaccine against Meningococcal B disease. Each dose of Trumenba is formulated to contain 60 micrograms of each fHBP variant subtype (120 micrograms total protein), 0.018 mg of polysorbate 80, and 0.25 mg of Al3+ as AlPO4 in 10 mM histidine buffered saline at pH 6.0.

9.2. Storage of IMP

9.2.1 ChAdOx1 MenB.1

The vaccine product will be stored at -80 °C with the CBF in a locked, alarmed and temperature monitored freezer until authorised for release. Once released, the IMP will be stored at -80 °C at the CCVTM.

Transport of the vaccine to the clinical site will be performed by the CBF, or a representative from the Oxford Vaccine Group Team, with all movements' temperature controlled, maintaining the cold chain at all times. All movements of study medication between the CBF and OVG, will be documented in accordance with relevant SOPs.

The study treatment will be stored at the OVG in temperature monitored freezers and refrigerators with an auditable temperature record in accordance with the manufacturer's instructions and relevant SOPs. Study fridges and freezers are connected to a monitoring system with 24-hour access to staff that are able to move the product in the event of significant temperature deviation, for example fridge malfunction.

During the study, the vaccine will be defrosted and then administered immediately. Dilution according to dose will be performed as per the SOP. The remaining half of the vaccine will be stored at 2 to 8 °C for up to two hours (based on stability data available in the IB), and either be administered to a second participant during this time or returned to the laboratory to be used for research purposes. After this time it will not be administered to a participant.

For the high-dose vaccine, the whole vial will be administered and no dilution is required. As the vial will be defrosted on participant arrival and immediately administered, there will be no need for further storage.

9.2.2 Bexsero and Trumenba

The Bexsero and Trumenba vaccines will be stored between 4°C-8°C until just prior to administration, as per the vaccine's SPC.

9.3. Compliance with Trial Treatment

The study treatment will be administered by trained study personnel and will be documented according to GCP guidelines and relevant SOPs. Issues related to compliance are therefore in hands of the study personnel which have received appropriate training.

9.4. Accountability of the Trial Treatment

The ChAdOx1 MenB.1 vaccine has been manufactured, packaged, labelled and supplied by the Clinical BioManufacturing Facility (CBF), University of Oxford. All vaccines are labelled with a label specifying 'For clinical trial use only' and no less than the following:

- The clinical trial identifier (by reference code)
- The content of each vial
- Dose route
- The batch number
- The chief investigator
- Expiry date

The vaccine will be stored at the CBF pending authorised release for use in the clinical trial.

The comparator vaccine, Bexsero and Trumenba, will be stored and administered according to manufacturer's guidelines and relevant SOPs.

9.5. Concomitant Medication

The use of all concomitant medication, prescribed or over-the-counter, will be recorded in the CRF. There is no restriction on the use of concomitant medication but the use of some prescribed medicines, such as immune suppressive agents, may result in the withdrawal of the participant at the discretion of the Investigator, while others, such as antibiotics or antipyretics (within 4 hours), may result in a temporary exclusion.

9.6. Post-trial Treatment

Study medication will not be continued beyond the trial period.

9.7. Genetically Modified Organism (GMO) Approval

As the trial IMP, ChAdOx1 MenB.1 involves use of a GMO, approval of IMP use and associated procedures (e.g. disposal) will be sought from the local GMO committee in line with The Genetically Modified Organisms (Contained Use) Regulations 2014.

10. SAFETY REPORTING

10.1. Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above. The threshold for an AE to be consider severe for each criteria (symptoms, laboratory value etc.) is detailed in Appendix A.

Any pregnancy occurring during the clinical trial and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect, at which point it would fall within the definition of “serious”.

10.2. Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual within the study team according to the following definitions:

No relationship:

- No temporal relationship to vaccine administration;
- Alternative aetiology (clinical, environmental or other intervention), and
- Does not follow pattern of recognised response to vaccine administration

Possible:

- Reasonable temporal relationship to vaccine administration, or
- Event not readily explained by alternative aetiology (clinical, environmental or other interventions), or
- Similar pattern of response to that seen to vaccine administration.

Probable

- Reasonable temporal relationship to vaccine administration, and
- Event not readily produced by alternative aetiology (clinical, environment, or other interventions), or
- Known pattern of response with vaccine administration.

