TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Randomized, Open-label Study to Evaluate the Immunogenicity of Anthrax Vaccine Adsorbed Alone or Concomitantly with Raxibacumab (GSK3068483)

Compound Number: GSK3068483

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Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2014N194186_00	2014-OCT-21	Original
2014N194186_01	2016-APR-25	Amendment No. 1
This amendment serves to update contraception requirements for study participation to be consistent with updated GSK guidance on reproductive issues in clinical studies. The amendment also updates the secondary medical monitor information.		

SPONSOR SIGNATORY:

PPD

25 April 2016

Helen Steel
Vice President, Head Unit Physician, Infectious Diseases Therapeutic Area Unit

Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

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Primary Medical Monitor	PPD PPD M.D. (Quintiles)	PPD PPD	PPD	PPD PPD	1801 Rockville Pike, Suite 300, Rockville, MD 20852
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Regulatory Agency Identifying Number(s): IND BB011069

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 201436.

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS

Rationale

Raxibacumab was approved for the treatment of inhalation anthrax by the United States (US) Food and Drug Administration (FDA) on December 14, 2012 under the Animal Efficacy Rule per the U.S. Code of Federal Regulations (CFR) (21 CFR § 314.610). Raxibacumab is a fully human monoclonal $IgG_1\lambda$ antibody (Ab) which binds the protective antigen (PA) component of the tripartite anthrax toxin, thus blocking the deleterious effects of lethal toxin and edema toxin. Raxibacumab may be administered for prophylaxis of inhalation anthrax when alternative therapies are not available or are not appropriate. Anthrax Vaccine Adsorbed (AVA, BioThrax) which is mainly composed of adsorbed PA, may also be administered as part of a prophylaxis regimen. Published results indicate that a polyclonal anti-PA antitoxin administered to rabbits with AVA resulted in essentially complete abrogation of the immune response to AVA [Malkevich, 2013]. Since the primary antigen in AVA is PA, it is possible that concurrent administration of AVA and raxibacumab would result in raxibacumab binding the PA from AVA, leading to a reduced immune response to the vaccine and decreased anti-PA Ab concentrations and toxin neutralizing activity (TNA) titers. This study, as a post-marketing commitment to the FDA, is designed to detect the effect of raxibacumab on AVA immunogenicity in a healthy volunteer population.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To compare the immunogenicity of AVA at 4 weeks after the first AVA dose, when AVA is administered alone or concomitantly with raxibacumab.	• Ratio of geometric mean concentrations (GMC) of anti-PA Ab at 4 weeks after the first AVA dose (prior to the third AVA dose), between the AVA alone and the AVA with raxibacumab treatment groups.
Secondary	
• To compare the immunogenicity of AVA at Weeks 8 and 26 after the first AVA dose, when AVA is administered alone or concomitantly with raxibacumab.	• Ratio of GMC of anti-PA Ab at Weeks 8 and 26 after the first AVA dose, between the AVA alone and the AVA with raxibacumab treatment groups.
• To estimate and compare seroconversion, defined as a $\geq$ 4-fold increase in TNA titer from baseline, at Weeks 4, 8 and 26 after the first AVA dose, when AVA is administered alone or concomitantly with raxibacumab.	• Percentage of subjects who seroconvert, at Weeks 4, 8 and 26 after the first AVA dose, between the AVA alone and the AVA with raxibacumab treatment groups.
• To describe the safety of AVA when co-administered with raxibacumab versus AVA alone.	• Rates of reported adverse events (AE) as well as review of vital signs, urinalysis and clinical laboratory data in the AVA alone and the AVA with raxibacumab treatment groups.

Overall Design

This is a randomized, open-label, parallel group, two arm study in healthy subjects who have not previously been immunized against PA. Although this is an open-label study, measures have been introduced to minimize bias.

Treatment Arms and Duration

Subjects will be randomized into one of the following treatment groups:

- Treatment Group1 - subjects will be administered subcutaneous (SC) 0.5 mL AVA doses on Days 1, 15, and 29 (0, 2, and 4 weeks),

- Treatment Group 2- subjects will be administered SC 0.5 mL AVA doses on Days 1, 15, and 29 (0, 2, and 4 weeks), with the first AVA dose administered immediately after completion of a single 40 mg/kg intravenous (IV) infusion of raxibacumab. Subjects will be premedicated with diphenhydramine (25-50 mg) up to 1 hour prior to the raxibacumab infusion to reduce the risk of infusion reactions.

Beginning with the screening visit, the total duration of study for each subject may be approximately 28 to 31 weeks. This study duration was selected because it allows for assessment of the durable immune response to AVA.

Type and Number of Subjects

This study will be conducted in healthy adult subjects who have not been previously immunized against PA.

A total of at least 534 subjects (267 analyzable subjects per treatment group) may be enrolled in the study, in 3 cohorts separated by interim analyses. The trial will continue to subsequent cohorts only if the prospective criteria for discontinuing the trial are not met at the interim analysis. If the outcome of this trial shows a large impact on immunogenicity, then the trial will likely be stopped at one of the two interim analyses.

Subjects will be enrolled in the study in up to 3 cohorts separated by 2 interim analyses. The trial will continue to subsequent cohorts only if the prospective criteria for discontinuing the trial are not met at the interim analysis.

- at least 30 subjects will be enrolled in Cohort 1,

- at least an additional 70 subjects will be enrolled in Cohort 2 if the study progresses beyond interim 1.

- and at least an additional 434 subjects will be enrolled in Cohort 3 if the study progresses beyond interim 2.

Analysis

At the final analysis, the non-inferiority test will be based on a comparison of the confidence interval (CI) for the ratio of anti-PA Ab (attributable to AVA) GMCs between the AVA and the AVA + raxibacumab groups at week 4. This analysis will be performed in the per protocol population. If the upper bound of the 90% CI is less than 1.5, non-inferiority will be established. This analysis will be repeated in the subset of the intent-to-treat population with available week 4 results and in the full ITT population with imputed results for those with missing data, as sensitivity analyses .

The GMC ratio and GMCs within each treatment group and corresponding CIs will be calculated by first log transforming all of the data by a log base 10. CIs will be calculated about the mean logs and the difference of the mean logs assuming these values follow a t-distribution. The results will be translated back to the original scale by exponentiation them, again using a base 10. The exponentiating differences of the sample mean logs will be the ratio of the sample geometric means of the untransformed results.

Two interim analyses are scheduled during this study. A two sample t-test for the log transformed data will be performed and used as the basis of determining whether the futility threshold has been crossed at the respective interim analyses. The futility thresholds for the interim analyses will be based on a rho (0.5) Type II error spending function.

As a secondary endpoint, ratios of the anti-PA Ab GMC for each treatment group at Weeks 8 and 26 will be calculated as described above.

TNA geometric mean titers (GMTs) along with 95% CI will be summarized for each treatment group at each timepoint. The percentage of subjects, along with 95% CI, who seroconvert, defined as a >4-fold increase in TNA titer will be summarized, at Weeks 4, 8 and 26 after the first AVA dose for both arms separately.

Clinical safety observations will include AEs, urinalysis, vital sign measurements, and clinical laboratory assessments. Safety data will be tabulated and, where appropriate, analyzed by the use of descriptive statistics. Safety data will be tabulated for the safety population.

2. INTRODUCTION

2.1. Brief Background

Anthrax is a bacterial zoonosis caused by the gram-positive, aerobic, spore-forming *Bacillus anthracis*. Depending on the route of transmission, anthrax presents in different forms: cutaneous, gastrointestinal, injectional and inhalational [Booth, 2010]. Inhalational anthrax is the most severe form of anthrax because of the rapid progression of the disease to hemorrhagic mediastinitis, toxemia, and massive pulmonary edema, and because of the difficulty in establishing the diagnosis quickly [Dixon, 1999]. The incubation period for inhalational anthrax in humans ranges from 1 to 43 days [Meselson, 1994].

Anthrax Vaccine Adsorbed (AVA) is a current United Sates (U.S.) Food and Drug Administration (FDA)-approved form of anthrax vaccine. The vaccine requires multiple injections over several weeks before immunity is initially established, so it may not be effective in the event of acute exposure to *B. anthracis* [Bartlett, 2002]

Raxibacumab is indicated for the treatment of adult and pediatric patients with inhalation anthrax due to *B. anthracis* in combination with appropriate antibacterial drugs. Raxibacumab is also indicated for prophylaxis of inhalation anthrax when alternative therapies are not available or are not appropriate [Raxibacumab Package Insert, 2012]. In contrast to the anthrax vaccine, a single intravenous (IV) dose of raxibacumab provides immediate protection. Section 6 of the raxibacumab Investigator's Brochure (IB, 2013, Version 8) provides a summary of the non-clinical data, including efficacy and the safety profile of raxibacumab in human volunteer studies to date.

2.2. Study Rationale

Raxibacumab was approved for the treatment of inhalation anthrax by the FDA on December 14, 2012 under the Animal Efficacy Rule per the U.S. Code of Federal Regulations (CFR) (21 CFR § 314.610). Raxibacumab is a fully human monoclonal $IgG_1\lambda$ antibody (Ab) which binds the protective antigen (PA) component of the tripartite anthrax toxin, thus blocking the deleterious effects of lethal toxin and edema toxin. Raxibacumab may be administered for prophylaxis of inhalation anthrax when alternative therapies are not available or are not appropriate. Anthrax Vaccine Adsorbed (AVA, BioThrax) which is mainly composed of adsorbed PA, may also be administered as part of a prophylaxis regimen. Published results indicate that a polyclonal anti-PA antitoxin administered to rabbits with AVA resulted in essentially complete abrogation of the immune response to AVA [Malkevich, 2013]. Since the primary antigen in AVA is PA, it is possible that concurrent administration of AVA and raxibacumab would result in raxibacumab binding the PA from AVA, leading to a reduced immune response to the vaccine and decreased anti-PA Ab concentrations and toxin neutralizing activity (TNA) titers. This study, as a post-marketing commitment to the FDA, is designed to detect the effect of raxibacumab on AVA immunogenicity in a healthy volunteer population.

