Immunogenicity of a U.S.-Licensed Meningococcal Serogroup B Vaccine (Trumenba) in Adults at Increased Risk of Meningococcal Disease Because of Occupational Exposure

NCT02569632
Document Date: 11/14/19

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I. Specific Aims

In October 2014, the FDA approved the first meningococcal B vaccine in the United States for persons 10 to 25 years (http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm420998.htm). The new vaccine (trade name "Trumenba®", Meningococcal Group B Vaccine), is manufactured by Pfizer Vaccines (Package insert, Appendix A). The antigens consist of two Factor H binding proteins (FHbp) expressed as recombinant lipoproteins (referred to herein as "Trumenba").

For over a decade, our laboratory has been investigating mechanisms by which FHbp vaccination confers protection against meningococcal disease using mouse and, more recently, non-human primate models. *Neisseria meningitidis*, however, is a strictly a human pathogen, and large gaps exist on understanding the basis of human immunity to FHbp. The recent licensure of the Trumenba vaccine in the U.S. provides an opportunity to investigate the breadth of protection against meningococcal disease in humans immunized with this new vaccine. As a secondary goal we will investigate underlying mechanisms by which human anti-FHbp antibodies elicit complement-mediated bactericidal activity. The results may form the basis of a future NIH grant application. This pilot study will be funded by existing funds in research accounts at CHORI and, therefore, will be independent of commercial influence.

Aim 1. Characterize the breadth of protective activity of serum anti-FHbp antibody responses of adults immunized with the Trumenba vaccine. During studies done by the manufacturer for licensing of this vaccine, the breadth of protection was defined by serum bactericidal assays using only four test strains (Trumenba Package Insert, Appendix A). There are more than 750 FHbp amino acid sequence variants in the public database. Because of strain variability in FHbp amino sequence and in FHbp expression, the results of testing bactericidal activity against only four isolates is unlikely to define the true breadth of protection. Therefore, in Aim 1, we will enroll 13 healthy adults who will be immunized with three doses of Trumenba vaccine at the recommended 0, 2 and 6 months schedule. We will only include adults with increased risk to o exposure to *N. meningitidis* such as microbiologist, physicians or nurses since they are at higher risk of meningococcal disease than the general population. Therefore, these persons have the most potential benefit from vaccination. Sera will be obtained before and after vaccination and will be assayed for IgG antibody responses to FHbp by ELISA, for bactericidal activity against a panel of genetically diverse meningococcal strains, and for the ability to inhibit binding of human Factor H (FH) to FHbp. FH is a complement down-regulator, which is present in high concentrations in serum. In immunized mice, the ability of anti-FHbp antibodies to inhibit binding of FH to the bacteria contributed to the breadth of bactericidal activity (with less bound FH, the bacteria became more susceptible to complement-mediated bactericidal activity)[1,2]. However, we don't know whether the anti-FHbp antibody repertoire of immunized humans blocks FH binding.

Aim 2. Define the antibody repertoire to FHbp. The antibodies to FHbp present in sera represent the products of multiple B cell clones. Because sera contain a mixture of antibodies with different epitope specificities, it is difficult to investigate antibody repertoire (i.e., FHbp epitopes recognized by the antibodies) in serum. Therefore, we will obtain an additional sample of blood from a sub-set of consenting subjects 7 to 10 days after vaccine dose 3 for isolation of peripheral blood mononuclear cells (PBMCs). The cells will be sorted to obtain individual B cells, which will be frozen for future studies that will use PCR to clone the heavy and light chain immunoglobulin variable region genes encoding anti-FHbp antibodies. The genes will be used to prepare recombinant anti-Fabs (antibody fragments expressing the antigen binding site). These studies are labor intensive and will likely require additional funding. Having available stored individual B cells from Trumenba-vaccinated humans will be helpful to secure the extramural support for a human anti-FHbp Fab project.