Definite

- Reasonable temporal relationship to vaccine administration and
- Event not readily produced by alternative aetiology (clinical, environment, or other interventions), and known pattern of response to vaccine administration

10.3. Procedures for Collecting and Recording Adverse Events

Expected AEs (as detailed in tables 10-13 in Appendix A) will be solicited via eDiary for 7 days after vaccination (solicited adverse events), with the exception of group 7 participants. Participants will be provided with a thermometer and tape measure to accurately record temperature and size of swelling, redness and induration during this period. Any AEs present at the end of the diary period will continue to be recorded in this manner until resolution. Participants will also be able to report any unexpected (unsolicited) AEs occurring at each visit. Vital signs will also be taken and recorded at each visit.

All AEs occurring during the study (from first vaccine administration until the last visit) observed by the investigator or reported by the participant, irrespective of their relatedness to the study medication, will be recorded in the AE section of the CRF.

AEs will be recorded using the following guidance:

- Pre-existing medical conditions (present before start of the AE collection period) are considered “concurrent medical conditions” and should not be recorded as AEs. However, if the participant experiences a worsening or complication of such a condition, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., “worsening of”)
- Each AE should be recorded to represent a single diagnosis. Accompanying signs or symptoms (including abnormal laboratory values) should not be recorded as additional AEs.

- Changes in laboratory values are only considered to be AEs if they are judged to be clinically significant, e.g., if some action or intervention is required. If abnormal laboratory values are the result of pathology for which there is an overall diagnosis the diagnosis only should be reported as one AE

The following information will be recorded in the CRF: description of the AE, the date of onset and end date, severity, assessment of relatedness to study vaccine(s) (as judged by a medically qualified investigator) and action taken. Follow-up information should be provided as necessary. AEs considered related to the study vaccine(s) will be followed until resolution, the event is considered stable or until a non-study causality is assigned.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from study. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of study assessment and be given appropriate care under medical supervision, by referral to their GP, until symptoms cease or the condition becomes resolved or is stable. If required, the investigator can refer the participant directly to hospital if the AE warrants it.

Any pregnancy occurring during the clinical study and the outcome of the pregnancy should be recorded and followed up until birth to monitor for any congenital abnormality or birth defect. Pregnancy notification and follow-up reports will be provided to the DSMC.

10.4. Reporting Procedures for Serious Adverse Events

All SAEs must be recorded on an SAE form and reported to the DSMC Chair within 24 hours of discovery or notification of the event (DSMC contact details will be available in the DSMC charter). Additional information received for a case (follow-up or corrections to the original case) need to be detailed on a new SAE form and faxed or emailed to the DSMC Chair. If the SAE is also a SUSAR, additional procedures for reporting are described below in section 10.6.

The chair of the DSMC (or a deputy nominated by the chair) will perform an independent review of SAEs and request any further information required in a manner adherent to the procedures and timelines of the DSMC Charter. Documentation of this review will be kept in the TMF.

The DSMC will provide independent real-time safety assessment throughout the study as described in section 10.7.

10.5. Expectedness

Expectedness will be determined according to the Investigators' Brochure for ChAdOx1 MenB.1 and the Summary of Product Characteristics for Bexsero and Trumenba.

10.6. SUSAR Reporting

All SUSARs will be reported by the CI to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

10.7. Safety Monitoring Committee

At the time of writing the DSMC will be Professor Robert Heyderman (UCL) (Chair), Prof Adam Finn (Bristol), Dr Andrew Riordan (Liverpool) & Hilary Watt (Imperial) (statistician).

The DSMC is independent and will review safety data throughout the study according to the DSMC Charter. The specific role of the committee will be as follows:

1. Formal review of the safety profile after 7 days of safety data has been collected from groups 1 before progression to group 2, and review of group 2 before enrolling groups 3 and 4, as described in section 6.
2. Independent review following any SAE deemed to be possibly, probably, or definitely related to the trial vaccine.
3. Unscheduled reviews on request of the study management committee at a demand and frequency determined by the severity of reported adverse events.

From these reviews the DSMC will make recommendations to the study investigators on whether there are any ethical or safety reasons why the trial should not continue. A summary of all AEs and SAEs to date will be provided to the DSMC on request.

The outcome of each DSMC review will be communicated directly to the study investigators and documentation of all reviews will be kept in the TMF.

The Chair of the DSMC will also be contacted for advice where the Chief Investigator feels independent advice or review is required.

10.8. Other safety reviews

In addition to formal DSMC review, there will also be local safety monitoring reviews. As described in section 6, there will be planned local reviews of safety 48 hours following vaccination of the first participants in groups 1 and 2. This will be to decide if further vaccination within that group proceeds and the decision will be made by either the Chief or Principal Investigator.