3. OBJECTIVE(S) AND ENDPOINT(S)

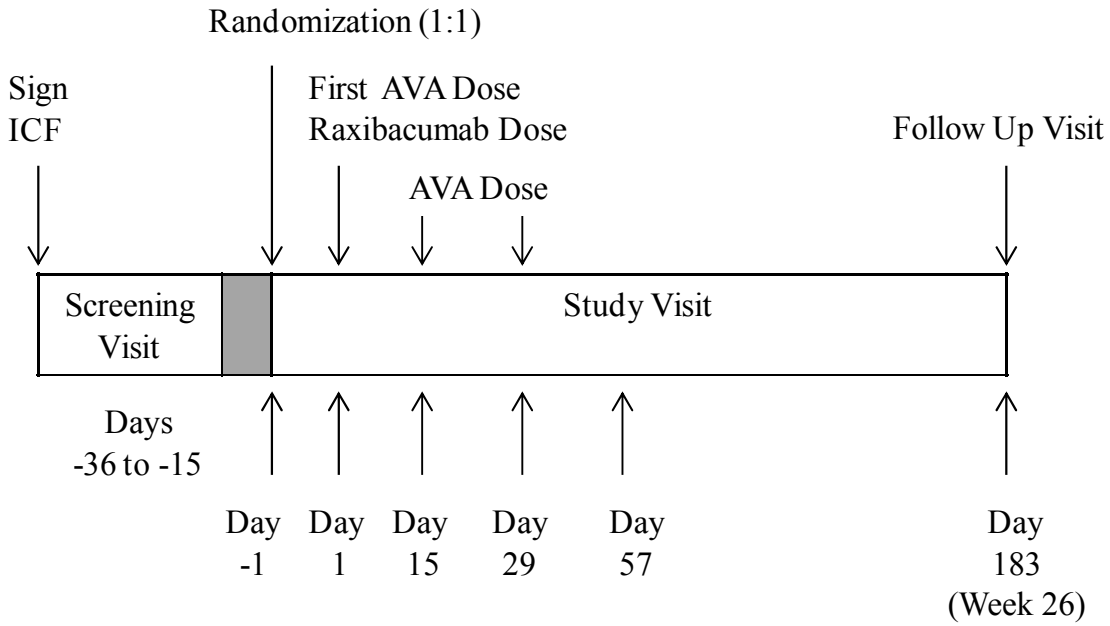
Objectives	Endpoints
Primary	
• To compare the immunogenicity of AVA at 4 weeks after the first AVA dose, when AVA is administered alone or concomitantly with raxibacumab.	• Ratio of geometric mean concentrations (GMC) of anti-PA Ab at 4 weeks after the first AVA dose (prior to the third AVA dose), between the AVA alone and the AVA with raxibacumab treatment groups.
Secondary	
• To compare the immunogenicity of AVA at Weeks 8 and 26 after the first AVA dose, when AVA is administered alone	• Ratio of GMC of anti-PA Ab at Weeks 8 and 26 after the first AVA dose, between the AVA alone and the AVA with

Objectives	Endpoints
or concomitantly with raxibacumab.	raxibacumab treatment groups.
• To estimate and compare seroconversion, defined as a ≥ 4-fold increase in toxin neutralizing activity (TNA) titer from baseline, at Weeks 4, 8 and 26 after the first AVA dose, when AVA is administered alone or concomitantly with raxibacumab.	• Percentage of subjects who seroconvert, at Weeks 4, 8 and 26 after the first AVA dose, between the AVA alone and the AVA with raxibacumab treatment groups.
• To describe the safety of AVA when co-administered with raxibacumab versus AVA alone.	• Rate of reported adverse events (AE) as well as review of vital signs, urinalysis and clinical laboratory data in the AVA alone and the AVA with raxibacumab treatment groups.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, open-label, parallel-group, two-arm study in healthy adult subjects who have not previously been immunized against PA. The schematic diagram below illustrates the study design:



4.2. Treatment Arms and Duration

Subjects will be randomized into one of the following two treatment groups:

- **Treatment Group 1**- subjects will be administered subcutaneous (SC) 0.5 mL AVA doses on Days 1, 15, and 29 (0, 2, and 4 weeks).

- **Treatment Group 2**- subjects will be administered SC 0.5 mL AVA doses on Days 1, 15, and 29 (0, 2, and 4 weeks), with the first AVA dose administered immediately after completion of a single IV infusion 40 mg/kg raxibacumab dose. Subjects will be premedicated with 25-50 mg of diphenhydramine up to 1 hour prior to the raxibacumab infusion to reduce the risk of infusion reactions.

Subjects will begin the study with a screening visit up to 35 days before the start of study treatment on Day 1. Results of the screening test for the anti-PA Ab levels must be available prior to randomization on Day -1. Study visits will occur at Days -1, 1, 15, 29, 57, and 183 (Week 26). The total study duration for each subject may be approximately 28 to 31 weeks.

4.3. Type and Number of Subjects

A total of at least 534 subjects (267 analyzable subjects per treatment group) may be enrolled in the study. Enrollment will occur in 3 cohorts separated by interim analyses. The trial will continue to subsequent cohorts only if the prospective criteria for discontinuing the trial are not met at the interim analysis:

- at least thirty subjects will be enrolled in Cohort 1,

- at least an additional 70 subjects will be enrolled in Cohort 2 if the study progresses beyond interim 1.

- and at least an additional 434 subjects will be enrolled in Cohort 3 if the study progresses beyond interim 2.

If a subject prematurely discontinues the study prior to the Day 29 primary endpoint measurement, additional subjects will be randomized to reach the required number of analyzable subjects for a given analysis (please refer to Section 9.3.1 for definition of an analyzable subject). The goal will be to only enroll the minimum number of subjects to reach the target number of analyzable subjects. Although the number of randomized subjects who will not be analyzable is unknown, based on expectations of study withdrawal and data from previous trials with AVA, it is estimated that no more than 620 subjects will be randomized to reach the target of 534 analyzable. The decision to randomize additional subjects will be made without knowledge of the ongoing comparative results; if ongoing comparative results are known to the Sponsor, no additional subjects may be enrolled.

4.4. Design Justification

This is a Phase 4 study to evaluate the immunogenicity of SC-administered AVA when administered alone or concomitantly with a single IV raxibacumab dose, in healthy adult volunteers who have not previously been immunized against the PA of *B. anthracis*. Subjects will receive the first AVA dose immediately after completion of a single 40 mg/kg raxibacumab IV infusion. Although this is an open-label study, measures have been introduced to minimize bias (refer to Section 6.3).

As a passive anti-toxin antibody, raxibacumab is expected to provide protection against PA for up to 28 days post dose [Migone, 2009]. The expected, but currently unapproved, use of AVA in combination with raxibacumab would be in the post-exposure prophylaxis setting. In that setting, raxibacumab would provide the initial toxin neutralizing activity while AVA immunization would generate a durable, toxin neutralizing anti-PA Ab response that maintains protection beyond 28 days, since raxibacumab levels may not be adequate for protection for more than 28 days post-infusion. Relative to this, 93% of subjects administered SC AVA doses at Weeks 0, 2, and 4 had at least a 4-fold increase in TNA titer by Week 4, with higher titers than for intramuscular (IM) doses administered according to the same schedule [Marano, 2008]. Based on these findings, this study will utilize SC-administered AVA rather than IM-administered AVA because the immunogenicity of SC-administered AVA early in the immunization series (at week 4) is of primary interest. Because of a lack of assay specificity for TNA response due to AVA when raxibacumab is present, it is not possible to specifically evaluate a 4 fold increase in the TNA titer due to AVA in this study. However, GSK developed analytical techniques which allow specific determination of anti-PA Ab concentrations in response to AVA vaccination, even in the presence of raxibacumab. Therefore, anti-PA Ab concentration will be assessed as the primary endpoint in this study, instead of >4-fold increase in TNA titers. Relative to this, a high correlation between anti-PA Ab levels and TNA has been reported [Crowe, 2010; Pittman, 2002; Pittman, 2005; Pittman, 2006; Quinn, 2004]. Thus, it is reasonable to expect that measurement of anti-PA Ab is reflective of a functional immune response.

Since an immune response to AVA requires some time to develop, it is anticipated that in the post-exposure prophylaxis setting the initial AVA dose would be in close temporal proximity to the raxibacumab dose. For this study, the first AVA dose will be administered immediately after completion of the raxibacumab IV infusion, so that raxibacumab levels are as high as possible when AVA administration starts. This should maximize the potential for raxibacumab to interfere with AVA immunogenicity. A finding of no effect of raxibacumab on AVA immunogenicity in this study can be extrapolated to other timings between raxibacumab and AVA administration since it represents the worst case scenario for a potential interaction between raxibacumab and AVA.

Based on published results, polyclonal anti-PA antitoxin administered to rabbits in combination with AVA resulted in essentially complete abrogation of the immune response to AVA [Malkevich, 2013]. Thus, it is possible that co-administration of raxibacumab with AVA will essentially eliminate any immunogenic response to AVA. Given that expectation, this study will enroll subjects in 3 cohorts, with two interim

analyses to allow early termination of the study if a large effect of raxibacumab on AVA immunogenicity is confirmed at the interim.

Additional description of the interim analyses, including justification for the timing and how they impact the operating characteristics of the study, can be found in Section 9.3.2.

The study duration of 26 weeks was chosen to allow evaluation of the secondary endpoint of AVA immunogenicity, including TNA titer, after raxibacumab is essentially completely eliminated as an assessment of the durable immune response to AVA. Week 26 is of interest since it represents the nadir response at the time when an AVA dose would be administered to boost response. In addition, that study duration allows collection of safety and tolerability data throughout the period of raxibacumab exposure. This is based on data from healthy volunteer studies indicating that >99% of subjects can be expected to attain raxibacumab wash-out (i.e., less than 5% of the administered dose remaining in the body) by week 24.

4.5. Dose Justification

Raxibacumab will be administered in accordance with approved product label dosing recommendations [Raxibacumab Package Insert, 2012]. Per the package insert, subjects will be premedicated with diphenhydramine (25-50 mg) up to 1 hour prior to the raxibacumab infusion to reduce the risk of infusion reactions.

AVA will be administered in accordance with the approved product label dosing recommendations [Anthrax Vaccine Adsorbed Package Insert, 2012]. This study will utilize the SC-administered AVA dosing schedule rather than the IM-administered AVA dosing schedule because the immunogenicity of AVA early in the immunization series (at Week 4) is of primary interest. Findings from Marano et al., 2008 indicate that the SC regimen affords superior geometric mean serum anti-PA Ab concentrations and >4-fold responder percentages at 4 weeks post-vaccination, relative to IM administration given on the same schedule. Hence, the SC regimen could be preferable in a post-exposure prophylaxis setting [Centers for Disease Control and Prevention, 2010].

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with raxibacumab (GSK3068483) can be found in the IB. Summaries of findings from both clinical and non-clinical studies conducted with AVA can be found in the prescribing information [Anthrax Vaccine Adsorbed Package Insert, 2012]. The following section outlines the risk assessment and mitigation strategy for this protocol

Clinical parameters will be monitored throughout the study in order to assess the safety and tolerability of AVA when administered alone or concomitantly with raxibacumab. The study design in place will allow in-stream blinded review of the aggregated safety and tolerability data during the study. Refer to protocol Section 7.1 for the timing of all clinical assessments.

Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Drug		
Infusion Site Reactions (ISRs)	Infusion-related reactions were reported during administration of raxibacumab in clinical trials in healthy volunteers including reports of rash, urticaria, and pruritus.	Subjects will be premedicated with 25-50 mg of diphenhydramine up to 1 hour prior to the raxibacumab infusion, as recommended in the product label. Close monitoring of clinical parameters and adverse events will be conducted to assess effects of infusion site reactions.
Other		
Injection-site reactions	The most common (≥10%) local (injection-site) adverse reactions observed in clinical studies with AVA were tenderness, pain, erythema, edema, and arm motion limitation.	Close monitoring of clinical parameters and adverse events will be conducted to assess effects of injection-site reactions.

4.6.1. Benefit Assessment

An individual may benefit from participation in this study due to the following:

- Physical exam and hematology and clinical chemistry assessments conducted as part of the study procedures.

- Participation in this study could contribute valuable information on the immunogenicity of AVA administered alone or concomitantly with raxibacumab.

Since no subject will receive the full AVA immunization series as part of this study, no subject should be considered to have a durable anti-PA Ab response at completion of the study. Hence, the subject should be considered to be at risk if exposed to anthrax.

4.6.2. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with this study are justified by the anticipated benefits that may be afforded to subjects.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GlaxoSmithKline (GSK) investigational product or other study treatment that may impact subject eligibility is provided in the raxibacumab, diphenhydramine, and AVA package inserts.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Healthy as determined by the Investigator or medically qualified designee based on a medical evaluation including medical history, physical examination and laboratory tests

2. Men and women between 18 to 65 years of age

3. Willing and able to adhere to the procedures stated in the protocol.

4. Female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum or urine human chorionic gonadotrophin (hCG) test), not lactating, and at least one of the following conditions applies:

A. Non-reproductive potential defined as:

- Pre-menopausal females with one of the following:
  - Documented tubal ligation
  - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
  - Hysterectomy
  - Documented Bilateral Oophorectomy
- Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment.

B. Reproductive potential and agrees to follow one of the options listed in Appendix 3 requirements, the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP), from 30 days prior to the first dose of study medication and until after the last dose of study medication and completion of the follow-up visit at Day 183 (at least five terminal half-lives for raxibacumab).

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or non-investigational study vaccine/product (pharmaceutical product or device).

2. Be a member of the military, a laboratory worker, first responder, health care worker, or otherwise be at higher risk of exposure to anthrax

3. History of regular alcohol consumption within 1 month of the study defined as:

   - An average weekly intake of >14 drinks for males or >7 drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 ml) of beer, 5 ounces (150 ml) of wine or 1.5 ounces (45 ml) of 80 proof distilled spirits.

4. Female planning to become pregnant or planning to discontinue contraceptive precautions before the Day 183 study visit.

5. Pregnant (confirmed by a serum or urine hCG test) or lactating female.

6. ALT and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).

7. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

8. Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease (e.g., malignancy, human immunodeficiency virus [HIV] infection) or immunosuppressive/cytotoxic therapy (e.g., medications used during cancer chemotherapy, organ transplantation or to treat autoimmune disorders).

9. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test results at screening or within 3 months prior to first dose of study treatment.

10. A positive pre-study drug/alcohol screen.

11. A positive test for HIV antibody.

12. History of sensitivity to any of the study medications, or components thereof (especially latex and aluminium) or a history of other known drug allergies that, in the opinion of the Investigator or GSK Medical Monitor, contraindicates their participation. Refer to raxibacumab, diphenhydramine and AVA package inserts for product specific information [Anthrax Vaccine Adsorbed Package Insert, 2012; Raxibacumab Package Insert, 2012; Diphenhydramine Package Insert].

13. Have previously been vaccinated against PA.

14. Have an anti-PA Ab concentration >2 times the lower limit of quantitation at screening.

15. Administration of immunoglobulins not included in this trial and/or any blood products within the 3 months preceding the first dose of study vaccine or planned administration during the study period.

16. Administration of long-acting immune-modifying drugs (e.g. infliximab) within six months prior to the first vaccine dose or expected administration at any time during the study period.

17. Chronic administration (defined as more than 14 consecutive days) of systemic immunosupressants or other immune-modifying drugs within six months prior to the first vaccine dose. Inhaled, topical and intra-articular corticosteroids are allowed.

18. Administration or planned administration of a vaccine not foreseen by the study protocol within the period starting 35 days before the first dose of study vaccine(s) and ending 30 days after the last dose of study vaccine. This includes

any type of vaccine such as (but not limited to) live, inactivated, and subunit vaccines. Influenza vaccines are permitted after Week 8.

19. Subjects must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication will not interfere with the study. Refer to Section 6.10.1 for permitted medications.

20. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

21. Any condition which, in the opinion of the investigator, prevents the subject from participating in the study.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events (SAE).

Subjects who initially do not meet eligibility criteria may be re-screened one time if their potential eligibility status has changed. Eligible subjects may then be enrolled in this study.

5.4. Withdrawal/Stopping Criteria

Criteria for study treatment withdrawal may include:

- Sponsor terminates the study
- Subject lost to follow-up
- Subject withdraws consent
- Protocol deviation
- Investigator discretion
- Subject experiences an adverse event(s) that is considered to be related to study drug or study procedures and is severe enough in nature to warrant treatment discontinuation.
- Pregnancy (confirmed by a serum or urine hCG test)

Subjects withdrawn from study treatment will be permitted to continue on the study. Subjects withdrawn from the study due to safety reasons or pregnancy will continue to be followed for safety data until resolution of the safety event and for pregnancy outcomes (please refer to Appendix 5 and Section 7.4.1 for additional information).

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

The reason(s) for a subject not completing the study will be recorded in the Case Report Form (CRF), and the investigator must document, if applicable, the reason (if specified by the subject) for withdrawal of consent.

5.4.1. Liver Chemistry Stopping Criteria

As experience in humans is limited, it is standard GSK practice to collect information on liver events if they occur.

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

If liver chemistry abnormalities are seen (e.g., ALT ≥ 3xULN and bilirubin ≥ 2xULN; ALT ≥ 5xULN; ALT ≥ 3xULN if associated with symptoms believed to be related to hepatitis or hypersensitivity), it is recommended that the physician obtains follow-up liver chemistries until resolved, stabilized or returned to baseline.

It is recommended that additional follow-up assessments (e.g., viral hepatitis serology, serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH), liver imaging) are performed as clinically indicated to further evaluate other potential causes of the abnormalities and to assess the severity of the injury.

Refer to Appendix 2 for liver safety required actions and follow-up assessments.

5.4.1.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

5.5. Subject and Study Completion

A completed subject is one who has completed all study visits including the follow-up visit.

The end of the study is defined as the last subject's last visit.

5.6. Definition of an Analyzable Subject

A subject will be considered to be analyzable if they meet all of the following criteria:

1. Receive at least the Day 1 and Day 15 AVA doses,
2. Receive the raxibacumab dose, if randomized to that treatment, and
3. Complete the primary study endpoint assessment (anti-PA Ab concentration at Week 4).

Any subject who meets these criteria will be included in data analysis for the primary endpoint.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

	Study Treatment[a]		
Product name:	**GSK3068483 raxibacumab**	**BioThrax**	**Diphenydramine**
Formulation description:	Raxibacumab drug product comprises 50 mg/mL protein in 0.13 mg/mL citric acid, 2.8 mg/mL sodium citrate, 10 mg/mL sucrose, 18 mg/mL glycine, and 0.2 mg/mL polysorbate 80, pH 6.5 34 mL and 1700 mg deliverable per vial	BioThrax is made from cell-free filtrates of microaerophilic cultures of an avirulent, nonencapsulated strain of *B. anthracis*. The production cultures are grown in a chemically defined protein-free medium consisting of a mixture of amino acids, vitamins, inorganic salts, and sugars. The final product, prepared from the sterile filtrate culture fluid contains proteins, including the 83kDa protective antigen (PA) protein, released during the growth period and contains no dead or live bacteria. The final product is formulated to contain 1.2 mg/mL aluminum, added as aluminum hydroxide in 0.85% sodium chloride. The final product is formulated to contain 25 mcg/mL benzethonium chloride and 100 mcg/mL formaldehyde, added as preservatives.	Diphenhydramine route of administration (oral or IV) should be based on the temporal proximity to the start of raxibacumab infusion. For formulation information, refer to the labelling of the specific product chosen for administration
Dosage form:	sterile, liquid formulation in single-use vials	Sterile, milky-white suspension, in multi-use vials.	Refer to the labelling of the specific product chosen for administration
Unit dose strength(s)/ Dosage level(s):	40 mg/ kg	0.5 mL dose	Diphenhydramine should be administered at 25 – 50 mg. Refer to the labelling of the specific product chosen for administration for unit dose strength.
Route of Administration	IV	SC	Route of administration (oral or IV) should be based on the temporal proximity to the start of raxibacumab infusion.

	Study Treatment[a]		
Product name:	**GSK3068483 raxibacumab**	**BioThrax**	**Diphenydramine**
Dosing instructions:	For the combination treatment group, the raxibacumab dose will be administered just prior to the first AVA dose.The calculated raxibacumab dose to be administered to the subject will be diluted in normal saline with a final volume of 250 mL. The rate of raxibacumab infusion should be set for 15 mL/hour for the first 20 minutes and then adjusted to 125 mL/hour for the remainder of the infusion period. With this schedule, approximately 250 mL should be infused over the course of 2 hours and 15 minutes.	For the combination treatment group, the first Biothrax dose will be administered immediately after completion of the raxibacumab IV infusion, in the opposite arm. Refer to Section 2 of the Biothrax product label for dosing instructions. Key points to consider are: • Shake the vial thoroughly; • inspect visually for particulate matter and discoloration prior to administration. Do not administer if present; • administer by SC route using a ⅝-inch, 25- to 27-gauge sterile needle and syringe; • use a different injection site (e.g. alternating arms) for each sequential injection;	For the combination treatment group, premedicate with diphenhydramine within 1 hour prior to raxibacumab infusion. Refer to the labelling of the specific product chosen for administration for dosing instructions
Physical description:	The drug product is filled into 50 mL USP Type I borosilicate glass vials, sealed with a 20 mm chlorobutyl rubber stopper and 20 mm flip-off aluminum seal, and stored at 2-8ºC protected from light	BioThrax is supplied in 5 mL multidose vials containing ten 0.5 mL doses, and stored at 2-8ºC (36° F to 46° F). Do not freeze.	Refer to the labelling of the specific product chosen for administration
Method for individualizing dosage:	Weight-based dosing.	None	None
a. Listed study products are commercially sourced			

6.2. Treatment Assignment

Subjects will be assigned to Treatment Group 1 or Treatment Group 2 in accordance with a balanced independent randomization schedule generated prior to the start of the study. A corresponding set of randomization envelopes (one per subject) will be generated. A

randomization envelope for each subject will be opened prior to dosing (on day -1) to reveal the subject's treatment assignment. This process will ensure that study personnel and the volunteers will have no knowledge of the next treatment to be assigned.

Once a randomization number has been assigned to a subject, it will not be re-assigned to another subject. Randomization numbers will be assigned sequentially as subjects become eligible for dosing.

6.3. Blinding

This will be an open-label study. However, measures will be taken to reduce introduction of bias and the following will apply.

- Investigators, site staff and the subject have direct access to each subject's individual study treatment only with the opening of the randomization envelope.
- The following measures will be incorporated to blind specific aspects of the study in order to minimize bias and maintain study integrity:
    - Within the clinic, only the pharmacy will have access to the full randomization schedule.
    - The Sponsor team will be blinded except for the laboratory personnel, who must meet the following criteria:
        1. All analysts will be trained to Good Laboratory Practice (GLP) and follow Standard Operating Procedure (SOP) on the analysis of samples, inclusive of having Quality Control (QC) checks of all their work throughout the entire analysis.
        2. The final data will be peer-reviewed, minimizing the opportunity for any bias to affect the results. All samples will be analyzed and reported in a validated computer system with documented audit trails.
    - An external statistician and clinician (ie. not involved in conduct of the trial) will be responsible for performing the interim analyses, and will be instructed to only communicate to the team whether or not the futility boundary has been crossed, and will not share any subject-specific or summary-level information with the Sponsor team.
    - Monitoring will be completed by unblinded GSK monitors who will not share blinded information with the Sponsor team. An unblinded Clinical Research Associate independent from the study team will review monitoring reports and specific protocol deviations outlined in the Protocol Deviation Management Plan.
    - Throughout the course of study, the raxibacumab Safety Review Team (SRT) will evaluate accumulating aggregate blinded clinical trial safety data to monitor for potential treatment related effects (such as the identification of new safety issues, as well as the identification of clinically relevant changes in known safety issues).
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff or delegates may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.5. Preparation/Handling/Storage/Accountability

Diphenhydramine, raxibacumab and AVA will be prepared, stored and administered according to current product label requirements [Anthrax Vaccine Adsorbed Package Insert, 2012; Raxibacumab Package Insert, 2012; Diphenhydramine Package Insert]. A description of the methods and materials required for preparation of raxibacumab and AVA will be detailed in a Study Specific Technical Agreement/Memo (TTS) or Pharmacy Manual which will be accompanied by a Quality Agreement.

When the individual dose of study treatments are prepared for a subject, the preparation of the dose will be confirmed by a second member of the study site staff.

Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).

Further guidance and information for final disposition of unused study treatment are provided in the Study Reference Manual (SRM).

Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.6. Compliance with Study Treatment Administration

Subjects will receive raxibacumab intravenously in accordance with the approved dosing recommendations for adults [Raxibacumab Package Insert, 2012] and/or AVA subcutaneously in accordance with the approved dosing recommendations for adults [Anthrax Vaccine Adsorbed Package Insert, 2012]. Raxibacumab and AVA will be administered in opposite limbs. Each sequential AVA injection will be administered in a different injection site (e.g. alternating arms). Diphenhydramine, 25 to 50 mg, should be administered within 1 hour prior to raxibacumab infusion to reduce the risk of infusion reactions. Diphenhydramine route of administration (oral or IV) should be based on the

temporal proximity to the start of raxibacumab infusion. Administration will be recorded in the source documents and reported in the CRF.

Subjects will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

Mild infusion site reactions have been observed in subjects dosed with raxibacumab, which have been successfully prevented using an anti-histamine prior to dosing. Hypersensitivity reactions have been reported with AVA. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgement. Subjects should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention.

The schedule for the administration of study treatment is outlined in the Time and Events Tables (Section 7.1). The site staff should monitor any subject who may experience a hypersensitivity reaction following the administration of study treatment. Refer to Section 7.4.1 and Appendix 4 for information on the procedures for recording and evaluating AEs/SAEs. The decision regarding the administration of the vaccine following a hypersensitivity reaction will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.7. Treatment of Study Treatment Overdose

For this study, any dose of study treatment greater than that described in the product label will be considered an overdose [Anthrax Vaccine Adsorbed Package Insert, 2012; Raxibacumab Package Insert, 2012; Diphenhydramine Package Insert].

GSK does not recommend specific treatment for a raxibacumab overdose

In the event of an overdose, the investigator should:

1. contact the Medical Monitor immediately
2. closely monitor the subject for AEs/serious adverse events (SAEs) and laboratory abnormalities until drug can no longer be detected
3. document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Since only AVA is dosed on more than one occasion, the decision regarding the administration of the second dose of vaccine will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.8. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because only healthy volunteers are eligible for study participation.

6.9. Lifestyle and/or Dietary Restrictions

Subjects who have a history of regular alcohol consumption as defined in Section 5.2 will be excluded from the study.

During each dosing session, subjects will abstain from alcohol for 24 hours prior to the study visit.

6.10. Concomitant Medications and Non-Drug Therapies

6.10.1. Permitted Medications and Non-Drug Therapies

Concomitant medication may be considered on a case by case basis by the investigator in consultation with the Medical Monitor if required. Any concurrent medication administered to the subject during the study should be recorded in CRF. Tylenol, effective methods of contraception (detailed in Appendix 3), and the influenza vaccine will be permitted.

6.10.2. Prohibited Medications and Non-Drug Therapies

Subjects must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication will not interfere with the study.

Medication prohibited during the course of this study include:

- immunoglobulins not included in this trial
- any blood products
- long-acting immune-modifying drugs (e.g. infliximab)
- chronic administration (defined as more than 14 consecutive days) of immunosupressants or other immune-modifying drugs (such as corticosteroids). Inhaled, topical and intra-articular corticosteroids are allowed.
- administration of a vaccine not foreseen by the study protocol. This includes any type of vaccine such as (but not limited to) live, inactivated, and subunit vaccines. Influenza vaccine is permitted after Week 8.
- Administration of an investigational or non-investigational study vaccine/product (pharmaceutical product or device).

7. STUDY ASSESSMENTS AND PROCEDURES

Informed consent must be obtained prior to enrollment in the study and conduct of any study procedures.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those

specified in the Time and Events Tables (Section 7.1), are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table (Section 7.1). All data collected for this study will be recorded in the subjects' CRF.

The timing and number of planned study assessments, including safety assessments may be altered during the course of the study based on newly available data to ensure appropriate monitoring.

The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.

The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form (ICF).

No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required. The Time and Events Tables (Section 7.1) detail the timings for study assessment.

7.1. Time and Events Table

Table 1 Screening assessments for subjects administered AVA or co-administered raxibacumab and AVA

Screening Assessments	Days -36 to -15[a]	Notes
Informed consent process	X	
Demographic information	X	
Inclusion/Exclusion criteria	X	
Medical history (includes substance usage and Family history of premature CV disease)	X	
Physical exam including height and weight	X	
Alcohol and Drug Screening	X	
Urinalysis	X	
Vital signs	X	
Hematology and clinical chemistry	X	Refer to Table 4 for specific laboratory tests.
HIV, Hep B and Hep C screen	X	
Review concomitant medications	X	
Serum or urine pregnancy test	X	
AE/SAE assessment	X	Will capture SAEs reported between Screening visit and Day -1.
Toxin Neutralizing Ab (TNA)	X	
Anti-PA Ab	X	

a. The screening window closes at Day -15 to allow all analyses to be completed to confirm subject eligibility.

Table 2 Treatment Group 1: Time and Events for subjects administered AVA

Protocol Activity	Study Visit						Notes
Assessments	**Day -1[a]**	**Day 1**	**Day 15 (± 2 days)**	**Day 29 (± 2 days)**	**Day 57 (± 2 days)**	**Day 183 (± 4 days)**	
Inpatient visit	←X→						
Outpatient visit			←------X------→				
Urinalysis					X		
Admit to unit	X						
Randomization	X						
Discharge from unit		X					The subject will be discharged from the unit after all assessments are completed.
Vital signs	X	X		X	X	X	
Hematology and clinical chemistry	X			X	X		Refer to Table 4 for specific laboratory tests. On Day 29 the specimen will be collected prior to AVA injection.
Review concomitant medications	X		X	X	X	X	
Serum or urine pregnancy test	X		X	X	X	X	
AVA administration		X	X	X			Each sequential AVA injection will be administered in a different injection site (e.g. alternating arms).
AE/SAE assessment	X	X	X	X	X	X	
Toxin Neutralizing Ab (TNA)		X		X	X	X	On Days 1 and 29 the specimen will be collected prior to AVA injection.
Anti-PA Ab		X		X	X	X	On Days 1 and 29 the specimen will be collected prior to AVA injection.

a. Day -1 is the calendar day preceding Day 1; the designation “Day 0” is not used in this study.

Table 3 Treatment Group 2: Time and Events Table for subjects co-administered raxibacumab and AVA

Protocol Activity / Assessments	Study Visit									Notes
		Day 1								
	Day -1[a]	pre-raxi infusion	0 hr	0.5 hr (± 5 min)	2-6 hrs	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 57 (± 2 days)	Day183 (± 4 days)	
Inpatient visit	←----------X----------→									
Outpatient visit						←----------X----------→				
Urinalysis								X		
Admit to unit	X									
Randomization	X									
Discharged from unit					X					The subject will be discharged from the unit after all assessments are completed.
Vital signs	X				X		X	X	X	
Hematology and clinical chemistry	X						X	X		Refer to Table 4 for specific laboratory test. On Day 29 the specimen will be collected prior to treatment administration.
Review concomitant medications	X					X	X	X	X	
Serum or urine pregnancy test	X					X	X	X	X	
Diphenhydramine administration		X								Diphenhydramine (25-50 mg) must be administered within 60 minutes prior to the raxibacumab infusion.
Raxibacumab administration			X							Raxibacumab infusion must be completely administered prior to first AVA dose on Day 1 and administered in opposite limb from AVA injection.
AVA administration			X			X	X			Each sequential AVA injection will be administered in a different injection site (eg. alternating arms).
AE/SAE assessment	X	X		X	X	X	X	X	X	
PK sampling		X		X	X	X	X	X	X	A blood specimen will be collected prior to raxibacumab infusion, 30 minutes post raxibacumab infusion (± 5 min), 2-6 hours post infusion on Day 1, and at Days 15, 29, and 57 (14, 28, and 56 days post raxibacumab administration). An additional sample will be collected at the Day 183 visit.
Anti-raxibacumab Ab		X						X	X	
Toxin Neutralizing Ab (TNA)		X					X	X	X	The Day 29 specimens will be collected prior to AVA administration.
Anti-PA Ab		X					X	X	X	The Day 29 specimens will be collected prior to AVA administration.

a. Day -1 is the calendar day preceding Day 1; the designation “Day 0” is not used in this study.

7.2. Screening and Critical Baseline Assessments

After written informed consent is provided, the following data will be collected at the screening visit for all subjects:

- Demographic parameters: year of birth, gender, race, and ethnicity.
- Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.
- Physical assessment data including vital signs (temperature, heart rate, systolic and diastolic blood pressure, respiratory rate), height and weight.
- Laboratory assessments (hematology, clinical chemistry)
- Urinalysis
- Alcohol, Drug, HIV, Hepatitis B and Hepatitis C screenings
- A serum or urine pregnancy test on women of childbearing potential
- Blood specimen for anti-PA Ab levels and TNA titers.
- Record of concomitant medications
- Monitoring and reporting of SAEs

The following will be collected as baseline data on Day -1:

- A serum or urine pregnancy test on women of childbearing potential
- Record of concomitant medications
- Vital signs
- Results from clinical chemistry and hematology laboratory evaluations (refer to Table 4 for specific assessments)
- Monitoring and reporting of AEs including SAEs

The following will be collected as baseline data on Day 1 prior to study treatment administration:

- Blood specimen for anti-PA Ab levels and TNA titers

Additionally, for subjects randomized to Treatment Group 2, the following will be collected as baseline data on Day 1 prior to study treatment administration:

- Blood specimen for anti-raxibacumab Ab level

- Blood specimen for serum raxibacumab concentrations

7.3. PA, TNA and Anti-raxibacumab Antibodies

Serum anti-PA Ab concentrations and raxibacumab will be determined by GSK PTS-DMPK. Serum AVA derived anti-PA Ab concentrations will be determined using an approved immunoassay. Additionally, serum raxibacumab concentrations will be determined using an approved method based on immunocapture and trypsin digest, followed by UHPLC/MS/MS analysis. All data will be held under the control of US (UM) GSK R&D GLP archive.

Serum TNA titers will be determined using a cell-based assay, under the auspices of Clinical Immunology, GSK.

Serum anti-raxibacumab Ab analysis will be performed under the control of Clinical Immunology, GSK. The presence of anti-raxibacumab Ab will be determined using validated ECL bridging assay.

Details of the anti-PA Ab concentration, TNA titer, and anti-raxibacumab Ab analyses and the archiving of raw data will be included in the SRM.

7.4. Safety

Clinical safety observations will include AEs, urinalysis, vital sign measurements, and clinical laboratory assessments. Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

Safety evaluations of data from clinical laboratory tests and spontaneous adverse event reporting will be performed for all subjects who receive study treatment. Details on specific safety assessments are provided below.

7.4.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 4.

AEs will be assessed for severity based on the modified Division of Microbiology and Infectious Diseases (DMID) toxicity tables in Appendix 6. For AEs not included in these toxicity tables, the following guidelines apply:

Mild	An event causing no limitation of usual activities
Moderate	An event causing some limitation of usual activities
Severe	An event causing inability to carry out usual activities
Life threatening*	An event that is potentially life threatening or disabling

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.4.1.1. Time Period and Frequency for Collecting AE and SAE Information

AEs and SAEs will be collected from the start of study treatment until the follow-up contact (see Section 7.4.1.3), at the timepoints specified in the Time and Events Table (Section 7.1).

Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.

Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 4.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 4.

7.4.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Appendix 4) will be followed until resolution, until the condition stabilizes,

until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 4.

7.4.1.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK or designee of SAEs and non-serious AEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.4.2. Pregnancy

Details of all pregnancies in female subjects will be collected after the start of dosing and until Day 183.

If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

7.4.3. Physical Exams

A complete physical examination will include, at a minimum, assessment of the cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.4.4. Vital Signs

Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate and respiratory rate.

For the Screening visit, three readings of blood pressure and pulse rate will be taken

- First reading should be rejected

- Second and third readings should be averaged to give the measurement to be recorded in the CRF.

At all other study visits where vital signs will be assessed (refer to Section 7.1), single measurements are permitted. If an abnormal reading occurs then repeat measurements should be taken as described above.

7.4.5. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 4, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM or the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

Hematology, clinical chemistry and additional parameters to be tested are listed in Table 4.

Table 4 Protocol Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th>Parameters</th></tr>
<tr><td>Hematology</td><td>
<table>
<tr><td>Platelet Count</td><td><u>RBC Indices</u>:</td><td><u>Automated WBC Differential</u>:</td></tr>
<tr><td>RBC Count</td><td>MCV</td><td>Neutrophils</td></tr>
<tr><td>WBC Count (absolute)</td><td>MCH</td><td>Lymphocytes</td></tr>
<tr><td>Reticulocyte Count</td><td>MCHC</td><td>Monocytes</td></tr>
<tr><td>Hemoglobin</td><td></td><td>Eosinophils</td></tr>
<tr><td>Hematocrit</td><td></td><td>Basophils</td></tr>
</table>
</td></tr>
<tr><td>Clinical Chemistry [1]</td><td>
<table>
<tr><td>BUN</td><td>Potassium</td><td>AST (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Chloride</td><td>ALT (SGPT)</td><td>Uric Acid</td></tr>
<tr><td>Glucose</td><td>Total CO_2</td><td>GGT</td><td>Albumin</td></tr>
<tr><td>Magnesium</td><td>Sodium</td><td>Calcium</td><td>Alkaline phosphatase</td></tr>
<tr><td>Total Protein</td><td colspan="3">Calculated Creatinine clearance – Cockcroft-Gault Calculation</td></tr>
</table>
</td></tr>
<tr><td>Other Screening Tests</td><td>
• Urinalysis (routine dipstick)
• HIV
• Hepatitis B (HBsAg)
• Hepatitis C (Hep C antibody)
• FSH and estradiol (as needed in women of non-child bearing potential only)
• Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)
• Urine or serum hCG Pregnancy test (as needed for women of child bearing potential)
</td></tr>
</table>

NOTES :
Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.4.1 and Appendix 2.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE) the results must be recorded in the CRF.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.5. Pharmacokinetics

Blood samples for pharmacokinetic (PK) analysis of raxibacumab will be collected from all the subjects in the AVA/raxibacumab treatment group at the time points indicated in Section 7.1, Time and Events Table. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Detailed processing, storage and shipping procedures are provided in the SRM.

7.5.1. Pharmacokinetic Analyses

Serum raxibacumab concentrations will be determined using a LC-MS/MS assay by DMPK, GSK. All pharmacokinetic data will be stored in the Archives, GSK R&D.

7.5.1.1. Pharmacokinetic Parameters

PK analysis will be the responsibility of the CPMS Department, Quantitative Sciences, GSK. PK analysis of serum raxibacumab concentration-time data will be conducted using non-compartmental methods.

The following PK parameters will be determined if data permit:

- maximum observed serum raxibacumab concentration (C_{max})
- time of occurrence for C_{max} (t_{max})
- area under the serum raxibacumab concentration-time curve to the time of the last measurable concentration (AUC_{0-t})
- area under the serum raxibacumab concentration-time curve to infinite time ($AUC_{0-\infty}$)

- percentage of $AUC_{0-\infty}$ that is extrapolated
- terminal elimination rate constant (λ_z)
- half-life of drug elimination in the terminal phase ($t_{1/2,z}$)
- mean residence time (MRT)
- clearance (CL)
- volume of distribution in the terminal phase (V_z)
- volume of distribution at steady-state (V_{ss})

8. DATA MANAGEMENT

For this study subject data will be entered into GSK defined eCRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.

Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.

CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

Given concentrations are often approximately log normally distributed, they are customarily analyzed on a logarithmic (log) scale; a difference in arithmetic means on a log scale becomes a ratio of geometric means when the results of analysis are converted back to the original data scale. Thus, each hypothesis is a statement regarding a ratio of geometric mean concentrations of the anti-PA Ab attributable to AVA.

The null and alternative hypotheses are as follows:

H_0: $\theta = \mu AVA / \mu AVA+Raxibacumab \geq 1.5$

H_A: $\theta = \mu AVA / \mu AVA+Raxibacumab < 1.5$

Where θ is the ratio of the geometric mean concentrations (GMCs); μAVA and μAVA+Raxibacumab are the population GMCs of the anti-PA Ab attributable to AVA for the two arms.

The null hypothesis is that the ratio of the GMC of anti-PA Ab attributable to AVA in the AVA arm to the GMC of anti-PA Ab in the AVA+ raxibacumab arm is greater than or equal to 1.5. The alternative hypothesis is that the ratio is less than 1.5.

As described above, the non-inferiority margin for the ratio of the geometric means was selected to be 1.5. This is the same margin selected in Marano et al. (2008) based on guidances from the FDA and ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) and literature precedent.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The sample size calculation is based on the assumption that the individual values will be analyzed after being transformed by $\log_{10}$ resulting in data that is approximately normal. In the transformed data the analysis of the ratio of the means is equivalent to a difference of mean values with a margin of $\log_{10}(1.5) = 0.176$.

The standard deviation of the $\log_{10}$ transformed data is assumed to be 0.75. This is selected based on the fact that the sample size in Marano et al. (2008) was based on a standard deviation of 0.45 based on the data from [Pittman, 2002], but the results from the Marano et al. (2008) study had higher standard deviations suggesting an estimate closer to 0.85.

The sample size is calculated assuming 1:1 randomization and two interim analyses for futility after 30 and 100 analyzable subjects. The boundaries for the futility analysis are based on Rho family error spending function with a rho of 0.5. For the purposes of the sample size calculation, the power will be calculated under the alternative hypothesis setting, where the ratio is 1, or equivalence between the two arms with respect to concentrations of anti-PA antibody. With a type 1 error of 5% one-sided a sample size of 534 subjects will allow for 80% power to make a claim of non-inferiority (margin of 1.5), if the true ratio between the geometric means is 1. In a trial of 534 patients, the largest observed GMC ratio between the AVA and the combination that results in a statistically significant non-inferiority result is an estimated ratio of 1.173. This can alternatively be viewed as a minimum observed anti-PA concentration due to the addition of AVA in the combination of ~85% of the concentration when AVA is administered alone. This is under the assumption that the observed variability in the study population is similar to the study design assumption.

9.2.2. Sample Size Sensitivity

Simulations were performed to estimate the chances of the study crossing the futility boundaries or ending in a result of non-inferiority under various true population ratios of geometric means. The inverse of the ratios, shown in the second column, represent the

percentage of the monotherapy AVA effect that is retained when given in combination with raxibacumab. The percentages shown in the table are based on 10,000 simulated trials for each scenario. Simulations were performed in East 5.4, assuming the log transformed data has a common standard deviation of 0.75 in each arm. The results are displayed in Table 5.

This table indicates that if the addition of raxibacumab has a very strong, almost nullifying, effect on the vaccine at week 4 (GMC ratio of 10 or higher), that the study will almost always end with a futility result after only 30 analyzable subjects. If the effect is a little less strong, but still below the non-inferiority margin, there will be a large probability that the study will end early for futility by the second interim analysis (100 analyzable subjects).

Given the study design, the probability of a non-inferiority result is 80% if the true GMC ratio is 1, i.e., if raxibacumab does not inhibit the immunogenicity of AVA at all. The trial is not designed to have sufficient power to detect non-inferiority in all instances where there is a small effect (that may not be clinically meaningful) on the immunogenicity. The chance of finding a non-inferiority result drops off fairly rapidly as the effect on the immunogenicity increases. Nearly twice as many subjects would be required to have an 80% chance of declaring non-inferiority (with a margin of 1.5) when the GMC of AVA in the combination arm is 90% of the AVA in the AVA alone arm.

Table 5 Simulated Operating Characteristics of the Trial Under Different True GMC Ratios (SD=0.75; 10,000 simulations each)

Ratio of Geometric Means	Percent Effect in combination	Probability of stopping at the First Interim	Probability of stopping at the Second Interim	Probability of stopping at either interim	Probability of Non-inferiority
20	5%	99.9%	0.1%	100%	0%
10	10%	97.5%	2.5%	100%	0%
4	25%	70.1%	29.3%	100%	0%
2	50%	29.2%	39.0%	68.2%	0.01%
1.5	67%	15.8%	22.5%	38.3%	4.5% (5%*)
1.25	80%	9.4%	12.0%	21.4%	29.6%
1.11	90%	6.7%	6.8%	13.5%	59.0%
1	100%	4.9%	3.8%	8.7%	80%*

* These values are not simulated, but are instead the theoretical true values based on the trial design of 5% one-sided type 1 error and 80% power.

A second set of simulations was performed to estimate the sensitivity of the results in Table 5 to the assumption regarding the standard deviation (SD). These simulations

assume that the standard deviation of the data after the log transformation is 0.90, higher than the originally assumed 0.75.

The increased variability leads to a lower probability of finding non-inferiority. The power for the study would be reduced to 65-70% with the higher standard deviation of 0.9. The chances of stopping at the interim would be fairly close to under the original assumptions. The chances of stopping at one of the interims is still over 95% if the true GMC ratio is greater than 4, indicating the addition of raxibacumab has a large effect on the vaccine immunogenicity.

Table 6 Simulated Operating Characteristics of the Trial Under Different True GMC Ratios (SD=0.9; 10,000 simulations)

Ratio of Geometric Means	Percent Effect in combination	Probability of stopping at the First Interim	Probability of stopping at the Second Interim	Probability of stopping at either interim	Probability of Non-inferiority
20	5%	99.2%	0.8%	100%	0%
10	10%	92.8%	7.2%	100%	0%
4	25%	61.3%	36.5%	100%	0%
2	50%	26.6%	36.6%	63.2%	0.1%
1.5	67%	15.1%	22.0%	37.1%	5.0%
1.25	80%	10.5%	13.6%	24.0%	23.7%
1.11	90%	8.2%	9.0%	17.0%	46.5%
1	100%	6.3%	5.7%	12.0%	67.6%

9.2.3. Sample Size Re-estimation or Adjustment

Sample size re-estimation is not planned.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

The Intent-to-Treat (ITT) population will comprise all randomized subjects.

The Per Protocol (PP) population will comprise all analyzable subjects and will be used for the primary analysis.

A subject will be considered to be analyzable if they meet all of the following criteria:

1. Receive at least the Week 0 and 2 AVA doses,

2. Receive the raxibacumab dose, if randomized to that treatment
3. Complete the primary study endpoint assessment (anti-PA Ab concentration at Week 4).

The Safety population will comprise all randomized subjects receiving at least one dose of study treatment and will be based on the actual treatment received if this differs from that to which the subjects were randomized. The Safety population will be the primary dataset used for the analysis of safety data. For analyses using the safety population only, subjects will be analyzed based on the treatment they received if this differs from the treatment to which they were randomized. That is, subjects randomized to receive both raxibacumab and AVA, who only receive AVA will be summarized with the other subjects who only received AVA. Subjects who only receive raxibacumab will not be included in the Safety population summaries and their data will be listed separately.

9.3.2. Interim Analysis

Based on published results, polyclonal anti-PA antitoxin administered to rabbits in combination with AVA resulted in essentially complete abrogation of the immune response to AVA (Malkevich, 2013). Thus, it is possible that co-administration of raxibacumab with AVA will essentially eliminate any immunogenic response to AVA. Given that expectation, this study will consist of 3 cohorts, with two interim analyses to allow early termination of the study if a large effect of raxibacumab on AVA immunogenicity is confirmed at the interim.

The first interim analysis will be performed after the first 30 analyzable subjects have reached the week 4 endpoint. The second interim will be performed after the first analyzable 100 subjects have reached the week 4 endpoint.

These sample sizes for the interim analyses were selected based on the goal to minimize exposure to subjects if the anti-PA antibody levels attributable to AVA in the combination treatment group were truly inferior to the AVA alone treatment group. The boundary for the first interim was selected such that it would nearly guarantee that the trial would end after only 30 subjects if the true GMC ratio was very large (>10), while simultaneously having a low probability that the trial would be ended prematurely (true GMC ratio near 1); see Table 5 for actual probabilities. If the results of this combination in humans taking a monoclonal antibody are similar to the results in rabbits receiving a polyclonal antibody in the Malkevich, 2013 paper, the GMC ratio could be considerably larger than 10.

A second interim was included to end the trial early for scenarios that fell in between the non-inferiority margin and the very large effects the first interim was designed to capture. This interim is designed to capture the case where there is still a fair impact due to the addition of raxibacumab, but there is a variation from the results seen in rabbits with the polyclonal antibody. As can be seen in Table 5 the addition of this second interim will result in a futility result at either interim with a 99% chance if the true GMC ratio is >4 and with high likelihood (>67%) if the true GMC ratio is >2.

The t-statistics for the boundaries, as calculated in East 5.4, are 1.0274 for interim 1, 0.4437 for interim 2 and -1.645 for the final analysis. These correspond to p-values for the t-test of p=.848 at interim 1, p=.671 at interim 2, and p=.05 for the final analysis.

The clinical interpretation of these thresholds is easier to evaluate if they are converted to thresholds for the GMC ratio. The challenge with this conversion is that the thresholds for the GMC ratios that will lead to a futility result or a result of non-inferiority will be dependent on the variability in the estimates observed in the trial. However, a conversion can be made assuming the standard deviation will match the one used in the sample size calculation of 0.75. Under this assumption, the log transformed scale the boundaries correspond approximately to an observed difference in the means of >.4575 at interim 1 and >.242 at interim 2, or observed GMC ratios of > 2.87 and >1.75 respectively. The threshold for success at the final analysis would be an observed GMC ratio of 1.173 or less.

Given the high level of variance of anti-PA antibody levels at week 4 with AVA (as observed in Marano, 2008), it is challenging to estimate either the GMC or the GMC ratios with precision without a very large sample size. The total sample size was determined based on how many subjects were required to have an 80% chance of ruling out that the GMC ratio was >1.5 when it was truly 1. Many more subjects would be required to estimate the actual ratio with considerable precision.

Similarly the interim analyses will not result in precise estimates of the GMC ratio. There will be sufficient data collected to determine whether it is futile to expect that the trial would result in a non-inferiority conclusion. The beta error spending boundary was chosen such that approximately 25% of the Type II error is spent in the first interim. There was a willingness to allow for this much error in the first interim after only 30 subjects, because it is assumed that there is a high likelihood the anti-PA antibody levels will be inferior when raxibacumab is given with AVA, based on the results of the Malkevich (2013) paper.

At the first interim the confidence interval for the ratio will be based on a t statistic with 28 degrees of freedom (for instance for a 90% CI the relevant t value is $t_{.05,28}$=1.701). The exact precision of the estimate will be dependent on the observed sample estimate of the standard deviations. Assuming both treatment groups have a sample standard deviation equivalent to the assumed 0.75, the assumed standard error would be 0.274. The 90% confidence interval will vary by ± .466. Translated back to the original scale, the GMC ratio will be scaled by .342 or 2.92.

For the second interim, the assumed standard error in the log transformed data would be .15. The 90% confidence interval would vary by ± .249 in the log transformed data and scaled 0.564 or 1.775 in the original scale GMC ratio.

At the final analysis, the assumed standard error in the log transformed data would be .065. The 90% confidence interval would vary by ± .107 in the log transformed data and scaled by 0.782 or 1.28 in the original scale GMC ratio.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

At the final analysis, the non-inferiority test will be based on a comparison of the CI for the ratio of anti-PA Ab (attributable to AVA) GMCs between the AVA and the AVA + raxibacumab groups at week 4. This analysis will be performed in the per protocol population. If the upper bound of the 90% CI is less than 1.5, non-inferiority will be established.

This analysis will be repeated in the subset of the intent-to-treat population with available week 4 results, as a sensitivity analysis. Another set of sensitivity analyses will use the full ITT population with imputation for subjects without week 4 anti-PA Ab concentration results. The first imputation will be as follows: In the AVA + raxibacumab arm, missing data will be imputed with the first quartile from the non-missing data in this arm. In the AVA arm, missing data will be imputed with the third quartile from the non-missing data in this arm. The second imputation will be as follows: In the AVA + raxibacumab arm, missing data will be imputed with the lower limit of quantitation (LLQ). In the AVA arm, missing data will be imputed with the maximum from the non-missing data.

The GMCs for each treatment group will be summarized along with the 95% confidence intervals for the week 4 timepoint as well as weeks 8 and 26.

The GMC ratio and GMCs within each cohort and corresponding CIs will be calculated by first log transforming all of the data by a log base 10. A t-test will be performed and CIs will be calculated about the mean logs and the difference of the mean logs. The results will be translated back to the original scale by exponentiating them, again using a base 10. The exponentiated differences of the sample mean logs will be the ratio of the sample geometric means of the untransformed results.

Sensitivity analyses will be performed to assess the sensitivity of the results to the assumption of equality of variances between the anti-PA Ab concentrations in the two treatment groups. Details will be described in the analysis plan.

9.4.2. Secondary Analyses

9.4.2.1. Anti-PA Antibodies

Anti-PA antibody concentrations will also be collected at weeks 8 and 26 after the first AVA dose. The GMCs along with 95% CI will be summarized for each treatment group at each timepoint. There will be no imputation for subjects with missing data at a given timepoint.

9.4.2.2. Toxin Neutralizing Activity (TNA)

TNA titers will be collected at weeks 4, 8 and 26 after the first AVA dose. The GMTs along with 95% CI will be summarized for each treatment group at each timepoint. There will be no imputation for subjects with missing data at a given timepoint.

The percentage of subjects, along with 95% CI, who seroconvert, defined as a >4-fold increase in toxin neutralizing activity (TNA) titer will be summarized, at Weeks 4, 8 and 26 after the first AVA dose for both arms separately.

9.4.2.3. Safety Analyses

Clinical safety observations will include AEs, urinalysis, vital sign measurements, and clinical laboratory assessments. Safety data will be tabulated and, where appropriate, analyzed by the use of descriptive statistics. Safety data will be tabulated for the Safety Population.

The number (%) of subjects withdrawing from the study will be summarized for each treatment group and the number (%) subjects withdrawing for each individual reason will be summarized by treatment group.

Reported AEs will be coded using MedDRA. The number (%) of subjects in each treatment group with treatment-emergent AEs will be compared for overall incidence and by system organ class and preferred term. Similar summaries will also be presented for deaths, all SAEs, AEs leading to withdrawal, and drug-related AEs. Severity of treatment-emergent AEs will also be summarized by system organ class, preferred term, and treatment group.

Additionally, the frequency of laboratory abnormality events along with shifts from baseline will be summarized, as well as changes over time in laboratory parameters, urinalysis and vital signs.

9.4.2.4. Statistical Analysis of Pharmacokinetic Data

Drug concentration-time data will be listed for each subject and summarized by descriptive statistics at each nominal collection time. PK parameters will be listed for each subject and summarized by descriptive statistics.

Specimens will also be analyzed for the presence of anti-raxibacumab antibodies. Those results will be descriptively and/or graphically summarized as appropriate to the data.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.

10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations including GCP, and GSK procedures, GSK or delegated monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant

documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.

If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.

If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.

If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

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12. APPENDICES

12.1. Appendix 1 Abbreviations and Trademarks

Abbreviations

Ab	Antibody
AE	Adverse event
ALT	Alanine amino transferase
AST	Aspartate amino transferase
AUC_{0-t}	Area under the serum raxibacumab concentration-time curve to the time of the last measureable concentration
$AUC_{0-\infty}$	Area under the raxibacumab concentration-time curve to the time of the last measurable concentration
AVA	Anthrax vaccine absorbed
B. anthracis	*Bacillus anthracis*
BUN	Blood urea nitrogen
C_{max}	Maximum observed serum raxibacumab concentration
CFR	U.S. Code of Federal Regulations
CI	Confidence interval
CL	Clearance
CO2	Carbon dioxide
CONSORT	Consolidated standards of reporting trials
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacology Modeling and Simulation
CRF	Case report form
DMID	Division of Microbiology and Infectious Diseases
DMPK	Drug Metabolism and Pharmacokinetics
FDA	Food and Drug Administration
FRP	Female of reproductive potential
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GCSP	Global clinical safety and pharmacovigilance
GLP	Good Laboratory Practices
GMC	Geometric mean concentration
GMT	Geometric mean titer
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotrophin
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
IB	Investigator's brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICF	Informed consent form
IEC	Independent ethics committee

IM	Intramuscular
IND	Investigational new drug
IRB	Institutional review board
ITT	Intent-to-treat
IV	Intravenous
LDH	Lactate dehydrogenase
MedDRA	Medical dictionary for regulatory activities
MRT	Mean residence time
MSDS	Medical Safety Data Sheet
PA	Protective antigen
PI	Package insert
PK	Pharmacokinetics
PP	Per protocol
QC	Quality control
RBC	Red blood cell
R&D	Research & Development
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SOP	Standard operating procedure
SRM	Study reference manual
SRT	Safety review team
t_{max}	Time of occurrence for C_{max}
$t_{½, z}$	Half-life of drug elimination in the terminal phase
TNA	Toxin neutralizing activity
TTS	Study specific technical agreement
UHPLC/MS	Ultra high performance liquid chromatography – mass spectrometry
ULN	Upper limit of normal
UM	Upper Merion
US	United States
V_{ss}	Volume of distribution in the terminal phase
V_z	Volume of distribution at steady-state
WBC	White blood cell

Trademark Information

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12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN

If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.

See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments following Liver Stopping Event</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)

MONITORING:

If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5

• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended

If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:

• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs
• Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline</td><td>• Viral hepatitis serology[3]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• A pharmacokinetic (PK) sample to be collected up to 7 days following the liver event.
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form

If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:

• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).
• Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009].
• Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.</td></tr>
</table>

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody

12.3. Appendix 3: GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

A. Contraceptive subdermal implant that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label
B. Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label
C. Oral Contraceptive, combined estrogen and progestogen [Hatcher, 2011]
D. Injectable progestogen [Hatcher, 2011]
E. Contraceptive vaginal ring [Hatcher, 2011]
F. Percutaneous contraceptive patches [Hatcher, 2011]
G. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.4. Appendix 4: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.4.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.4.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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.
c. Requires hospitalization or prolongation of existing hospitalization NOTE: • In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in disability/incapacity NOTE: • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.4.3. Recording of AEs and SAEs

AEs and SAE Recording:
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. • The investigator will then record all relevant information regarding an AE/SAE in the CRF • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.4.4. Evaluating AEs and SAEs

Assessment of Intensity
AEs will be assessed for severity based on the modified Division of Microbiology and Infectious Diseases (DMID) toxicity tables in Appendix 6. The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories: • Mild: An event causing no limitation of usual activities • Moderate: An event causing some limitation of usual activities • Severe: An event causing inability to carry out usual activities. • Life-threatening: An event that is potentially life threatening or disabling.

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. • A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated. • The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment. • For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.** • The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. • The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.4.5. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor or the SAE coordinator • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor or the SAE coordinator by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will discontinue study medication and will continue to be followed for pregnancy outcome.

12.6. Appendix 6: Modified Division of Microbiology and Infectious Diseases (DMID) Toxicity Tables

HEMATOLOGIC	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5-10.9 g/dL	8.0-9.4 g/dL	6.5-7.9 g/dL	< 6.5 g/dL
Leukocytes	3000/mm^3 to < LLN OR > ULN to 13,000/mm^3	2000 to < 3000/mm^3 OR > 13,000 to 15,000/mm^3	1000 to < 2000/mm^3 OR > 15,000 to 30,000/mm^3	< 1000/mm^3 OR > 30,000/mm^3
Absolute neutrophil count (ANC)	1000 to 1500/mm^3	750 to < 1000/mm^3	500 to < 750/mm^3	< 500/mm^3
Platelets	75,000 to < 100,000/mm^3	50,000 to < 75,000/mm^3	20,000 to < 50,000/mm^3	< 20,000/mm^3
Lymphocyte count	800/mm^3 to < LLN	500 to < 800/mm^3	200 to < 500/mm^3	< 200/mm^3
% Polymorphonuclear leukocytes + band cells	80-90%	> 90-95%	> 95%	---
Abnormal fibrinogen	Low: 100-200 mg/dL High: 400-600 mg/dL	Low: 50 to < 100 mg/dL High: > 600 mg/dL	Low: < 50 mg/dL ---	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin split product	20-40 mcg/mL	41-50 mcg/mL	51-60 mcg/mL	> 60 mcg/mL
Prothrombin time (PT)	> 1.0-1.25 x ULN	> 1.25-1.5 x ULN	> 1.5-3.0 x ULN	> 3.0 x ULN
Activated partial thromboplastin time (APPT)	> 1.0-1.66 x ULN	> 1.66-2.33 x ULN	> 2.33-3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0-9.9%	10.0-14.9%	15.0-19.9%	≥ 20%

LLN = lower limit of normal; ULN = upper limit of normal. Modified DMID Adult Toxicity Tables (Version 2.0, Aug 2004)

(continued)

CHEMISTRIES	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 mEq/L OR Abnormal sodium with mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L OR Abnormal sodium with mental status changes or seizures
Hypokalemia	3.0-3.4 mEq/L	2.5-2.9 mEq/L	2.0-2.4 mEq/L OR	< 2.0 mEq/L OR Abnormal potassium with paresis, ileus, or life-threatening arrhythmia
Hyperkalemia	5.6-6.0 mEq/L	6.1-6.5 mEq/L	Intensive replacement therapy or hospitalization required 6.6-7.0 mEq/L	> 7.0 mEq/L OR Abnormal potassium with life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	< 30 mg/dL OR Abnormal glucose with mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116-160 mg/dL	161-250 mg/dL	251-500 mg/dL	> 500 mg/dL OR Abnormal glucose with ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	7.8-8.4 mg/dL	7.0-7.7 mg/dL	6.1-6.9 mg/dL	< 6.1 mg/dL OR Abnormal calcium with life-threatening arrhythmia or tetany
Hypercalcemia (corrected for albumin)	10.6-11.5 mg/dL	11.6-12.5 mg/dL	12.6-13.5 mg/dL	> 13.5 mg/dL OR Abnormal calcium with life-threatening arrhythmia
Hypomagnesemia	1.2-1.4 mEq/L	0.9-1.1 mEq/L	0.6-0.8 mEq/L	< 0.6 mEq/L OR Abnormal magnesium with life-threatening arrhythmia
Hypophosphatemia	2.0-2.4 mg/dL	1.5-1.9 mg/dL OR	1.0-1.4 mg/dL OR	< 1.0 mg/dL OR Abnormal phosphate with life-threatening arrhythmia
Hypoalbuminemia	3.00-3.49 g/dL	Replacement therapy required 2.50-2.99 g/dL	Intensive therapy or hospitalization required 2.00-2.49 g/dL	< 2.00 g/dL

CHEMISTRIES	Grade 1	Grade 2	Grade 3	Grade 4
Hyperbilirubinemia	> 1.25-2.5 x ULN	> 2.5-5.0 x ULN	> 5.0-10 x ULN	> 10 x ULN
Hypothyroid	Asymptomatic, no treatment required	Symptomatic, not interfering with ADLs; thyroid replacement indicated	Symptoms interfering with ADLs; hospitalization required	Life-threatening myxedema coma

ADLs = activities of daily living; LLN = lower limit of normal; ULN = upper limit of normal. Modified DMID Adult Toxicity Tables (Version 2.0, Aug 2004)

(continued)

CHEMISTRIES (continued)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hyperthyroid	Asymptomatic, no treatment required	Symptomatic, not interfering with ADLs; thyroid suppression therapy indicated	Symptoms interfering with ADLs; hospitalization required	Life-threatening consequences (eg, thyroid storm)
Blood urea nitrogen (BUN)	1.25-2.5 x ULN	> 2.5-5.0 x ULN	> 5.0-10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5-10.0 mg/dL	10.1-12.0 mg/dL	12.1-15.0 mg/dL	> 15.0 mg/dL
Creatinine	1.1-1.5 x ULN	> 1.5-3.0 x ULN	> 3.0-6.0 x ULN	> 6.0 x ULN OR Dialysis required

ADLs = activities of daily living; LLN = lower limit of normal; ULN = upper limit of normal. Modified DMID Adult Toxicity Tables (Version 2.0, Aug 2004)

ENZYMES	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.25-2.5 x ULN	> 2.5-5.0 x ULN	> 5.0-10 x ULN	> 10 x ULN
ALT (SGPT)	1.25-2.5 x ULN	> 2.5-5.0 x ULN	> 5.0-10 x ULN	> 10 x ULN
Gamma glutamyl transpeptidase (GGT)	1.25-2.5 x ULN	> 2.5-5.0 x ULN	> 5.0-10 x ULN	> 10 x ULN
Alkaline phosphatase	1.25-2.5 x ULN	> 2.5-5.0 x ULN	> 5.0-10 x ULN	> 10 x ULN
Amylase	1.1-1.5 x ULN	> 1.5-2.0 x ULN	> 2.0-5.0 x ULN	> 5.0 x ULN
Lipase	1.1-1.5 x ULN	> 1.5-2.0 x ULN	> 2.0-5.0 x ULN	< 5.0 x ULN

ULN = upper limit of normal. Modified DMID Adult Toxicity Tables (Version 2.0, Aug 2004)

(continued)

URINALYSIS	Grade 1	Grade 2	Grade 3	Grade 4
Proteinuria	1+ OR	2+ to 3+ OR	4+ OR	Nephrotic syndrome
Hematuria	< 0.3 g/dL Microscopic only OR	0.3 to 1.0 g/dL Gross, no clots OR	> 1.0 g/dL Gross with clots OR	Obstructive uropathy OR
	< 10 RBCs/hpf	≥ 10 RBCs/hpf	RBC casts	Transfusion required

RBC = red blood cell; hpf = high power field. Modified DMID Adult Toxicity Tables (Version 2.0, Aug 2004)

CARDIOVASCULAR	Grade 1	Grade 2	Grade 3	Grade 4
Cardiac rhythm	---	Asymptomatic, transient signs; no treatment required	Recurrent/persistent dysrhythmia; symptomatic treatment required	Unstable dysrhythmia; hospitalization and treatment required
Hypertension	Transient increase > 20 mmHg; no treatment required	Recurrent; chronic increase > 20 mmHg; treatment required	Acute treatment required (outpatient or hospitalized)	End organ damage OR Hospitalization required
Hypotension	Transient orthostatic hypotension, with heart rate increased by < 20 bpm or SBP decreased by < 10 mmHg; no treatment required	Symptoms due to orthostatic hypotension or SBP decreased by < 20 mmHg; correctable with oral fluid treatment	IV fluids required; no hospitalization required	Mean arterial pressure < 60 mmHg or end organ damage or shock OR Hospitalization and vasopressor treatment required
Pericarditis	Minimal effusion	Mild/moderate asymptomatic effusion; no treatment required	Symptomatic effusion, pain, ECG changes	Tamponade OR Pericardiocentesis OR Surgery required
Hemorrhage, Blood loss	Microscopic/occult	Mild, no transfusion required	Gross blood loss or 1 to 2 units transfused	Massive blood loss or > 2 units transfused

bpm = beats per minute; ECG = electrocardiogram; SBP = systolic blood pressure. Modified DMID Adult Toxicity Tables (Version 2.0, Aug 2004)

(continued)

RESPIRATORY	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Cough	Transient; no treatment	Persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	---
Bronchospasm, acute	Transient; no treatment required; FEV_1 70% to < 80% of peak flow	Treatment required; normalizes with bronchodilator; FEV_1 50% to < 70% of peak flow	No normalization with bronchodilator; FEV_1 25% to < 50% of peak flow OR Retractions	Cyanosis; FEV_1 < 25% of peak flow OR Intubation required
Dyspnea	Dyspnea on exertion	Dyspnea with normal activity	Dyspnea at rest	Dyspnea requiring O_2 treatment

FEV_1 = forced expiratory volume in 1 second. Modified DMID Adult Toxicity Tables (Version 2.0, Aug 2004)

GASTROINTESTINAL	Grade 1	Grade 2	Grade 3	Grade 4
Constipation	Stool softener or dietary modification required	Laxatives required	Obstipation requiring manual evacuation or enema	Obstruction or toxic megacolon
Diarrhea	Mild or transient; 3 to 4 loose stools per day OR Mild diarrhea lasting < 1 wk	Moderate or persistent; 5 to 7 loose stools per day OR Diarrhea lasting ≥ 1 wk	Bloody diarrhea OR Diarrhea accompanied by orthostatic hypotension or electrolyte imbalance OR > 7 loose stools per day OR > 2 L IV fluids required	Hypotensive shock OR Physiologic consequences requiring hospitalization
Oral discomfort/Dysphagia	Mild discomfort or mild soreness with erythema; no difficulty swallowing	Erythema with ulcers; some limits on eating & drinking	Ulcers and/or very limited eating & talking; unable to swallow solid foods	Unable to drink fluids; IV fluids required

See "Flu-like Symptoms" for nausea and vomiting.

Modified DMID Adult Toxicity Tables (Version 2.0, Aug 2004)

(continued)

NEUROLOGIC	Grade 1	Grade 2	Grade 3	Grade 4
Mood alteration (*specify*) -Anxiety -Agitation -Depression	Mild mood alteration, but not interfering with function	Moderate mood alteration interfering with function but not with ADLs; treatment indicated	Severe mood alteration interfering with ADLs	Suicidal ideation; danger to self or others
Insomnia	Occasional difficulty sleeping, but not interfering with function	Difficulty sleeping, interfering with function but not with ADLs	Frequent difficulty sleeping, interfering with ADLs	Disabling
Neuro - cerebellar	Slight incoordination OR Dysdiadochokinesia	Intention tremor OR Dysmetria OR Slurred speech OR Nystagmus	Locomotor ataxia	Incapacitated
Neuro - muscular	Subjective weakness; no objective signs/symptoms	Mild, objective signs/symptoms; no decrease in function	Objective weakness; limited function	Paralysis
Neuro - sensory	Mild impairment of sensations (eg, vibratory, pinprick, hot/cold to great toes) in focal area or symmetrical distribution OR Change in taste, smell, vision, and/or hearing	Moderate impairment of sensations (eg, vibratory, pinprick, hot/cold to ankles) and/or joint position OR Mild impairment that is not symmetrical	Severe impairment (decreased or loss of sensation to knees or wrists) OR Loss of sensation of at least moderate degree in multiple different body areas (ie, upper & lower extremities)	Sensory loss involving limbs & trunk OR Paralysis OR Seizures
Paresthesia (burning, tingling, etc)	Mild discomfort; no treatment required	Moderate discomfort; non-narcotic analgesic required	Severe discomfort; narcotic analgesic required, with symptomatic improvement	Incapacitating; not responsive to narcotic analgesic

ADLs = activities of daily living.

Modified DMID Adult Toxicity Tables (Version 2.0, Aug 2004)

(continued)

SKIN/DERMATOLOGIC	Grade 1	Grade 2	Grade 3	Grade 4
Alopecia	Minimal hair loss	Moderate, patchy hair loss	Complete hair loss; reversible	Nonreversible hair loss
Mucocutaneous	Erythema or pruritus	Diffuse maculopapular rash or dry desquamation	Vesiculation, moist desquamation, or ulceration	Exfoliative dermatitis, mucous membrane involvement, erythema multiforme, Stevens-Johnson syndrome/TEN, or necrosis requiring surgery
Induration	< 15 mm	15 to 30 mm	> 30 mm	---
Erythema	< 15 mm	15 to 30 mm	> 30 mm	---
Edema	< 15 mm	15 to 30 mm	> 30 mm	---
Rash at injection site	< 15 mm	15 to 30 mm	> 30 mm	---
Pruritus	Slight itching at injection site	Moderate itching at injection extremity	Itching over entire body	---

TEN = toxic epidermal necrolysis. Modified DMID Adult Toxicity Tables (Version 2.0, Aug 2004)

MUSCULOSKELETAL	Grade 1	Grade 2	Grade 3	Grade 4
Arthritis	Mild pain with inflammation, erythema or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema or joint swelling, interfering with function but not with ADLs	Severe pain with inflammation, erythema or joint swelling, interfering with ADLs	Permanent and/or disabling joint destruction

ADLs = activities of daily living. Modified DMID Adult Toxicity Tables (Version 2.0, Aug 2004)

See “Flu-like Symptoms” for arthralgia and myalgia.

(continued)

SYSTEMIC	Grade 1	Grade 2	Grade 3	Grade 4
Allergic reaction	Pruritus without rash	Localized urticaria	Generalized urticaria; angioedema	Anaphylaxis
Weight gain/loss	5.0-9.9%	10.0-19.9%	≥ 20.0%	---

See "Flu-like Symptoms" for headache, chills, fever, fatigue, and malaise.

Modified DMID Adult Toxicity Tables (Version 2.0, Aug 2004)

FLU-LIKE SYMPTOMS	Grade 1	Grade 2	Grade 3	Grade 4
Arthralgia	Joint pain, but no effect on daily function	Joint pain, moderate decrease in daily function	Joint pain, incapacitating to daily function	---
Chills	Mild to moderate shaking	Severe shaking	Rigors, incapacitating to daily function	---
Fatigue	Fatigue, but no effect on daily function	Fatigue, moderate decrease in daily function	Fatigue, incapacitating to daily function	---
Fever	38.0-38.6ºC (100.4-101.5ºF)	> 38.6-40ºC (> 101.5-104ºF)	> 40ºC (> 104ºF)	Fever with hypotension
Headache	< 2 hr, no analgesic required	2 to 24 hr, non-narcotic analgesic required	> 24 hr, multiple doses of non-narcotic analgesic required	Intractable; repeated narcotic analgesic treatment required
Malaise	< 24 hr duration	24 to 48 hr duration	Persistent, > 48 hr duration	---
Myalgia	Muscle pain, but no effect on daily function	Muscle pain, moderate decrease in daily function	Muscle pain, incapacitating to daily function	---
Nausea	Occasional and transient	Persistent, > 24 hr	Persistent, > 24 hr, with daily vomiting	---
Vomiting	Sporadic emesis, not occurring daily	Daily emesis	Daily emesis, intolerable; treatment required	Intractable vomiting

Modified DMID Adult Toxicity Tables (Version 2.0, Aug 2004)

(concluded)

12.7. Appendix 7: Protocol Changes

The following changes were made, where text in strikethrough is deleted and text in bold is added.

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD PPD M.D. (Quintiles)	PPD PPD	PPD	PPD PPD	1801 Rockville Pike, Suite 300, Rockville, MD 20852
~~Secondary Medical Monitor~~	PPD PPD ~~M.D. (GSK)~~	PPD PPD	PPD	PPD PPD	~~1250 S. Collegeville Road, Collegeville, Pennsylvania, 19426~~
Secondary Medical Monitor	PPD PPD **M.D. (GSK)**	PPD PPD	PP PPD	**N/A**	**Stockley Park West, 1-3 Ironbridge Road, Uxbridge, Middlesex, UB11 1BT, United Kingdom**
SAE contact information	PPD (Quintiles)	PPD PPD	PPD	PPD PPD	5927 S. Miami Blvd Morrisville, NC 27560

Section 6.2 Treatment Assignment

Aligned the text with the Time and Events Table that states that randomization is occurring on day -1 of the study.

A randomization envelope for each subject will be opened ~~just~~ prior to dosing **(on day -1)** to reveal the subject's treatment assignment.

Appendix 2: Liver Safety Required Actions and Follow up Assessments

Added PK assessments to Follow up Assessments.

Required Actions and Follow up Assessments following Liver Stopping Event	
Actions	Follow Up Assessments
• Discontinue study treatment • Report the event to GSK within 24 hours • Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below) MONITORING: If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5 • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs • Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Viral hepatitis serology[3] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • **A pharmacokinetic (PK) sample to be collected up to 7 days following the liver event.** • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

Appendix 3: GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP):

A. Contraceptive subdermal implant that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label

B. Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label ~~[Hatcher, 2007(a)]~~

C. Oral Contraceptive, ~~either~~ combined ~~or~~ estrogen and progestogen ~~alone~~ [Hatcher, 20**11**~~07(a)~~]

D. Injectable progestogen [Hatcher, 20**11**~~07(a)~~]

E. Contraceptive vaginal ring [Hatcher, 20**11**~~07(a)~~]

F. Percutaneous contraceptive patches [Hatcher, 20**11**~~07(a)~~]

G. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject ~~[Hatcher, 2007(a)]~~. **The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.**

~~H. Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository) [Hatcher, 2007(b)]~~

Section 11, References:

~~Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(a): 24. Table 3-2.~~

~~Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(b): 28.~~

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, Policar MS, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, 2011: 50. Table 3-2.