II. Background

Neisseria meningitidis causes meningitis and severe infections of the blood stream. Despite antibiotic treatment mortality rates range from 5 to 20% and approximately 20% of survivors are left with permanent sequelae such seizures, deafness or limb amputations[3,4]. The highest incidence of disease is in the first year of life with a secondary peak in adolescents and young adults. Nearly all disease in the U.S. is caused by strains with capsular serogroups C, Y or B. Currently, meningococcal quadrivalent A, C, Y, and W polysaccharide-protein conjugate vaccination is recommended for all adolescents in the U.S. Vaccination is also recommended for infants and children <11 years of age and for adults over 20 years who are at increased risk of meningococcal disease because of underlying medical conditions (i.e., complement deficiency, hypo-splenic function including sickle cell disease, or HIV infection) [5], or increased risk of exposure to the organism such as from travel to areas of the world with epidemic meningococcal disease, exposure to outbreaks, or occupational exposure. Occupation exposure includes clinical and research microbiologists who are at more than a 100-fold greater risk of meningococcal disease compared to the general population [6-9]. The Advisory Committee on Immunization Practices (ACIP) has not yet completed formulation of recommendations for use of the new meningococcal serogroup B vaccine (recommendations will be voted on at the next meeting in February 35-27, 2015). However, at the October 2014 ACIP meeting, the group was considering a broad recommendation for vaccination of all persons 10 years of age or older who are in high risk groups for which meningococcal conjugate vaccination currently is recommended (http://www.cdc.gov/vaccines/acip/meetings/meetings-info.html). Recommendations also may be extended to all teenagers and college-age students.

The incidence of serogroup B meningococcal disease was too low to conduct a randomized, controlled trial to determine the actual efficacy of the new Trumenba vaccine. Instead vaccine efficacy was inferred from serum bactericidal antibody responses using four test strains. Approximately 80% to 90% of persons immunized had four-fold or greater increases in bactericidal titer, which were defined as protective responses (Apendix A, Trumenba Package Insert). However, because of strain variability of FHbp amino acid sequence (there are more than 750 sequence variants

described) and strain variability of FHbp expression[10], bactericidal data on only four strains are unlikely to be sufficient to predict the actual strain coverage by the vaccine. There also are gaps in knowledge about the underlying mechanisms by which human antibodies to FHbp elicit complement mediated bactericidal activity. Binding of complement FH by FHbp down-regulates complement activation onto the pathogen's surface. In sera from immunized mice, serum anti-FHbp antibodies inhibit binding of FH to the bacterial surface. With less bound FH, the bacteria becomes more susceptible to bactericidal activity [1,2]. However, binding of FH to FHbp is specific for human FH[11] . Therefore in vaccinated humans the vaccine antigen is expected to form a complex with FH right after immunization. Our hypothesis, supported by data from studies of other FHbp antigens in a human FH transgenic mouse model[12,13 14,15] (see Appendix B), is that binding of human FH to the vaccine antigen skews the antibody repertoire to FHbp epitopes located outside of the FH combining site. The resulting antibodies would be expected not to inhibit binding of FH to the bacteria. This hypothesis will be investigated in Trumenba-immunized humans as part of studies in Aim 1 (and in future studies of recombinant human anti-FHbp Fabs that will be enabled by obtaining DNA from individual B cells, described in Aim 2).

III. PRELIMINARY STUDIES AND PROGRESS REPORT

In preliminary studies we used a previously characterized human Factor H transgenic BALB/c mouse line[16] to investigate the effect of human FH on immunogenicity of a FHbp-containing vaccine (4CMenB) licensed by Novartis in Europe, Canada and Australia[15] (Appendix B). Our most important findings were that, compared with wild-type mice whose mouse FH doesn't bind to FHbp, the transgenic mice had lower serum IgG anti-FHbp antibody responses, and lower serum bactericidal antibody responses against a group B strain with all of the antigens mismatched to the 4CMenB vaccine except FHbp. The mechanism responsible for the lower FHbp immunogenicity in the transgenic mice is not known. FHbp is relatively sparsely exposed on many meningococcal strains [10]. In previous studies a critical determinant of anti-FHbp bactericidal activity was the ability for low-level C3b deposited by activation of the classical pathway to be amplified by the alternative pathway [1], which was enhanced if the anti-FHbp antibodies inhibited binding of FH to FHbp [1]. We found that while the serum anti-FHbp antibodies elicited by 4CMenB in wild-type mice inhibited binding of FH to FHbp, the corresponding antibodies elicited in human FH transgenic mice enhanced FH binding. The lack of FH inhibition in the transgenic mice suggested that the anti-FHbp antibody repertoire was skewed towards FHbp epitopes outside of the FH combining site. We do not however understand, however, the molecular basis for the FH enhancement. Conceivably, binding of antibodies to certain FHbp epitopes outside of the FH combining site resulted in conformational changes in FHbp that rendered the molecule more accessible for FH binding.