10.9. Group holding rules

See section 6.2.1 for detailed information about vaccination schedules of volunteers and relationships between the groups, safety reviews and dose escalations. In general terms, if ≥2 of the first three or six participants in groups 1 or 2 develop an unacceptable adverse reaction (defined as an unacceptable adverse reaction is defined by a severe adverse event which lasts more than 48 hours and/or the occurrence of a serious adverse event), then recruitment to that group will be paused pending a DSMC review.

If a holding rule has been met and following a safety review by the DSMC it is deemed appropriate to restart dosing, a request to restart dosing with pertinent data must be submitted to the regulatory authority as a request for a substantial amendment. The DSMC safety review will consider:

- The relationship of the AE or SAE to the vaccine.
- The relationship of the AE or SAE to the vaccine dose, or other possible causes of the event.
- If appropriate, additional screening or laboratory testing for other volunteers to identify those who may develop similar symptoms and alterations to the current Study Information Booklet (SIB) are discussed.
- New, relevant safety information from ongoing research programs on the various components of the vaccine.

The local ethics committee, MHRA and vaccine manufacturers will also be notified if a holding rule is activated or released.

All vaccinated volunteers will be followed for safety until resolution or stabilisation (if determined to be chronic sequelae) of their AEs.

10.10. Individual holding rules

In addition to the above stated group holding rules, stopping rules for individual volunteers will apply (i.e., indications to withdraw individuals from further vaccinations):

- **Local reactions:**
  - Injection site ulceration, abscess or necrosis

- **Laboratory AEs:**
  - the volunteer develops a Grade 3 laboratory adverse event considered possibly, probably or definitely related within 7 days after vaccination, persisting continuously at Grade 3 for > 72hrs.

- **Solicited adverse events (see section 10.3 for definition):**
  - the volunteer develops a Grade 3 systemic solicited adverse event considered possibly, probably or definitely related within 2 days after vaccination (day of vaccination and one subsequent day), persisting continuously at Grade 3 for > 72hrs.

- **Unsolicited adverse events (see section 10.3 for definition):**
  - the volunteer has a Grade 3 adverse event, considered possibly, probably or definitely related to vaccination, persisting continuously at Grade 3 for >72hrs,
  - the volunteer has a serious adverse event considered possibly, probably or definitely related to vaccination, or
  - the volunteer has an acute allergic reaction or anaphylactic shock following the administration of vaccine investigational product.

If a volunteer fulfils any of the temporary exclusion criteria (see section 7.4) at the scheduled time of a second administration of investigational product, the volunteer will not receive the vaccine at that time. The vaccine may be administered to that volunteer at a later date within the time window specified in the protocol (see Tables 1-6) or they may be withdrawn from the study at the discretion of the Investigator.

All vaccinated volunteers will be followed for safety until the end of their planned participation in the study or until resolution or stabilisation (if determined to be chronic sequelae) of their AEs, providing they consent to this.

10.11. Stopping Rules

The trial will be discontinued in the event of any of the following:

- New scientific information is published to indicate that subjects in the trial are being exposed to undue risks as a result of administration of the IMP, or as a result of the trial procedures or follow-up schedule.
- Serious concerns about the safety of the IMP arise as a result of one or more vaccine related SAE(s) occurring in the subjects enrolled in this or any other on-going trial of the ChAdOx1 MenB.1 vaccine or vaccines containing the ChAdOx1 vector.
- For any other reason at the discretion of the Chief Investigator or DSMC.

Additionally, the DSMC can temporarily pause the trial if time is required to reach a decision regarding stopping the trial e.g. to determine causality for SAE.

10.12. Development Safety Update Reports

The CI will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, Host NHS Trust and Sponsor.

11. STATISTICS

11.1. Description of Statistical Methods

The analyses for this study will be descriptive in purpose and will not include any hypothesis testing or presentation of p values for group comparisons or power calculation therefore in.

11.2. The Number of Participants

47-50 participants will be recruited to the study allocated to groups 1-6 as detailed in section 5 and 6.2. The size of group 1 may vary according to the dose-finding protocol. Participants will be replaced if they do not reach the Day 28 due to withdrawal from the study.

32-40 further participants will be recruited to groups 7-8, depending on consent from individuals in group 6 (n=8) to provide a serum standard sample. Participants will be replaced if they do not complete V12 due to withdrawal from the study.

There has been no power calculation to determine these numbers as the study is primarily descriptive. The numbers have been therefore chosen on the maximal number able within budgetary and practical constraints.

11.3. The Level of Statistical Significance

There will be no statistical significance testing. All confidence intervals for descriptive analyses will be set at 95%.

11.4. Criteria for the Termination of the Trial

The Chief Investigator and Data Safety Monitoring Committee will have the right to terminate the study at any time on grounds of participant safety. If the study is prematurely terminated the investigator will promptly inform the participants and will ensure appropriate therapy and follow-up. If the study is halted, the MHRA and relevant Ethics Committee will be notified within 15 days of this occurring.

In the event of the trial being terminated early, follow-up of enrolled participants will still continue as detailed in tables 1-6 for safety reasons, with the exception that booster vaccine doses in groups 3, 4 & 6 will not be given.

11.5. Procedure for Accounting for Missing, Unused, and Spurious Data.

All available data will be used in the analyses and there will be no imputations for missing data. Participants will be analysed according to the group to which they were assigned.

11.6. Inclusion in Analysis

All participants with any available data will be included in the analyses.

12. DATA MANAGEMENT

12.1. Source Data

Source documents are original documents, data, and records from which participants' CRF data is populated. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. In this study CRF entries will be considered source data where it is the site of the original recording. All documents will be stored safely under strict confidentiality and with restricted access. On all study-specific documents, other than the signed consent and the participant contact sheet, the participant will be referred to by the study participant number/code only.

12.2. Access to Data

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

12.3. Data Recording and Record Keeping

The investigators will populate the content of participants' CRFs, which will be in a paper and/or electronic format using an OpenClinica™ database. This database is stored on a secure Rackspace™ server in the UK, has restricted access, and is password-protected with accountability records. This data includes safety data, laboratory data (both clinical and immunological) and outcome data. All information transcribed to and from the OpenClinica™ database is by encrypted (Https) transfer.

Each study participant will have a unique screening number which will be allocated at the time a screening visit is booked and all names and/or identifying details are not included in any study data electronic file. After enrolment the participants will be identified by a study specific participants number and/or code. Samples sent to laboratories for processing will be identified by trial number and participant number only.

The study team will use names and contact details to contact participants about the research study, and make sure that relevant information about the study is recorded for their care, in relation to their health during the study and to oversee the quality of the study. At the completion of the study, unless participants consent otherwise (e.g. requesting to be informed of other trials), participant's personal details will not be used to contact them other than exceptional circumstances concerning their safety. If consent is provided by participants to take part in another study carried out by the study site, personal information and medical information including blood test results may be accessed to avoid unnecessary repetition. If participants provide specific consent, we will use personal identifiable data to invite participants for future research.

Bank details will be stored for 7 years in line with University financial policy.

12.3.1 Data integrity

Data collection and storage will be inspected throughout the study by internal (performed by the Oxford Vaccine Group) and external (by the study Sponsor, University of Oxford, CTRG) monitoring.

12.3.2 Data archiving and storage

We will keep identifiable personal information such as contact details for a minimum of 5 years after the study has finished. Study records including medical information, signed consent forms and anonymised scientific data will be stored by Ardington Archives storage (Faringdon, Oxford) according to the latest SOP. The need to store this information for longer in relation to licensing of the vaccine will be reviewed every 5 years. Files will be confidentially destroyed if storage is no longer required. For effective vaccines that may be licensed, secure storage of research data may be required for at least 15 years after the end of the study, subject to adjustments in clinical trials regulations. Prof Andrew J Pollard, or his successor, as the Director of the Oxford Vaccine Group will have the responsibility for custody of the data.

13. QUALITY ASSURANCE PROCEDURES

13.1. Investigator procedures

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures. Approved and relevant SOPs will be used at all clinical and laboratory sites.

13.2. Monitoring

Monitoring will be performed according to ICH Good Clinical Practice (GCP) by CTRG. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. The investigator sites will provide direct access to all trial related source data/documents and reports for the purpose of monitoring and auditing by the sponsor and inspection by local and regulatory authorities

13.3. Modification to protocol

No amendments to this protocol will be made without consultation with, and agreement of, the Sponsor. Any amendments to the trial that appear necessary during the course of the trial must be discussed by the Investigator and Sponsor concurrently. If agreement is reached concerning the need for an amendment, it will be produced in writing by the Chief Investigator and will be made a formal part of the protocol following ethical and regulatory approval.