IV. EXPERIMENTAL DESIGN AND METHODS

General study design. This is a pilot study for immunizing 13 healthy adults, ages 18 to 55 years. The subjects will be from groups at increased risk of meningococcal disease because of higher likelihood of exposure to the organism (i.e., microbiologists

and physicians, nurses, respiratory therapists and medical students). All subjects will receive three doses of a U.S.-licensed meningococcal vaccine (Trumenba) according to the recommended 0, 2 and 6 months after the first dose.

Three blood samples will be obtained from all 13 subjects. These will be obtained immediately before doses 1 (30 ml), and three to six weeks after doses two and three (75 ml at each time point). In subjects that consent for an additional sample, we also will obtain a 60 ml blood sample 7-10 days after vaccination dose 3 for isolation of B cells. The cells will be used for studies of recombinant anti-FHbp Fabs for investigation of antibody repertoire (Aim 2).

The sera will be assayed for IgG antibody responses to FHbp, bactericidal activity against a panel of meningococcal strains, and other studies of meningococcal immunity such as inhibition of binding FH to FHbp, or passive protection against meningococcal bacteremia in an infant rat model [17].

The meningococcal B vaccine is approved in the U.S. for individuals 10 to 25 years because the data provided by the manufacturer to the FDA supporting safety and effectiveness only was limited to that age group. Most persons who are at increased risk of meningococcal disease because of occupational exposure to the bacteria are older than 25 years. Our study will include individuals with ages 18 to 55 years, which includes persons older than 25 years, an age group considered as “off label” use. There is no reason to anticipate that the vaccine will be less effective or less safe in otherwise healthy persons ages 26 to 55 compared to 10 to 25 years. As described above (II. Background), the U.S. Advisory Committee on Immunization Practices (ACIP) is considering an expanded age range that includes 26 to 55 years for vaccination of persons at increased risk of meningococcal disease. Also, in Europe, another meningococcal B vaccine called Bexsero, which contains a similar FHbp antigen as in the meningococcal B vaccine being tested in our study (Trumenba), is licensed for persons up to age 55 years. Detailed safety data in our study will be limited to collection of information on notable severe or serious adverse events only, which will be obtained at the time of each scheduled visit.

Patient selection: Healthy adults, ages 18 to 55 years, of either sex will be recruited from physicians, nurses, respiratory therapists or microbiology laboratory personnel working at the UCSF Benioff Children Hospital Oakland. Medical students attending UCSF or other accredited U.S. medical schools also will be eligible.

Inclusion criteria*:* Individuals eligible to be enrolled in the study are those: 1. in the risk groups summarized above (see Patient Selection); 2. able to comprehend and follow all required study procedures; 3. willing and able to sign an informed consent form; 4. available for all the visits scheduled in the study; 5. are in good health as determined by a brief medical history; and 6. for females of child bearing age a negative urine pregmancy test will be required . Note, according to the FDA, Trumenba should be used in pregnancy only when clearly indicated. While microbiologists working with serogroup B meningococci might be in that category because of their high risk of disease, in a clinical study it is prudent not to enroll women who are pregnant or planning to become pregnant during the six months required for completing three doses of the vaccine.

Exclusion criteria: Individuals who should not be enrolled in the study are those: 1, who are not in the risk groups summarized above; 2, who have not given or are unable to give

written informed consent to participate in the study; 3, females of child bearing potential who are pregnant, or planning on becoming pregnant during the study period. 4, Persons with a past history of having Guillain-Barré Syndrome (GBS), or a family history of GBS in a parent or sibling, will be excluded from participation in this study. 5. Persons with presence or suspected presence of serious chronic disease including but not limited to chronic cardiac disease, autoimmune disease, diabetes, hepatitis B/C, HIV, progressive neurological disease or seizure, leukemia, lymphomas, or neoplasm. 6. Persons who have participated in any other investigational drug or received any other vaccine within the last 30 days.7. Persons who received a dose of a meningococcal serogroups A, C, Y, W conjugate vaccine within the previous 30 days or wish to receive a dose of this vaccine during the six month study period; 7. a history of anaphylactic shock, asthma, urticaria or other allergic reaction after previous dose of Trumenba; 8. who have experienced fever (oral temperature above 38.0°C) within the past 3 days or are suffering from a present acute infectious disease; 9. who are planning to leave the area of the study site before the end of the study period; 10. who have obesity (BMI higher than 30); or 11. with any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

Procedures

Trumenba Meningococcal Group B Vaccine (Wyeth/Pfizer Pharmaceuticals). The vaccine is a suspension for intramuscular injection in 0.5 mL single-dose prefilled syringes. Each 0.5 mL dose contains 60 micrograms of each FHbp variant (total of 120 micrograms of protein), 0.018 mg of PS80 and 0.25 mg of Al^{3+} as AlPO4 in 10 mM histidine buffered saline at pH 6.0. Trumenba is administered as a three dose series (0.5 mL each) according to a 0-, 2-, and 6-month schedule. Table 1 summarizes the various visits and procedures that will be performed during the 7-month study.

Table 1: Trumenba Meningococcal Group B vaccine study: Summary of visits and events (total of 13 subjects)

Activity	**Day 0**	**2 months (60 to 80 day)**	**3 months (3-to 6 weeks Post Dose 2)**	**6 months**	**7 to 10 Days Post Dose 3**	**7 months (3 to 6 Weeks Post Dose 3)**
Screen for inclusion and exclusion criteria	X	X		X		
Informed written consent	X				X (Review for obtaining optional blood sample)	
Targeted physical exam and medical history	X	X		X		
Blood draw	30 ml (Sample A)		75 ml (Sample B)		60 ml* (Sample D)	75 ml (Sample C)
Type of blood sample	Serum only		Serum only		*Anti-coagulated for PBMC)	Serum only
Immunization	X	X (Dose 2)		X (Dose 3)		
Collect information on SAE and severe reactions		X	X	X	X	X

Note, total volume of serum for all subjects having three blood samples is 180 ml; for those providing optional blood sample, 240 ml.

Blood specimens. Blood specimens will consist of 30 ml obtained immediately before immunization with dose 1, and 75 ml obtained three to six weeks after dose 2 and dose 3 (total of 3 blood draws, designated A, B, and C, in all 13 subjects). Sera will be separated and stored frozen for serologic assays. In consenting subjects, an additional 60 ml of anti-coagulated blood (Sample D) will be obtained 7 to 10 days after vaccine dose 3 for isolation of individual B cells for preparation of recombinant anti-FHbp Fabs (Aim 2).

Safety and immunization. On enrollment, subjects will undergo a brief history and directed physical exam. Subjects who meet all inclusion criteria and no exclusion criteria will receive an immunization at visit 1 (study day 0), visit 2 (2 months; range 40 to 80 days) and visit 4 (6 months, range 180 to 240 days). Visits 3 and 6 will consist of blood draws only at 3 to 6 weeks after doses 2 and 3, respectively. At each visit information will be obtained on notable adverse events occurring within 7 days of vaccination, and

any serious adverse event (SAE) occurring during the 7-month study period. The FDA defines a SAE as “Death, life-threatening, or requiring hospitalization (not necessarily caused by the vaccine).

Immunologic assessment. Sera will be assayed by ELISA for titers of anti-FHbp antibodies and the ability of the antibodies to inhibit or enhance binding of FH to FHbp. Complement-mediated bactericidal activity will be measured with human complement using a panel of diverse strains. Other assays for meningococcal immunity may also be performed such as antibody binding to live bacteria measured by flow cytometry, and the ability of the serum antibodies to confer passive protection in an infant rat bacteremia model. All of these methods have been performed routinely in our laboratory for more than a decade (see for example, citations [1,2,18,19]). All of the assays using live meningococci will be performed in a BL2+ facility using protocols approved by the CHORI Institutional Biosafety Committee (IBC).

Data Safety Monitoring Plan

The study is slightly above minimal risk because the age group 26 to 55 years is considered currently “off-label” for use of an FDA-approved vaccine for the age group 10 to 25 years. No serious adverse events are anticipated related to vaccination. The other study procedures include three to four blood draws over seven months from healthy adults in which a total of less than 240 ml of blood will obtained (approximately half of the volume that can be safely drawn at a single blood donation at the blood bank).

ADVERSE REACTIONS

Clinical Trials Experience: (From the package insert). The safety of Trumenba was evaluated in 4,282 subjects 11 through 25 years of age in 7 clinical studies (4 randomized controlled and 3 supportive non-controlled studies) conducted in the US, Europe, and Australia. A total of 4,250 adolescents (11 through 18 years of age) and 32 adults (19 through 25 years of age) received at least one dose of Trumenba. A total of 1,004 subjects 11 through 25 years of age in the control groups received saline placebo and/or one of the following vaccines: Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant [HPV4]; a non-US licensed tetanus toxoid, reduced diphtheria toxoid, acellular pertussis and inactivated polio virus vaccine; or Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Sanofi Pasteur Ltd.). The safety evaluation in the 7 studies included an assessment of: (1) solicited local and systemic reactions, and (2) use of antipyretic medication after each vaccination

Solicited Local and Systemic Adverse Reactions: The Trumenba vaccine was generally well-tolerated although most patients (85-93%) experienced injection site reactions; fatigue (43-64%), headache (35-57%), muscle pain (31-42%), or chills (16-30%). These reactions were usually of mild to moderate severity and transient. In general the rates of these reactions were only slightly higher than those of subjects

receiving comparator control vaccines (including a U.S.-licensed quadrivalent human papilloma vaccine).

Serious Adverse Events: Among the 4 controlled studies (Trumenba N=2557, control N=1004), serious adverse events were reported in 44 (1.7%) subjects who received Trumenba and 16 (1.6%) control subjects, for individuals who received at least one dose.

Non-serious Adverse Events: Among the 4 controlled studies (Trumenba N=2557, control N=1004), AEs that occurred within 30 days of vaccination were reported in 739 (28.9%) subjects who received Trumenba and 313 (31.2%) subjects in the control group, for individuals who received at least one dose. AEs that occurred at a frequency of at least 2% and were more frequently observed in subjects who received Trumenba than subjects in the control group were injection site pain and headache.

In summary, in this study we will vaccinate healthy adults with a FDA-approved vaccine. The subjects enrolled will have increased risk of acquiring meningococcal serogroup B disease because of occupational exposure. The approved age group for Trumenba is 10 to 25 years, while the proposed age group in our study is 18 to 55 years, which includes off-label use in subjects over 25 years. However, most persons with occupational exposure to *N. meningitidis* are over 25 years of age and there is no reason to expect that the vaccine effectiveness or safety will be different in this older age group than in the group 18 to 25 years. Also at discussions at the Advisory Committee on Immunization Practices (October 30, 2014 meeting), they intend to harmonize their recommendations for Trumenba vaccination to be consistent with current recommendations for use of meningococcal A,C,Y,W conjugate vaccine, which includes the age group up to 55 years (http://www.cdc.gov/vaccines/acip/meetings/meetings-info.html).

Any serious adverse events will be promptly reported to the IRB. In addition, all changes in protocol procedures will be submitted for review and approval of the IRB.

V. BIOSTATISTICAL DESIGN AND ANALYSIS

Sample size and justification.

Immunologic analyses. The proposed study is a pilot study and is descriptive with the following objectives. 1. Characterization of the functional activity of serum anti-FHbp antibody responses of adults immunized with a newly licensed meningococcal FHbp vaccine, 2, Obtain individual B cells for preparation and characterization of human recombinant anti-FHbp Fabs. The proposed 13 immunized adults is a **convenience sample** and is based on the number of subjects that we can practically enroll in a pilot study with the resources available. Based on published data and data in the package insert, we expect that 80% to 90% of subjects will have 4-fold or greater increases in serum bactericidal activity (comparing titers after dose 3 to those present before dose 1) when measured against four test strains similar those used by the manufacturer in pre-

licensure studies. We expect that by testing additional test strains expressing FHbp variants with less cross-reactivity with the vaccine antigens, and/or lower expression of FHbp, that protective responses will be lower (ranging from 30 to 50% with 4-fold or greater increases in titer).

Summary statistics. The respective bactericidal titers at each visit will be logarithmically transformed (base 10). For each visit, GMT's and associated 95% confidence intervals will be computed by exponentiation of the corresponding means and 95% confidence limits calculated on the logarithmic scale. Titers below the limit of detection will be assigned values half of the lower limit. The percentages of subjects developing protective bactericidal titers of 1:4 or greater, or showing four-fold or greater increases in serum bactericidal activity, will be tabulated for each visit along with the respective 95% confidence intervals.

Safety. The frequency and percentage of subjects reporting serious adverse events, and severe local or systemic adverse events, or early withdrawal from study will be tabulated.

VI. HUMAN SUBJECTS

a) Subject Population:

13 adults, ages 18 to 55 years, will be immunized with the Trumenba vaccine. We will make an effort to include persons of different race (particularly African Americans) and both men and women. In our pilot study, we are interested in defining antibody responses of healthy persons with increased risk primarily from occupational exposure. Therefore persons at increased risk because of underlying diseases known to affect immune responses (such as sickle cell disease), or with complement deficiencies will be excluded. Pregnant women also will be excluded since the safety of the vaccine has not been established during pregnancy. Children <18 years of age will be excluded because this study focuses on responses of healthy adults at increased risk because of occupational exposure, currently the group with the greatest benefit from vaccination.

Study Title: Immunogenicity of a U.S.-licensed meningococcal serogroup B vaccine (Trumenba) in adults at increased risk of meningococcal disease because of occupational exposure.

Total Planned Enrollment: 13

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	2	1	3
Not Hispanic or Latino	5	5	9
Ethnic Category Total of All Subjects*	7	6	13
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	2	2	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	4	3	6
Racial Categories: Total of All Subjects *	7	6	13

*The “Ethnic Category Total of All Subjects” must be equal to the “Racial Categories Total of All Subjects.”

b) Sources of material:

Blood specimens from living human subjects. The material will be obtained specifically for research purposes.

c) Recruitment plans:

Subjects will be recruited from hospital employees and from medical students. Potential volunteers will have the study explained to them verbally by the study coordinator, research nurse or physician. If they express interest, they will be given an “informed consent form.” which will inform them further about the purpose of this study, what is known about the vaccine that will be administered, and the blood sampling procedures that will be done should they decide to enroll in the study. The form also will contain information on the risks and benefits of participating. They will be asked to read

this form carefully and ask questions before deciding to enroll. Prospective volunteers may take as much time as they like to make up their minds. They will be informed that participation is voluntary. Should they decide not to participate, they will be informed that they may receive the vaccine outside the study by going to their physician or employee health.

d) Potential risks:

Vaccine-related risks include local reactions such as erythema, induration, pain at injection site, which occur in up to 50% of subjects. Systemic reactions such as fever, chills, malaise nausea, headache, fatigue, myalgia or arthralgia occur in approximately 90% of immunized persons. These side effects are usually of mild severity and last less than 1 or 2 days and are similar to side effects experience with most vaccines. Blood drawing may cause some discomfort, local bruising, and rarely, infection. Some donors may experience transient light-headedness. The total volume of blood obtained over the six months duration of this study (<200 ml) is less than taken on one occasion during routine donation of a unit of blood at a blood bank.

e) Protection against risks:

Subjects will have a targeted physical examination performed and medical history to ensure that they are in good health. Subjects who meet all inclusion criteria and no exclusion criteria will have a 30 ml blood specimen obtained. They will then receive the immunization. Immunization will be repeated at months 2 and 6. Blood samples (75ml) will be obtained three to six weeks after doses 2 and 3. Optionally, a fourth blood sample (60 ml) will be obtained 7 to 10 days after dose 3. Should light-headedness occur during or immediately after blood drawing, subjects will be placed in a reclining position with legs elevated, and provided supplemental oral hydration, such as juice. The procedures will be performed in a facility designed for performing clinical studies by a licensed nurse or physician. Epinephrine will be available should anaphylaxis occur. These procedures should minimize risk of the study.

f) **Confidentiality of data** collected during the study will be protected. Consent forms, results of physical examinations and medical histories, will be maintained in a secure file cabinet within the PI's office. Identity of the subjects will not be revealed during presentations or publications of the results.

g) Potential benefits:

The vaccine confers protection against meningococcal disease caused by serogroup B strains and potentially also protects against some strains from serogroups A, C, Y and W. Serogroup B strains currently account for approximately 40% of cases of disease in the U.S.

The results will increase our understanding of the breadth of protection elicited by this new serogroup B vaccine and the functional basis of vaccine-induced anti-FHbp immunity to group B meningococci. The results could lead to better public health recommendations for use of the vaccine and, eventually, to better and safer vaccines. The data will establish whether there is a relationship between antibody functional activity ability of the anti-FHbp antibodies to either enhance or block hFH binding to the bacteria.

VII. NEED FOR THE PCRC

Use of the PCRC facilities to conduct research visits has been requested and tentative approval given.

PROJECTED USE TABLE	2014	2015	2016	2017	2018
Number of enrolled subjects per year		13			
Number of completed subjects per year		13			
Total inpatient days per year		0			
Total outpatient days per year		60 to 72			
Total scatter nurse visits per year		0			
Total scatterbed days per year		0			

Total Number of Subjects to be Enrolled 13

Total Number of Subjects to Complete Study 10-12

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IX. RELATED OTHER SUPPORT. None.

X. Appendix

A. Trumenba package insert