An administrative change to the protocol is one that modifies administrative and logistical aspects of a protocol but does not affect the subjects' safety, the objectives of the trial and its progress. An administrative change does not require NHS REC approval.

The Investigator is responsible for ensuring that changes to an approved trial, during the period for which NHS REC approval has already been given, are not initiated without NHS REC review and approval except to eliminate apparent immediate hazards to the subject.

13.4. Protocol deviation

Any deviations will be documented in a protocol deviation form and filed in the TMF.

13.5. Audit & Inspection

The QA manager will conduct internal audits to check that the trial is being conducted, data recorded, analysed and accurately reported according to the protocol and in compliance with ICH GCP, meeting the requirements of the MHRA. The audits will also include laboratory activities according to an agreed audit schedule taking into consideration the 2009 MHRA guidelines for GCP in the laboratory. The internal audits will supplement the external monitoring process and will review processes not covered by the external monitor.

The sponsor may carry out audit to ensure compliance with the protocol, GCP and appropriate regulations. GCP inspections may also be undertaken by the MHRA to ensure compliance with protocol and the Medicines for Human Use (Clinical Trials) Regulations 2004.

13.6. Trial Progress

The progress of the trial will be overseen by the Chief Investigator.

14. SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial”.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the NHS host organisation within seven calendar days.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

15.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

15.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

15.4. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

15.5. Participant Confidentiality

The study staff will ensure that participants' anonymity is maintained. Study participants will be identified by initials and a participant ID number on the CRF. Two study identifiers are used to prevent errors in documentation and avoid mislabelling of samples. Any electronic databases and documents with participant identifying details will be stored securely and will only be accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

15.6. Participant Reimbursement

Each participant is compensated for their time and for the inconvenience based on the following figures:

- Travel expenses: £15 per visit
- Inconvenience of blood tests: £10 per visit
- Time required for visits: £20 per visit

Remuneration is on a *pro rata* basis should a participant fail to complete all visits and/or study requirements. Each participant can therefore receive £160 – £630 depending on the visit schedule of their arm. Payments will be made in instalments after V0, V5, V8, V12 and V13.

Additional reimbursement for unscheduled visits at £45 per visit will be provided up to maximum of £135 (the equivalent of three unscheduled visits). This will not be given unless an unscheduled visit occurs.

15.7. Incidental Findings

It is possible that during the study, we will detect incidental findings at screening or during the trial unrelated to the trial but of potential health concern to the participant (e.g. high blood pressure). The participant will be informed of this and, with their permission, their GP will be informed to provide any necessary follow-up as per local SOPs.

16. FINANCE AND INSURANCE

16.1. Funding

The clinical trial is funded by grants from the Medical Research Council (MRC) and the National Institute of Healthcare Research (NIHR) / British Research Council (BRC). The serum standard arm of the study is funded by the National Institute for Biological Standards and Control (NIBSC).

16.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

17. PUBLICATION POLICY

Authorship of any publications arising from this study should fulfil the following criteria:

- Made a substantial contribution to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work; and
- Drafted or substantively reviewed or revised the publication; and
- Approved the final version of the publication; and
- Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work could be appropriately investigated and resolved.

The Investigator will co-ordinate dissemination of data from this study. All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study will be reviewed by each sub-investigator prior to submission.

18. REFERENCES

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19. APPENDIX A: GRADING THE SEVERITY OF ADVERSE EVENTS

Labelling of an AE as severe will be defined by the severity threshold highlighted in each table.

Table 10: Grading of fever AE

Adverse event	Grade	Definition (in degrees Celsius)
Temperature	0	< 37.6
	1	37.6 – 38.0
	2	38.1 – 39.0
	3 (severe)	> 39.0

Table 11: Grading of solicited symptom AE's

Adverse event	Grade	Definition
Any symptom	0	Absence or resolution of symptom
	1	Awareness of symptom but tolerated; transient or mild discomfort; little or no medical intervention required
	2	Discomfort enough to cause limitation of usual activity; some medical intervention or therapy required
	3 (severe)	Significant interference with daily activity
	4 (severe)	Emergency department visit or hospitalisation
Injection Site reaction (erythema, induration and swelling)	0	No reaction
	1	1 to ≤10mm
	2	11 to ≤25mm
	3 (severe)	26 to ≤50mm
	4 (severe)	51 to ≤ 100mm
	5 (severe)	>100mm

Table 12: Grading of visit observations AE's

Observation	Grade 1	Grade 2	Grade 3 (severe)
Oral temperature (C)	37.6 – 38.0	38.1 – 39.0	39.1 or greater
Tachycardia (beats/min)	101-115	116-130	>130
Bradycardia (beats/min)	50-54	45-49	<45
Systolic hyper-tension (mmHg)	141-150	151-155	>155
Diastolic hyper-tension (mmHg)	91-95	96-100	>100
Systolic hypo-tension (mmHg)	85-89	80-84	<80

The following ranges are considered normal physiological ranges and are recorded as Grade 0:

Oral temperature between 35.5 and 37.5°C

Resting heart rate between 55 and 100 beats/minute

Systolic blood pressure between 90 and 140 mmHg

Table 13

. Grading of laboratory solicited AE's

	Grade 1 (Mild)	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Potentially life threatening)**
Haemoglobin (female): decrease from baseline value (gm/l)	< 15	15-20	21-50	>50
Haemoglobin (male): decrease baseline value (gm/l)	< 15	15-20	21-50	>50
White cell count: elevated (cell/mm^3)	10,800–15,000	15,001–20,000	20,001–25,000	>25,000
White cell count: depressed (cells/mm^3)	2500-3500	1500-2499	1000-1499	<1000
Neutrophil count (cells/mm^3)	1500-2000	1000-1499	500-999	<500
Platelets (cells/mm^3)	125,000-140,000	100,000-124,000	25,000-99,000	<25,000
Sodium: hyponatraemia (mEq/L)	132–134	130–131	125–129	<125
Sodium: hypernatraemia (mEq/L)	144–145	146–147	148–150	>150
Potassium: hyperkalaemia (mEq/L)	5.1–5.2	5.3–5.4	5.5–5.6	>5.6
Potassium: hypokalaemia (mEq/L)	3.5–3.6	3.3–3.4	3.1–3.2	<3.1
Urea (mmol/L)	8.2–8.9	9.0–11	>11	RRT
Creatinine (µmol/L)	132-150	151-176	177-221	>221 or RRT
ALT and/or AST (IU/L)	1.1–2.5 x ULN	>2.6–5.0 x ULN	5.1-10 x ULN	>10 x ULN
Bilirubin, with increase in LFTs (umol/L)	1.1–1.25 x ULN	1.26–1.5 x ULN	1.51–1.75 x ULN	>1.75 x ULN
Bilirubin, with normal LFTs (umol/L)	1.1–1.5 x ULN	1.6–2.0 x ULN	2.0–3.0 x ULN	>3.0 x ULN
Alkaline phosphatase (U/L)	1.1–2.0 x ULN	2.1–3.0 x ULN	3.1–10 x ULN	>10 x ULN
Albumin: hypoalbuminaemia (g/L)	28–31	25–27	<25	Not applicable
C-reactive protein	>10-30	31-100	100-200	>200

20. APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.1	13-Nov-2017	Meriel Raymond	Clarification of inclusion criteria relating to sexual abstinence in response to MHRA remarks
2	2.2	23-Nov-2017	Danielle Campbell	15.5 Participant Confidentiality – addition of rationale for using 2 participant identifiers (participant number and initials)
3	3.0	20-Sep-2018	Meriel Raymond, Danielle Campbell, Christine Rollier, Edward Choi, Blanche Oguti	• Addition of serum standard sample to group 6 • Addition of groups 7-8 to enable safety comparison with Trumenba, and to collect serum standards to Bexsero and Trumenba • Clarification of the consent process for group 6 • Correction of "Meningitis B" to "Meningococcal B" • Simplification of secondary objectives to Bexsero and Trumenba • Mention of innate immune activation in exploratory analysis • Addition of extra blood sample (20ml) at visit 9 for groups 3 and 4 • Clarification of GP summary being adequate to proceed with enrolment, rather than GP opinion • Addition of blood glucose to screening (groups 1-6) • Correction of typographical errors • Clarification of data collection and processing (GDPR)
4	3.1	03-May-2019	Blanche Oguti	Correction of time point for functional genomics blood test for Group 8 - to occur during study visits and not screening visit as with other Groups
5	3.2	11-Jul-2019	Blanche Oguti	Correction of table 9 to include missing asterisks indicating which bloods are only taken from the subset of 10 (as written on page 20)

6	3.3	12-Nov-2021	Megan Stone	Extension of end of trial date to 30/06/2022

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA.