Phase I/II Study of Safety and Immunogenicity of Quadrivalent Meningococcal Conjugate Vaccine in HIV-Infected Children and Youth (Versions 1.0 – 3.0)

And

Open Label Immunogenicity Study of a Booster Dose of MCV4 in Previously Immunized HIV-Infected Children and Youth (Version 4.0)

A Multicenter Domestic Trial of the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network

This file contains the current IMPAACT P1065 protocol, which is comprised of the following documents, presented in reverse chronological order:

- Clarification Memorandum #1, dated 2 September 2011
- Letter of Amendment #1, dated 20 December 2010
- Protocol Version 4.0, dated 24 November 2010
To: IMPAACT Principal Investigators and Study Coordinators at Sites Participating in IMPAACT P1065 Version 4.0

From: IMPAACT P1065 Protocol Team

Date: September 2, 2011

Re: Clarification Memo #1 for Protocol P1065, “Phase I/II Study of Safety and Immunogenicity of Quadrivalent Meningococcal Conjugate Vaccine in HIV-Infected Children and Youth (Versions 1.0 – 3.0)” And “Open Label Immunogenicity Study of a Booster Dose of MCV4 in Previously Immunized HIV-Infected Children and Youth (Version 4.0),” Version 4.0, dated November 24, 2010

This Clarification Memo is being re-issued to correct the equivalent number of days for the eligibility window. The number of days should be 1,460 and not 1,490.

This is Clarification Memo #1 for IMPAACT P1065, Version 4.0, dated November 24, 2010. This Memo can be obtained from the [P1065] Protocol Specific Web Page (PSWP) tab on the IMPAACT web site https://impaactgroup.org/. Enter the Member/MIS area using your individual username and password. Search for the study number. From the protocol [P1065] web page you will have the option to click the PSWP tab. The document is located under the section titled Current Version - 4.0, Dated 11/24/2010.

The purpose of this memo is to clarify three points:

1. As stated in Letter of Amendment #1 dated December 20, 2010, the eligibility window for entry into P1065 Version 4.0 (Step 3) is 3 ½ years ± 6 months from the first dose of MCV4 in a previous version of P1065.

The equivalent in number of days for the eligibility window is 1,460 days from the first dose of MCV4 in a previous version of P1065.

Since this is an eligibility criterion for Step 3, the protocol Team is not authorized to allow any exceptions to this window.

2. CRF completion guidelines for Step 3:
   - Diagnoses, signs and symptoms that occurred within 90 days of entry into Step 3 should be reported in the CRF (i.e. PE6850 and PE6830). If there was a diagnosis, sign or symptom that was ongoing at the Week 72 visit, it should be reported in Step 3 and a stop date should be entered if applicable.
   - All concomitant medications taken within 90 days of entry into Step 3 should be reported in the CRF (i.e. PE0411). If a concomitant medication


was ongoing at the Week 72 visit, it should be reported in Step 3 and a stop date should be entered if applicable.

- All antiretroviral medications taken from the time the subject completed the Week 72 visit up to entry into Step 3 should be reported in the CRF (i.e. PE0420).

3. The designated laboratory address in Appendix III, Immunology Collection and Shipping Instructions, has been updated. The new address is:

Sanofi Pasteur
Attention: James Stoback
Global Clinical Immunology
Building 53
Discovery Drive
Swiftwater, PA 18370-0187

This clarification will be included in the next version of the protocol when it is amended. Please contact the protocol team at actg.teamp1065@fstrf.org if you have any questions.

Thank you for your participation in IMPAACT P1065.
TO: IMPAACT Principal Investigators & Study Coordinators at Sites Participating in P1065 Version 4.0

FROM: P1065 Protocol Team

DATE: December 20, 2010

RE: Letter of Amendment #1 for Protocol P1065, “Phase I/II Study of Safety and Immunogenicity of Quadrivalent Meningococcal Conjugate Vaccine in HIV-Infected Children and Youth (Versions 1.0 – 3.0)” And “Open Label Immunogenicity Study of a Booster Dose of MCV4 in Previously Immunized HIV-Infected Children and Youth (Version 4.0),” Version 4.0, dated November 24, 2010

IND #: BB 13340; DAIDS ES #: 10396

THE FOLLOWING INFORMATION IMPACTS THE P1065 STUDY AND MUST BE FORWARDED TO YOUR INSTITUTIONAL REVIEW BOARD (IRB)/ETHICS COMMITTEE (EC) AS SOON AS POSSIBLE FOR THEIR REVIEW. THIS LETTER OF AMENDMENT MUST BE APPROVED BY YOUR IRB/EC BEFORE IMPLEMENTATION.

THE FOLLOWING INFORMATION MAY IMPACT THE SAMPLE INFORMED CONSENT. YOUR IRB/EC WILL BE RESPONSIBLE FOR DETERMINING THE PROCESS OF INFORMING SUBJECTS OF THE CONTENTS OF THIS LETTER OF AMENDMENT.

UPON RECEIVING FINAL IRB/EC AND ANY OTHER APPLICABLE REGULATORY ENTITY (RE) APPROVAL(S) FOR THIS LOA, SITES SHOULD IMPLEMENT THE LOA IMMEDIATELY. SITES ARE STILL REQUIRED TO SUBMIT A LOA REGISTRATION PACKET TO THE DAIDS PROTOCOL REGISTRATION OFFICE (DAIDS PRO) AT THE REGULATORY SUPPORT CENTER (RSC). SITES WILL RECEIVE A REGISTRATION NOTIFICATION FOR THE LOA ONCE THE DAIDS PRO VERIFIES THAT ALL THE REQUIRED LOA REGISTRATION DOCUMENTS HAVE BEEN RECEIVED AND ARE COMPLETE. A LOA REGISTRATION NOTIFICATION FROM THE DAIDS PRO IS NOT REQUIRED PRIOR TO IMPLEMENTING THE LOA. A COPY OF THE DAIDS PRO LOA REGISTRATION NOTIFICATION ALONG WITH THIS LETTER AND ANY IRB/EC CORRESPONDENCE SHOULD BE RETAINED IN THE SITE’S REGULATORY FILES.

This Letter of Amendment can be obtained from the P1065 Protocol Specific Web Page (PSWP) tab on the IMPAACT web site https://impaactgroup.org/. Enter the Member/MIS area using your individual username and password. Search for the study number. From the protocol [P1065] web page you will have the option to click the PSWP tab. The document is located under the section titled Current Protocol Related Documents.

This Letter of Amendment serves to make the following changes:

1. The vaccine eligibility window for Version 4.0 has been changed from 3 years ± 6 months to 3 ½ years ± 6 months. This change applies to all sections of the protocol where the eligibility window is stated. The window stated in those sections should now be 3 ½ years ± 6 months.

2. Section 4.3, Inclusion Criteria for Step 3 (Version 4.0), has been updated to add the vaccine eligibility window. The added inclusion criterion is as follows:

   4.34 Subject must be within 3 ½ years ± 6 months from the first MCV4 dose received in a previous version of P1065.
3. In Appendix VI, Sample Informed Consent for Step 3 (Version 4.0), in the subsection “Why is this study being done?”, the first bullet in the list of the purposes of the study extension should be modified to read as follows:

To see how well the antibodies (substances the body makes in response to an infection or vaccination to help fight off disease) lasted 3 ½ years ± 6 months after the original dose of the vaccine

4. In Appendix III, Immunology Collection and Shipping Instructions, the contact numbers for the designated laboratory have been updated. The contact numbers should now be:

   Phone: (570) 957-3488, (570) 957-2850
   Fax: (570) 957-3013

This information will be added to the next version of the protocol. Please contact the protocol team at actg.teamp1065@fstrf.org if you have any questions or concerns about the information provided in this letter. Please file with your protocol documents.
IMPAACT P1065

Phase I/II Study of Safety and Immunogenicity of Quadrivalent Meningococcal Conjugate Vaccine in HIV-Infected Children and Youth (Versions 1.0 – 3.0)

And

Open Label Immunogenicity Study of a Booster Dose of MCV4 in Previously Immunized HIV-Infected Children and Youth (Version 4.0)

A Multicenter Center Domestic Trial of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)

Sponsored by:
The National Institute of Allergy and Infectious Diseases (NIAID)
and
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Pharmaceutical Support Provided by:
Sanofi Pasteur, Inc.

IND # BB-IND# 13340

IMPAACT Complications of HIV Scientific Committee Chair: Sharon A. Nachman, M.D.

Protocol Co-Chair: George K. Siberry, M.D., M.P.H.

Protocol Co-Chair: Jorge Lujan-Zilbermann, M.D., M.S.

DAIDS Medical Officer: Patrick Jean-Philippe, M.D.

NICHD Medical Officer: Jennifer S. Read, M.D., M.S., M.P.H., D.T.M.&H.

Clinical Trials Specialist: Jhoanna C. Roa, M.D.

Version 4.0
FINAL
November 24, 2010
IMPAACT P1065 PROTOCOL TEAM ROSTER

All questions concerning this protocol should be sent via e-mail to actg.teamp1065@fstrf.org. Remember to include the subject's PID when applicable. The appropriate team member will respond to questions via e-mail with a "cc" to actg.teamp1065@fstrf.org. A response should generally be received within 24 hours (Monday - Friday). For protocol registration questions, e-mail protocol@tech-res.com (301-897-1707). For EAE questions, e-mail rscesafetyoffice@tech-res.com or call 1-800-537-9979. To order study drug, call the Clinical Research Products Management Center at (301) 294-0741. For randomization or enrollment questions, call (716) 834-0900.

Protocol Co-Chair
George K. Siberry, M.D, M.P.H.
Medical Officer
Pediatric, Adolescent, and Maternal AIDS (PAMA) Branch
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
6100 Executive Boulevard, Room 4B11H
Bethesda, MD 20892-7510
Phone: 301-496-7350
Fax: 301-496-8678
e-mail: siberryg@mail.nih.gov

Protocol Co-Chair
Jorge Lujan-Zilbermann, M.D., M.S.
Associate Professor of Pediatrics
Division of Infectious Diseases, Department of Pediatrics
University of South Florida College of Medicine
17 Davis Boulevard, Suite 200, Room 223
Tampa, FL 33606
Phone: (813) 259-8800
Fax: (813) 259-8805
Email: jlujanzi@health.usf.edu

Protocol Vice-Chair
Sharon Nachman, M.D.
Professor of Pediatrics
Dept. of Pediatrics
HSC SUNY Stony Brook
Stony Brook, NY 11794-8111
Phone: (631) 444-7692
Fax: (631) 444-7292
Email: sharon.nachman@stonybrook.edu
Division of AIDS Medical Officer  
Patrick Jean-Philippe, M.D.  
Medical Officer  
Pediatric HIV Research Branch  
Therapeutic Research Program  
NIH/NIAID/DAIDS  
6700B Rockledge Drive, Room 5221  
Bethesda, MD 20892  
Phone: (301) 451-2760  
Fax: (301) 480-4582  
Email: jeanphilippep@niaid.nih.gov

Senior Statistician  
Paige L Williams, Ph.D.  
Senior Lecturer on Biostatistics and Senior Statistician  
Department of Biostatistics and Center for Biostatistics in AIDS Research  
655 Huntington Avenue  
Boston, MA 02115  
Phone: (617) 432-3872  
Fax: (617) 432-2832  
Email: paige@sdac.harvard.edu

NICHD Medical Officer  
Jennifer S. Read, M.D., M.S., M.P.H., D.T.M.&H.  
Pediatric, Adolescent, and Maternal AIDS (PAMA) Branch  
National Institute of Child Health and Human Development (NICHD)  
National Institutes of Health (NIH)  
Executive Building, Room 4B11C  
6100 Executive Boulevard MSC 7510  
Bethesda, MD 20892-7510  
Phone: (301) 435-6872  
Fax: (301) 496-8678  
Email: jennifer_read@NIH.GOV

Statistician  
Meredith Warshaw, M.A.  
Biostatistician II  
Center for Biostatistics in AIDS Research  
Harvard School of Public Health  
651 Huntington Avenue, FXB-547  
Boston, MA 02115  
Phone: (617) 432-2481  
Fax: (617) 432-3163  
Email: mwarshaw@sdac.harvard.edu

Clinical Trials Specialist  
Jhoanna C. Roa, M.D.  
IMPAACT Operations Office  
8757 Georgia Avenue  
Silver Spring, MD 20910  
Phone: (301) 628-3196  
Fax: (301) 628-3304  
Email: jroa@s-3.com

Protocol Data Manager  
Barbara Heckman, B.S.  
Frontier Science and Technology Research Foundation, Inc.  
4033 Maple Road  
Amherst, NY 14226-1056  
Phone: (716) 834-0900 x 7231  
Fax: (716) 834-8675  
E-mail: heckman.barbara@fstrf.org
Protocol Pharmacist
Katherine Shin, Pharm. D.
Pharmaceutical Affairs Branch
NIH, NIAID, DAIDS
6700-B Rockledge Drive, STE 4221
Bethesda, MD 20892-7624
Phone: (301) 496-8213
Fax: (301) 402-1506
Email: KaShin@niaid.nih.gov

Protocol Immunologist
Stephen A. Spector, M.D.
University of California, San Diego
Department of Pediatrics
Division of Infectious Diseases
Stein Clinical Research Bldg, Room 430
9500 Gilman Dr., Mail Code 0672
La Jolla, CA 92037-0672
Phone: (858) 534-7055
Fax: (858) 534-7111
Email: saspector@ucsd.edu

Laboratory Technologist
William B. Kabat, B.S.
Lab Manager
The Children's Memorial Hospital
Special Infectious Diseases Laboratory
2300 Children's Plaza, Box 20
Chicago, IL 60614-3394
Phone: (773) 880-4907
Fax: (773) 975-8795
Email: bkbabat@childrensmemorial.org

Laboratory Data Coordinator
Adam Manzella, M.A.
Lab Data Coordinator
Frontier Science and Technology Research Foundation, Inc.
4033 Maple Road
Amherst, NY 14226
Phone: (716) 834-0900 Ext. 7418
Fax: (716) 833-0655
Email: manzella@fstrf.org

Westat Clinical Research Associate
Scott Watson, R.N., B.S.
Westat Regional CRA
Phone: (415) 494-5575
Fax: (415) 859-9029
Email: scottwatson@westat.com

Pharmaceutical Company Representatives
Michael Decker, M.D., M.P.H.
Vice president
Scientific & Medical Affairs
Sanofi Pasteur Inc.
Discovery Drive
Swiftwater PA 18370
Phone: (570) 957-5018
Fax: (570) 957-2038
Email: Michael.Decker@sanofipasteur.com

David Johnson, M.D., M.P.H.
Senior Director
Scientific & Medical Affairs
Sanofi Pasteur Inc.
2 Avenue Pont Pasteur
Lyon, France 69007
Phone: +33 (4) 37 65 67 76
Fax: +33 (4) 37 37 71 71
Email: dr.johnson@sanofipasteur.com

Field Representative
Donna Picard, R.N.
Department of Pediatrics
Lawrence Family Health Center/UMASS
73D Winthrop Avenue
Lawrence, MA 01841-2884
Phone: (978) 689-6731
Fax: (978) 685-4280
Email: dpicard@glfhc.org
TABLE OF CONTENTS

SUMMARY OF CHANGES...........................................................................................................8
SCHEMA......................................................................................................................................13
1.0 INTRODUCTION ...................................................................................................................17
  1.1 Background.......................................................................................................................17
  1.2 Rationale ..........................................................................................................................29
  1.3 Rationale for Addition of Group 3 ..................................................................................31
  1.4 Background and Rationale for Step 3 (Version 4.0).........................................................33
2.0 STUDY OBJECTIVES...........................................................................................................35
  2.1 Primary Objectives (Groups 1 and 2)............................................................................35
  2.2 Primary Objectives (Group 3)........................................................................................35
  2.3 Primary Objectives (Groups 1 and 3 – Step 3).................................................................36
  2.4 Secondary Objectives (Groups 1 and 2).........................................................................36
  2.5 Secondary Objectives (Group 1 – Step 3).......................................................................36
3.0 STUDY DESIGN..................................................................................................................37
  3.1 Study Design for Steps 1 and 2 (Versions 1.0 – 3.0).........................................................37
  3.2 Study Design for Step 3 (Version 4.0)............................................................................38
4.0 SELECTION AND ENROLLMENT OF SUBJECTS............................................................39
  4.1 Inclusion Criteria for Step 1.............................................................................................39
  4.2 Inclusion Criteria for Step 2.............................................................................................40
  4.3 Inclusion Criteria for Step 3 (Version 4.0).......................................................................40
  4.4 Exclusion Criteria for Step 1..........................................................................................41
  4.5 Exclusion Criteria for Step 2..........................................................................................42
  4.6 Exclusion Criteria for Step 3 (Version 4.0).......................................................................43
  4.7 Disallowed Medications.................................................................................................46
  4.8 Enrollment Procedures ..................................................................................................46
  4.9 Co-Enrollment Guidelines .............................................................................................47
5.0 STUDY TREATMENT...........................................................................................................47
  5.1 Drug Regimens, Administration, and Duration...............................................................47
  5.2 Drug Formulation ............................................................................................................49
  5.3 Drug Supply, Distribution, and Pharmacy .......................................................................49
6.0 SUBJECT MANAGEMENT................................................................................................50
  6.1 Toxicity Management.......................................................................................................50
  6.2 Study Management Plan ...............................................................................................52
  6.3 Criteria for Deferral of Second Dose of Vaccine (Versions 1.0 – 3.0)............................53
  6.4 Criteria for Permanent Exclusion from Second Dose of Vaccine (Versions 1.0 – 3.0).......53
6.5 Criteria for Discontinuation from the Study .............................................................55

7.0 EXPEDITED ADVERSE EVENT REPORTING .............................................................55
7.1 Expedited Adverse Event Reporting to DAIDS .......................................................55
7.2 Reporting Requirements for this Study .....................................................................56
7.3 Grading of Severity of Events ..................................................................................56
7.4 Expedited AE Reporting Period ...............................................................................56

8.0 STATISTICAL CONSIDERATIONS .........................................................................56
8.1 General Design Issues ...............................................................................................56
8.2 Outcome Measures ...................................................................................................57
8.3 Randomization and Stratification (Versions 1.0 – 3.0) .............................................58
8.4 Sample Size and Accrual (Groups 1 and 2) ................................................................58
8.5 Sample Size and Accrual (Group 3) .........................................................................61
8.6 Sample Size and Accrual (Step 3 – Version 4.0) ....................................................62
8.7 Monitoring ...............................................................................................................63
8.8 Analysis ....................................................................................................................66

9.0 HUMAN SUBJECTS ..................................................................................................74
9.1 Institutional Review Board (IRB) Review and Informed Consent ..........................74
9.2 Subject Confidentiality .............................................................................................75
9.3 Disposition of Subject Specimens ............................................................................75
9.4 Study Discontinuation ..............................................................................................75

10.0 PUBLICATION OF RESEARCH FINDINGS ..........................................................76

11.0 BIOHAZARD CONTAINMENT ..............................................................................76

12.0 REFERENCES ..........................................................................................................77
APPENDICES

I. SCHEDULE OF EVALUATIONS

IA – SCHEDULE OF EVALUATIONS FOR STEPS 1 AND 2 (VERSIONS 1.0 – 3.0)

IB – SCHEDULE OF EVALUATIONS FOR STEP 3 (VERSION 4.0)

II. GENETICS STORAGE SPECIMEN COLLECTION AND SHIPPING INSTRUCTIONS

III. IMMUNOLOGY COLLECTION AND SHIPPING INSTRUCTIONS

IV. DAIDS IMPAACT SAMPLE INFORMED CONSENT TEMPLATE: GROUPS 1 AND 2 (≥11 – <25 YEAR OLDS)

V. DAIDS IMPAACT SAMPLE INFORMED CONSENT TEMPLATE: GROUP 3 (≥2 to <11 YEAR OLDS)

VI. DAIDS IMPAACT SAMPLE INFORMED CONSENT TEMPLATE: STEP 3 (VERSION 4.0)

VII. FACT SHEET AND TEMPLATE CONSENT FORM FOR SPECIMEN STORAGE AT REPOSITORIES FUNDED BY THE NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD) – PARENT FACT SHEET

VIII. FACT SHEET AND TEMPLATE CONSENT FORM FOR SPECIMEN STORAGE AT THE REPOSITORY OF THE NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD) – YOUTH FACT SHEET
SUMMARY OF CHANGES

P1065

Phase I/II Study of Safety and Immunogenicity of Quadrivalent Meningococcal Conjugate Vaccine in HIV-Infected Children and Youth (Versions 1.0 – 3.0)
And
Open Label Immunogenicity Study of a Booster Dose of MCV4 in Previously Immunized HIV-Infected Children and Youth (Version 4.0)

All changes in this version appear in boldface type. Major changes are listed below. Editorial changes, corrections of typographical errors, and other changes required to update information that do not affect regulatory issues or patient consent may also be included.

Please note that all references to Step 3 correspond to Version 4.0 of the protocol.

1. The title has been updated for Version 4.0.
2. The phone number to be used for protocol registration questions and the email address to be used for EAE questions has been updated.
3. The protocol team roster has been updated.
4. The Table of Contents has been updated.
5. The Schema now includes Step 3 (Version 4.0) in the title, design, sample size, population, regimen, study duration, primary objectives and secondary objectives.
6. Section 1.17, Safety of Meningococcal Vaccines, has been updated to include new information on GBS and MCV4.
7. Section 1.187, Meningococcal conjugate vaccine in HIV-infected patients, has been updated to add new information obtained from this study.
8. Section 1.3, Rationale for Addition of Group 3, has been updated to replace “Cohort” with “Group” in the title.
9. Section 1.4 has been added to provide the Background and Rationale for Step 3 (Version 4.0).
10. Section 2.3 has been added to provide the Primary Objectives for Step 3 (Version 4.0).
11. Section 2.5 has been added to provide the Secondary Objectives for Step 3 (Version 4.0).

12. Section 3.0, Study Design, has been subdivided into 2 subsections:
   - 3.1, Study Design for Steps 1 and 2 (Versions 1.0 – 3.0)
   - 3.2, subsection added for Study Design for Step 3 (Version 4.0)

13. Section 3.1 has been updated to specify Appendix IA as the Schedule of Evaluations for Steps 1 and 2 (Versions 1.0 – 3.0).

14. Item 4.21 has been updated to delete the words “for steps” between criteria and 4.15.

15. Section 4.3 has been added to include the Inclusion Criteria for Step 3 (Version 4.0).

16. Item 4.57 has been updated to correctly reference that the disallowed medications are listed in section 4.7.

17. Item 4.510 has been updated to add the phrase “inhaled, intranasal, or topical” before corticosteroid.

18. Section 4.6 has been added to include the Exclusion Criteria for Step 3 (Version 4.0).

19. Section 4.7, Disallowed Medications, has been updated to correctly reference items in section 4.4, Exclusion Criteria for Step 1.

20. Section 4.8, Enrollment Procedures, has been updated following the new protocol registration requirements of DAIDS.

21. Section 4.9, Co-Enrollment Guidelines, has been subdivided into: 4.91, Steps 1 and 2 (Versions 1.0 – 3.0) and 4.92, Step 3 (Version 4.0). The first section contains the guidelines for Steps 1 and 2 (Versions 1.0 – 3.0). The second section contains the guidelines for Step 3 (Version 4.0).

22. Section 5.11, Regimen, has been updated to include the study regimen for Step 3 (Version 4.0).

23. Section 5.13, Duration, has been updated to specify the duration for Steps 1 and 2. The Study Duration for Step 3 (Version 4.0) has also been added to this section.

24. Section 5.2, Drug Formulation, has been updated to change the name of the Regulatory Compliance Center to Regulatory Support Center and provide the new web address.

25. Section 6.1, Toxicity Management, has been updated as follows:
   a. Addition of vaccine adverse reactions evaluation for Step 3 (Version 4.0)
26. Section 6.2, Study Management Plan, has been updated to correctly reference the section 8.712 for the specific early stopping algorithm.

27. The title of section 6.3, Criteria for Deferral of Second Dose of Vaccine, has been updated to specify that the section applies to Versions 1.0 – 3.0.

28. The title of section 6.4, Criteria for Permanent Exclusion from Second Dose of Vaccine, has been updated to specify that the section applies to Versions 1.0 – 3.0.

29. Item 6.47 has been updated to correctly reference that the disallowed medications are listed in section 4.7.

30. Section 6.5, Criteria for Discontinuation from the Study, was updated to replace “T cell” with “Hematology” as one of the clinically ordered tests that will be used at Early Discontinuation. It has also been updated to reference Appendix IA and IB.

31. Section 7.1, Expedited Adverse Event Reporting to DAIDS, has been updated to the new Manual Version 2.0 for Expedited Reporting of Adverse Events and the DAIDS Adverse Experience Reporting System (DAERS).

32. Section 7.2, Reporting Requirements for this Study, has been updated following the new requirements of DAIDS for information on the protocol reporting requirements.

33. Section 7.3 has been added to provide the Grading of Severity of Events information following the new requirements of DAIDS.

34. Section 7.4 has been added to provide the Expedited AE Reporting Period following the new requirements of DAIDS.

35. Section 8.1, General Design Issues, has been updated to include the design issues related to Step 3 (Version 4.0).

36. Section 8.2, Outcome Measures, has been updated to include the outcome measures for Step 3 (Version 4.0).
37. The title of section 8.3, Randomization and Stratification, has been updated to specify that the section applies to Versions 1.0 – 3.0.

38. Section 8.6 has been added to provide the Sample Size and Accrual for Step 3 (Version 4.0).

39. Section 8.7, Accrual, has been updated as follows:
   a. Updated the title to specify that the section applies to Versions 1.0 – 3.0.
   b. Updated the table referenced in the 2nd paragraph, 1st sentence to Table 14.

40. Section 8.7, Safety, has been updated to include the safety endpoint evaluation for Step 3 (Version 4.0).

41. Section 8.7, Interim Monitoring by Independent Safety Monitoring Committee, has been updated to correctly reference Table 14.

42. Section 8.8, Analysis, has been added to include the analysis of the Primary Objectives for Step 3 (Version 4.0).

43. Item 8.8 has been corrected. The word “primary” in the 1st sentence has been replaced with the word “secondary”.

44. Section 8.8, Analysis, has been added to include the analysis of the Secondary Objectives for Step 3 (Version 4.0).

45. Section 9.1, Institutional Review Board (IRB) Review and Informed Consent, has been updated to list all the appendices that correspond to the informed consent documents.

46. Section 9.3, Disposition of Subject Specimens, was updated to include information that for the subjects who participate in Step 3 (Version 4.0) the blood samples left over after testing will be stored instead of being destroyed. The information also includes what the left-over stored samples will be used for.

47. Section 12.0, References, has been updated.

48. Appendix I, Schedule of Evaluations, has been updated and subdivided into:
   ▪ IA – Schedule of Evaluations for Steps 1 and 2 (Versions 1.0 – 3.0)
     The following additional updates were made to Appendix IA:
     1) Indicated as not to be used for Step 3, Version 4.0.
     2) The phrase “for the most current version of this document” was deleted from footnote 7 and added to footnote 6.
     3) Footnote 12 was updated to correctly reference Appendix II.
     4) Footnote 13 was updated to correctly reference Appendix III.
   ▪ IB – Schedule of Evaluations for Step 3 (Version 4.0)
49. Appendix II, Genetics Storage Specimen Collection and Shipping Instructions, has been updated to indicate that it should not be used for Group 1 in Step 3 (Version 4.0).

50. Appendix VI, Sample Informed Consent for Step 3 (Version 4.0), has been added.

51. Appendix VII, Fact Sheet and Template Consent Form For Specimen Storage at Repositories Funded by the National Institute of Child Health and Human Development (NICHD) – PARENT FACT SHEET, has been added.

52. Appendix VIII, Fact Sheet and Template Consent Form for Specimen Storage at the Repository of the National Institute of Child Health and Human Development (NICHD) – YOUTH FACT SHEET, has been added.
SCHEMA

PHASE I/II STUDY OF SAFETY AND IMMUNOGENICITY OF QUADRIVALENT MENINGOCOCCAL CONJUGATE VACCINE (MCV4) IN HIV-INFECTED CHILDREN AND YOUTH (VERSIONS 1.0 – 3.0)
And
OPEN LABEL IMMUNOGENICITY STUDY OF A BOOSTER DOSE OF MCV4 IN PREVIOUSLY IMMUNIZED HIV-INFECTED CHILDREN AND YOUTH (VERSION 4.0)

DESIGN:
Phase I/II, randomized – Ages ≥11 to <25 (Groups 1 and 2)
Phase I/II, open label – Ages ≥2 to <11 (Group 3)

STEP 1: Groups 1, 2 and 3: MCV4 vaccination
STEP 2: Group 1: Randomization to 1-dose or 2-dose arm
Groups 2 and 3: Second dose of MCV4
STEP 3: MCV4 booster dose to participants in Groups 1 and 3 of P1065 who meet inclusion criteria for Step 3 (Version 4.0)

SAMPLE SIZE:
Total of 352 subjects
[256 subjects in Group 1; 40 subjects in Group 2; 56 subjects in Group 3]

STEP 3 (VERSION 4.0): Total of 158 to 180 subjects from Group 1 who completed Version 2.0 of P1065 up to a maximum of 226 subjects and total of 34 to 40 subjects from Group 3 who completed Version 3.0 of P1065 up to a maximum of 49 subjects (see inclusion criteria)

POPULATION:
HIV-infected youth ≥11 to <25 years of age (Groups 1 and 2)
HIV-infected children ≥2 to <11 years of age (Group 3)

STEP 3 (VERSION 4.0): Subjects who were stratified into Group 1 at the time of entry in P1065 Version 2.0 or entered into Group 3 at the time of entry in P1065 Version 3.0

STRATIFICATION:
Subjects in groups 1 and 2 will be stratified by CD4 % at screening into 2 groups:

Group 1: CD4% ≥15, N=256 (closed to accrual)
Group 2 CD4% <15, N=40 (closed to accrual)
Subjects in group 3 will comprise those who have a screening CD4 $\geq 25\%$. At least 20% of Group 3 subjects must be in the $\geq 2$ to $<6$ year-old age range and at least 20% in the $\geq 6$ to $<11$ year-old age range.

Accrual to Group 1 will be stratified so that there are equal numbers of subjects with $15\% < \text{CD4}\% < 25\%$ and $\text{CD4}\% \geq 25\%$ (target of N=128 in each CD4\% stratum).

Randomization at Step 2 to one dose (Group 1A) vs. two doses (Group 1B) will occur in a 1:1 ratio within each of the two CD4\% strata.

**REGIMEN:** The Meningococcal Conjugate Vaccine (MCV4) will be administered to all subjects during the study entry visit as a single intramuscular dose of 0.5 mL. Study Groups 1B, 2 and 3 will also receive a second dose 24 weeks after the initial dose.

**Subjects participating in Step 3 (Version 4.0) will be administered a single intramuscular dose of MCV4 at study entry (3 years +/- 6 months post first MCV4 dose in a previous version of P1065).**

**STUDY DURATION:** Subjects will be followed on study for 72 weeks.

**Subjects participating in Step 3 (Version 4.0) will be followed on study for 6 months post vaccination.**

**PRIMARY OBJECTIVES (Groups 1 and 2):**

1) To estimate the immunogenic response to MCV4 after two doses of MCV4, where an immunogenic response is defined as a 4-fold or greater increase in serum bactericidal antibody titers at Week 28 compared to baseline;

2) To estimate the short-term (4 and 24 weeks) immunogenicity of the MCV4 vaccine in HIV-1 infected youth for those in Group 1 (CD4\% $\geq 15$);

3) To estimate the long-term (at 72 weeks) immunogenicity of the MCV4 vaccine in HIV-1 infected youth;

4) To evaluate the safety of the MCV4 vaccine in HIV-1 infected youth, including short-term local and systemic reactions following each administration of the vaccine.
PRINCIPAL OBJECTIVES (Group 3)

1) To estimate the immunogenic response to MCV4 in HIV-1 infected ≥2 to <11 year old children with CD4% ≥ 25, after two doses of MCV4, where an immunogenic response is defined as a 4-fold or greater increase in serum bactericidal antibody titers at Week 28 compared to baseline;

2) To estimate the short-term (4 and 24 weeks) immunogenicity of the MCV4 vaccine in HIV-1 infected ≥2 to <11 year old children with CD4% ≥ 25;

3) To estimate the long-term (at 72 weeks) immunogenicity of 2 doses of the MCV4 vaccine in HIV-1 infected ≥2 to <11 year old children with CD4% ≥ 25;

4) To evaluate the safety of a two-dose series of MCV4 in HIV-1 infected ≥2 to <11 year old children with CD4% ≥ 25.

PRINCIPAL OBJECTIVES (Groups 1 and 3 – Step 3):

1) To assess the level of protective antibody titers (rSBA ≥ 1:128) 3 years +/- 6 months post-initial immunization with MCV4.

2) To estimate the proportion of subjects who have evidence of immunologic memory (7-8 days) to a booster dose of MCV4 3 years +/- 6 months after initial immunization with MCV4.

3) To estimate the rates of immunologic primary response (4 weeks) to a booster dose of MCV4 3 years +/- 6 months after initial immunization with MCV4 in children who lack evidence of immunologic memory to the initial immunization.

4) To estimate the short-term (4 and 24 weeks) immunogenicity of the booster dose of MCV4.

SECONDARY OBJECTIVES (Groups 1 and 2):

1) To examine whether the short and long-term immunogenicity of the MCV4 in HIV-1 infected youth varies as a function of the study subjects’ immune status at the time of vaccination;

2) To compare the long-term immunogenicity (at 72 weeks) of the MCV4 in HIV-1 infected youth between a 1-dose vs. 2-dose regimen for those in Group 1 (CD4% ≥ 15);

3) To evaluate whether the safety of the MCV4 vaccine varies by immune status based on CD4% at the time of vaccination;
4) To evaluate whether, in subjects with CD4% < 15%, 2 doses of MCV4 can produce an immunogenic response (defined as a 4-fold or greater increase in serum bactericidal antibody titers reaching at least 1:8);

5) To identify host genetic determinants of immunity that may affect the response to MCV4.

SECONDARY OBJECTIVES (Group 1 – Step 3):

1) To compare long-term (3 years +/- 6 months) antibody levels as evidence of long-term immunogenicity to 1 dose vs. 2 doses of meningococcal conjugate vaccine.

2) To compare rates of immunologic memory response 7-8 days after a booster dose of MCV4 between HIV-infected youth who have previously received 1 dose vs. 2 doses of MCV4.

3) To compare rates of immunologic response 4 weeks after a booster dose of MCV4 between HIV-infected youth who have previously received 1 dose vs. 2 doses of MCV4.

4) To compare the short-term (4 and 24 weeks) immunogenicity of the booster dose of MCV4 between HIV-infected youth who have previously received 1 dose vs. 2 doses of MCV4.

5) To evaluate the safety of the booster dose of MCV4.
1.0 INTRODUCTION

1.1 Background

1.11 Meningococcus and its epidemiology

*Neisseria meningitidis* (meningococcus) is a non-motile, Gram negative coccus. To date 13 different serogroups of meningococci have been identified. The antigen responsible for serogroup specificity is the capsular polysaccharide. Only five serogroups (A, B, C, Y, and W-135) cause nearly all human disease.

*N. meningitidis* causes two major clinical syndromes, meningitis and sepsis/meningococcemia in previously healthy people. The mortality rate due to meningococcal disease overall is 7 to 19%, and for meningococcemia, 18-53%. Despite susceptibility of *N. meningitidis* to many antibiotics, approximately 10-20% of individuals with meningococcal disease experience permanent sequelae (e.g. limb loss, neurosensory hearing loss, cognitive deficits, seizure disorder).

The highest rate of meningococcal disease in the United States occurs in children younger than one year of age, but individuals 15-24 years also represent a high risk group. Centers for Disease Control and Prevention (CDC) surveillance has reported a fatality rate of 14% for patients with meningococcal disease in this age group. *N. meningitidis* is now the most common cause of bacterial meningitis among adolescents and young adults in the US. Large epidemics of serogroup A disease continue to occur in many developing countries, including the “meningitis belt” of sub-Saharan nations that have also been hit hard by the HIV worldwide epidemic. Students going to live in college dormitories for the first time are at particularly increased risk. In addition, there is an increased risk of invasive meningococcal disease in people with functional or anatomical asplenia, terminal complement deficiency, properdin deficiency and in travelers to high risk geographic areas (“meningitis belt”).

Immunization against meningococcal disease using a recently licensed tetravalent meningococcal conjugate vaccine has been recommended by the CDC Advisory Committee on Immunization Practices (ACIP) for members of these high risk groups who are 11-55 years old as well as for healthy adolescents.
1.12 Meningococcal disease in HIV-infected patients

HIV infection can lead to T-cell dependent B-cell dysfunction which increases the risk of invasive disease due to encapsulated organisms, such as pneumococcus. This immune dysfunction may increase the risk of invasive meningococcal disease in HIV-infected patients as well, but few cases have been reported.(7-11) In a case-control study during a meningococcal A outbreak in Uganda, the prevalence of HIV infection was no more common among meningococcal cases than a cohort of pregnant women selected as controls.(10) In a retrospective cohort study of a population of 2900 HIV-infected patients followed over 10 years in London(9) , only two cases of invasive meningococcal disease were identified, but this annualized rate of 6.9/100,000 was substantially higher than population-based studies of meningococcal disease in similar areas. In a population-based study of invasive meningococcal disease in Atlanta, Georgia(11), there was, as expected, a higher annual rate of disease among 18-24 years old (1.17 per 100,000) compared to that of all adults (0.5 per 100,000), but the estimated annual rate among HIV-infected adults was substantially higher (11.2 per 100,000). These data are suggestive but not definitive of an increased risk of invasive meningococcal disease in HIV-infected populations.

1.13 Meningococcal conjugate vaccine

The tetravalent meningococcal polysaccharide-protein conjugate vaccine (MCV4) is a meningococcal polysaccharide diphtheria toxoid conjugate vaccine. The vaccine contains Neisseria meningitidis serogroup A, C, Y, and W-135 capsular polysaccharide antigens individually conjugated to diphtheria toxoid protein. The vaccine is administered intramuscularly. The four meningococcal components, present as individual serogroup-specific glycoconjugates, compose the final formulated vaccine. No preservative or adjuvant is added during the manufacturing process. The vaccine is manufactured as a sterile, clear to slightly turbid liquid. Each 0.5 mL dose of vaccine is formulated in sodium phosphate buffered isotonic sodium chloride solution to contain 4 μg each of meningococcal A, C, Y, and W-135 polysaccharides conjugated to approximately 48 μg of diphtheria toxoid protein carrier. MCV4 is available only in single-dose vials.(12)(13)

The vaccine was approved by the FDA on January 18, 2005. The meningococcal work group of the ACIP has made a recommendation that adolescents 11-12 years of age receive the vaccine at their
preadolescent physician visit. ACIP’s final recommendations also included vaccination of adolescents at approximately 15 years of age (high-school entry), and incoming college freshmen living in dormitories. By 2008, ACIP’s goal will be routine vaccination with MCV4 of all adolescents beginning at age 11 years.(6)

Immunization against meningococcal disease using MCV4 has been recommended by the CDC ACIP for:

1) Young adolescents (defined as persons aged 11-12 years);
2) Before high-school entry (at approximately age 15 years) for those adolescents who have not previously received MCV4;
3) College freshmen living in dormitories;
4) Microbiologists who are routinely exposed to isolates of *N. meningitidis*;
5) Military recruits;
6) Persons who travel to or reside in countries in which *N. meningitidis* is hyperendemic or epidemic, particularly if contact with the local population will be prolonged;
7) Persons who have terminal complement component deficiencies; and
8) Persons who have anatomic or functional asplenia.

1.14 Correlates of protection against invasive meningococcal disease

While the reference standard for evidence of protection against invasive meningococcal disease caused by serogroup C was demonstration of titers ≥4 using a serum bactericidal antibody assay in which human sera are used as the exogenous complement source (hSBA), limited availability of human sera for the assay has led to substitution of baby rabbit sera as the exogenous complement source (rSBA). rSBA is considered the standard correlate of clinical protection against serogroup C meningococcal disease by the World Health Organization,(14) and rSBA titers of < 8 have been proposed to be predictive of susceptibility to invasive meningococcal disease. rSBA titers ≥1:128 have been found to be highly predictive of protection, but the range of 1:8-1:64 were equivocal.(15) Based on additional analyses, rSBA titers of ≥ 8 have been proposed to correlate with short-term protection.(6) During an outbreak of serogroup C infection in a university setting, for instance, all infected students had rSBA titers of <4.(16)

A fourfold rise in rSBA titers pre- to post-vaccination has been proposed as a correlate of protection, particularly for those cases in
which rSBA titer falls in the equivocal range of 1:8-1:64. (15) This four-fold rise in rSBA was the principal immunogenicity outcome measure used for the trial of MCV4 in healthy 11-18 year olds (17), used as the basis for licensure of MCV4 in the US for this age group [see below]. No direct efficacy measures of this vaccine were used for the basis of licensure. Monovalent (serogroup C) meningococcal conjugate vaccines (MenC) were first licensed in the United Kingdom on the basis of their ability to induce serum bactericidal activity as a correlate of efficacy without explicit efficacy data. (15) A reduction in the incidence of bacterial meningitis caused by serogroup C was observed in the United Kingdom after immunization campaigns with MenC were introduced. (18) Based on these data, we would propose using 4-fold rise in rSBA titers to serogroup C as the primary measure upon which sample size for studying immunogenicity should be calculated.

1.15 Host genetic determinants of *Neisseria meningitidis* infections

Complement deficiencies and defects in opsonophagocytic pathways including Toll-like receptor-4 (TLR4) single nucleotide polymorphisms (SNPs) and combinations of Fcγ-receptor polymorphisms have been associated with susceptibility to meningococcal disease. (19) Severe meningococcal disease has been associated with FcγRIIa and plasminogen activator inhibitor type 1 (PAI1) variants. Survival from meningococcal disease has been associated with SNPs in properdin, PAI1, interleukin-1β and interleukin-RN and variably in TNF-α. There are no data as to whether these genetic variants alter the response to meningococcal vaccines as detected by antibody response or to the ultimate failure in specific vaccine recipients. Thus, we will examine those genetic variants that have the highest probability of altering the immune response to the MCV4 vaccine. These genetic variants occur at sufficiently high frequencies (see Table 1) to be detected in a study of this size.
Table 1: Gene Allelic Frequencies Associated with Immune Response to Meningococcal Disease

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genetic variations</th>
<th>wt allele frequency</th>
<th>variant allele frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin (IL)-1</td>
<td><em>IL1B</em> (-511)-C/T</td>
<td>C = 0.67</td>
<td>T = 0.33</td>
</tr>
<tr>
<td><em>IL1RN</em></td>
<td><em>IL1RN</em> (+2018)-C/T</td>
<td>C = 0.70</td>
<td>T = 0.30</td>
</tr>
<tr>
<td>IL-1RN VNTR</td>
<td><em>IL1RN</em>-1/2 repeats</td>
<td>1 = 0.70</td>
<td>2 = 0.30</td>
</tr>
<tr>
<td>IL-6</td>
<td>G</td>
<td>G-6 -174 C</td>
<td>G = 0.57</td>
</tr>
<tr>
<td>IL-10</td>
<td>IL</td>
<td>10-1082-G/A</td>
<td>G = 0.55</td>
</tr>
<tr>
<td>TNF-α</td>
<td>-308-G/A</td>
<td>G = 0.52</td>
<td>A = 0.48</td>
</tr>
<tr>
<td>-238-G/A</td>
<td>G = 0.94</td>
<td>A = 0.06</td>
<td></td>
</tr>
<tr>
<td>Fc gamma receptor type RIIA</td>
<td>arginine (R) or a histidine (H) at position 131 aa</td>
<td>R = 0.52</td>
<td>H = 0.48</td>
</tr>
</tbody>
</table>

1.16 Safety and immunogenicity trial of MCV4 vs. MPSV4 in healthy youth

The randomized controlled trial conducted among persons aged 11-18 years by Keyserling et al.(17) compared immunogenicity of MCV4 with that of MPSV4 at 28 days post-vaccination. A similar percentage of subjects achieved at least a fourfold rise in rSBA titers in both groups (Table 2).

Table 2: Comparison of bactericidal antibody responses to MCV4 and MPSV4 28 days post-vaccination in participants 11-18 years of age

<table>
<thead>
<tr>
<th>Serogroup</th>
<th>Fourfold or greater increase in rSBA titer</th>
<th>rSBA geometric mean titer ≥128</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>MCV4 %</td>
<td>MPSV4 %</td>
</tr>
<tr>
<td>C</td>
<td>92.7</td>
<td>92.4</td>
</tr>
<tr>
<td>Y</td>
<td>91.7</td>
<td>88.7</td>
</tr>
<tr>
<td>W-135</td>
<td>81.8</td>
<td>80.1</td>
</tr>
<tr>
<td></td>
<td>96.7</td>
<td>95.3</td>
</tr>
</tbody>
</table>
This trial performed at 11 sites in the US compared the tolerability, immunogenicity, and immune memory of MCV4 with those of MPSV4. Both vaccines were highly immunogenic after initial vaccination; similar proportions of participants had four-fold or greater increases in rSBA titers, range 80 – 97%, to the four serogroups. When only those participants with baseline rSBA titers <1:8 were included, 98-100% of MCV4 recipients and 99-100% of MPSV4 recipients demonstrated a four-fold increase in rSBA titer at 28 days (though detailed data about baseline rRBA titers were not provided). Overall, more than 98.5-100% of all participants had titers of 128 or more against all four serogroups after the initial vaccination. At three years of follow-up the percentage of participants with SBA titers >128 ranged from 71-95% for the MCV4 group and from 57-83% for the MPSV4 group.

A subgroup of study participants in this study received a dose of MCV4 vaccine 3 years after the initial vaccination with MCV4 or MPSV4. Among all those adolescents who received the 3-year dose of MCV4, those adolescents who initially received MCV4 exhibited higher geometric mean bactericidal titers and higher rates of protective SBA titers (≥128) to all vaccine serotypes compared with those who had initially received MPSV4. In addition, the finding of a peak, robust antibody response at 8 days after the second vaccine dose was suggestive of high-avidity antibody response seen in booster responses. Thus, a second dose of MCV4 appeared to be safe and produced an apparent anamnestic response with rapid rise to protective antibody levels in these healthy youth.

No patients with any type of immunodeficiency were included in these trials. There were also low numbers of persons of color in any of these trials. Thus, we have no specific data about whether the response rates in youth of color would be equivalent or potentially lower than those in white youth, and will not be able to distinguish whether lower response rates in the proposed study will be due to HIV-related factors or due to ethnic/genetic differences.

1.17 Safety of meningococcal vaccines

Adverse events in vaccine trials: Among persons aged 11-18 years, safety of MCV4 and MPSV4 was assessed in two randomized controlled trials. The percentage of subjects reporting systemic adverse events was similar for persons who received either vaccine. Fever was reported by 5.1% of those who received MCV4 and 3% of those who received MPSV4. Local adverse reactions were more
common among those persons who received MCV4 than among those who received MPSV4; 13% of those who received MCV4 reported pain that limited movement in the arm of injection, compared with 3% of those who received MPSV4. These differences in frequency of local reactions have been attributed to the amount of diphtheria toxin contained in MCV4 vaccine. The frequency of local adverse reactions reported after MCV4 was similar to that reported after Td vaccine.

Serious adverse events reported within a 24 week period after vaccination occurred at the same rate in both groups and were consistent with events expected among healthy adolescents. (12) (13) Because the stopper of the MCV4 vaccine vial contains dry natural rubber latex, patients with hypersensitivity to latex were excluded from receiving the vaccine.

Potential adverse effect of repeated doses of MCV4 vaccine: Among those healthy youth who received a dose of MCV4 three years after initial vaccination with MCV4 or MPSV4 (17), there was no reported increase in adverse events and there was no evidence of antibody hyporesponsiveness following the second vaccine dose. The lack of antibody hyporesponsiveness is in agreement with the results of previous studies of conjugated meningococcal C vaccine in subjects who had previously received MPSV4, (20;21) and different from the antibody hyporesponsiveness observed in some studies of repeated doses of MPSV4. (21) There does not appear to be any evidence that 2 doses of MCV4 or a vaccination with MCV4 in healthy subjects who have received MPSV4 in the past results in decreases in meningococcal antibody titers.

Guillain-Barré Syndrome (GBS): On October 4, 2005, the Vaccine Adverse Event Reporting System (VAERS) received five reports of GBS in persons after receipt of MCV4 vaccination. All reported GBS cases occurred among persons aged 17 to 18 years who were vaccinated during June 10 through July 25 and had symptom onset 14 to 31 days after MCV4 vaccination. One patient reported another acute illness before onset of neurological symptoms. The five patients received vaccine from four different lots. These cases were reported from Pennsylvania (two), and one case each from New York, Ohio, and New Jersey. (13) In follow up publications, the total number of reported cases of GBS occurring within 6 weeks of MCV4 vaccination through September 2006 was seventeen. (22) At the Advisory Committee on Immunization Practices (ACIP) Meeting of January 2007 it was mentioned that two new cases of GBS within 6 weeks of MCV4 vaccination had been reported, bringing the total up to 19
At the June 2010 ACIP meeting, results of a Harvard Medical School/Harvard Pilgrim Healthcare study of almost 12.6 million 11-21 year-olds were presented: No cases of GBS occurred within 6 weeks of in any of the 1.4 million participants who received MCV4 (Menactra) doses, leading the ACIP to vote to remove precautionary language about GBS from its MCV4 vaccine statement. (23)

Preliminary studies conducted by Sanofi Pasteur of approximately 7,000 recipients of MCV4 revealed no GBS cases. CDC has conducted a rapid survey by using available Vaccine Safety Datalink (VSD) and other health-care organization databases. No cases of GBS have been detected among nearly 110,000 MCV4 recipients represented in these databases. Data from two VSD sites indicated that 86% to 97% of vaccine recipients had 6 weeks of follow-up via automated data collection. Subsequent CDC analyses of data from VAERS and the VSD, which includes all 17 cases of GBS reported since June 2005, suggest a small increased risk for GBS after MCV4 vaccination, but the CDC authors recommend caution in interpreting these findings because of the inherent limitations of VAERS and the uncertainty regarding background incidence rates for GBS. With the knowledge of these 17 cases and this updated analysis, the CDC continued to recommend routine vaccination with MCV4 for adolescents, college freshmen living in dormitories, and other populations at increased risk. These data do not rule out an association between MCV4 and GBS. At the June 2010 meeting, ACIP voted to remove all precautionary language about GBS related to MCV4 in light of reassuring data from the large, Harvard/Pilgrim Health study.

To date, evidence is insufficient to conclude that MCV4 causes GBS. An ongoing known risk for serious meningococcal disease exists. Whether receipt of MCV4 vaccine might increase the risk for recurrence of GBS is unknown; the ACIP has recommended that persons with a history of GBS should not be vaccinated with MCV4 unless they are at elevated risk for meningococcal disease.

1.18 Immunizations in HIV infection

1.181 Primary response to vaccination in HIV Infection:

In addition to CD4+ T cell depletion and decreased cell-mediated immunity, subjects with HIV infection have impaired antibody responses to neoantigens, whether introduced by infectious agents or by vaccination.(24;25) Humoral immunity
often depends on CD4+ T cell help, but HIV also down regulates B cell function, with consequent decreased specific antibody production against T-dependent and independent antigens, defective class switch, and increased production of nonspecific antibodies.(26)

1.182 Immunogenicity of conjugate vaccines in HIV-infected children:

Conjugate vaccines are important in HIV-infected patients because they lead to a T-cell dependent response as opposed to a T-cell independent response when only the polysaccharide antigen is included in the vaccine. T-cell dependent response leads to the activation and formation of memory B cells a critical component of protective immunity against infection with encapsulated bacteria.

In theory, even in the absence of circulating antibody, an individual primed with a conjugate vaccine should be protected from infection because of an ability to produce an anamnestic response rapidly after subsequent contact with the cross-reacting antigen. Although this may be the case for vaccine recipients with an intact immune system, circulating specific antibody titers may be particularly important for HIV-infected patients in whom the anamnestic response is impaired.(27) This impairment is caused by a variety of factors including the reported loss of CD45RO positive memory.(28)

Reports of immunogenicity of the *Haemophilus influenzae* type b (Hib) conjugate vaccine in HIV-infected children vary. The percentage of HIV-infected children achieving titers of anti-Hib polysaccharide antibody of ≥ 1 µg/mL, a correlate of long-term protection varies between 46 and 88%. (27;29;30) HIV-infected children were also less likely to have persistent protective antibody titers of ≥ 1 µg/mL one year after immunization when compared to uninfected control children (57% vs. 89%, respectively).(27) One recent study from South Africa evaluated the effectiveness of Hib conjugate vaccine. Vaccine effectiveness was significantly reduced in HIV-infected children (44%) when compared with uninfected children (97%).(30)

Several immunogenicity studies of pneumococcal conjugate vaccine have demonstrated lower antibody titers in HIV-
infected children compared to uninfected children. A study of heptavalent pneumococcal conjugate vaccine (PCV) in HIV-infected infants receiving HAART demonstrated no difference in antibody responses for all serotypes between asymptomatic and symptomatic patients. However, infants with symptomatic HIV disease seemed to be at higher risk for adverse events. These severe adverse events included severe induration, erythema, limited leg movement, high-pitched crying, and fever. Infants were vaccinated with three doses at 8 week intervals starting at 2 months of age. The majority of HIV-infected children included in this study were receiving antiretroviral therapy (ART) (82%) and pediatric subjects with AIDS were excluded.

In a South African study of nine-valent PCV, vaccination reduced the incidence of a first episode of invasive pneumococcal disease due to serotypes included in the vaccine by 65% among HIV-infected children and by 83% in uninfected children. However, HIV-infected children constituted eight of the eleven vaccine failures (73%). This study included all clinical categories of HIV infection and patients were immunized at 6, 10, and 14 weeks of age. A nested study of this nine-valent PCV that included only HIV-exposed infected and uninfected children revealed that although HIV-infected children have similar qualitative antibody responses their quantitative antibody responses were poorer. In children with acquired immunodeficiency syndrome (AIDS) the antibody concentrations were actually lower for five of the serotypes than in children who had asymptomatic or mildly asymptomatic HIV infection. HIV-infected PCV recipients were less likely to have measurable functional antibody to all three studied serotypes than HIV-uninfected children.

A Spanish study of antibody responses against three of the serotypes in the heptavalent PCV in children and adolescents with perinatal HIV infection showed that immune responses differed between serotypes. PCV elicited a significant quantitative and qualitative increase in antibody response.

1.183 Other vaccines in HIV-infected children:

Other studies have demonstrated that other routine immunizations including measles, varicella(36), and hepatitis
A (37) are immunogenic and well tolerated in HIV-infected patients, though immunogenicity is less reliable in patients with more advanced immunosuppression. (31) Both CD4 and viral load seem to be independent predictors of response to vaccination. Data from PACTG 1024 suggests that subjects with <15% CD4 responded poorly to conjugate vaccines. (38) In PACTG 1008 study of Hepatitis A vaccine (HAVV) in HIV+ children with CD4 ≥ 20%, low HIV replication strongly correlated with robust responses to primary immunization.

HIV-infected children with CD4 ≥ 20% responded better to primary HAVV immunization if they had undetectable HIV RNA. The standard 2-dose HAVV regimen generated low responses with limited persistence of protective titers. A 3rd dose of HAVV was safe and increased the antibody titers suggesting that boosted immunization schedules may be warranted in this population (37), similar to the data for pneumococcal conjugate vaccine. Predictors of response included higher antibody concentration at entry, higher immune stratum (based on nadir CD4% prior to HAART and CD4% at screening), lower viral RNA, longer duration of the entry HAART regimen, and age <7 years. Response was more consistently correlated to screening CD4% than nadir CD4%. (39)

1.184 Use of additional doses of vaccines in HIV-infected children:

In PACTG protocol 265, 41 susceptible children with at least CD4% ≥ 25% were immunized with the varicella vaccine. Even after two doses, only 60% of the children had anti-varicella antibodies and 83% had lymphoproliferative responses to varicella antigen. (36) Based on this experience, the CDC recommended that HIV-infected children receive two doses of the varicella vaccine instead of the single dose recommended in the routine immunization schedule at that time.

A recent study of hepatitis A virus vaccine in HIV-infected children demonstrated that the standard 2-dose immunization regimen generated low antibody titers that lasted for shorter periods of time. A third vaccine dose was safe and raised the antibody titers, suggesting that additional immunizations may be helpful in this patient population. (37)
The standard three dose regimen of hepatitis B virus vaccine (HBVV) in HIV-infected children has been associated with low seroconversion rates (only 35-45%), and a more rapid serum antibody decline. These investigators have suggested that increasing the dose and frequency of this vaccine may improve the response in immunodeficient children.(40;41) In a study of HIV-infected adults, giving an additional three doses of HBVV at a dose 20 mcg improved the response rate from 55% to 78%.(42)

1.185 Immunogenicity of conjugate vaccines in HIV-infected adults:

A study of HIV-infected adults receiving a tetravalent PCV showed that individuals with low CD4 counts (≤ 200 X 10^6/l) have an impaired antibody response upon vaccination compared with HIV-infected individuals with higher CD4 counts and healthy controls.(43) Higher pneumococcal antibody concentrations were achieved in HIV-infected individuals after sequential vaccination with PCV and 23-valent pneumococcal polysaccharide vaccine (PPSV) compared with PPSV vaccination alone.

In a double-blinded, randomized trial, HIV-infected adults with ≥200 CD4 cells/µl received placebo, heptavalent PCV or PPSV in one of two-combinations given 8-weeks apart: PCV-PCV, PCV-PPSV, placebo-PPSV, and placebo-placebo. Persons receiving the first two combinations had higher antibody concentrations and opsonophagocytic titers after the second dose when compared to persons receiving placebo-PPSV. However the second dose with either PCV or PPSV following the first PCV dose produced no further increase in immune response.(44) An apparently nonefficient booster immune response occurs in these patients. The Spanish study had similar findings among children and adolescents.(35)

1.186 Meningococcal polysaccharide vaccine in HIV-infected patients:

There are very limited data about antibody response to MPSV4 in HIV-infected patients, and there are no published reports about immunogenicity or efficacy of MCV4 in HIV-infected patients. In one study, 15/21 (71%) of young HIV-infected adults developed a 4-fold increase or 1:1024 titer of antibody to serotype C after a single injection of MPSV4.(45) The
probability of responding was not greater for patients with higher CD4 counts in this small study. Also MPSV4 has inherent limitations. It is poorly immunogenic among children <2 years of age, it does not confer long-lasting immunity, it does not cause a sustainable reduction of nasopharyngeal carriage of *N. meningitidis* and therefore does not substantially interrupt transmission to elicit herd immunity.(6)

1.187 Meningococcal conjugate vaccine in HIV-infected patients

Patients with HIV infection are likely at increased risk for meningococcal disease, although not to the extent that they are at risk for invasive pneumococcal infection. Although the efficacy of MCV4 among HIV-infected patients is unknown, HIV infection is not a contraindication to receiving MCV4 and patients may elect vaccination.(6;46) However, most HIV-infected patients in the United States are at least 11 years old and would therefore be eligible to be immunized with MCV4 on the basis of their age (PACTG 219-C database and ATN Managerial Database March, 2003). Data from this study (P1065) have demonstrated that MCV4 appears to be safe for HIV-infected children and youth and that most HIV-infected children and youth make an immunogenic response to MCV4 (47). (See Section 1.4 for updated information on this topic.)

Based on the concern that HIV-infected children in the ≥2 to <11 year old range are likely at increased risk of meningococcal disease, the ACIP advises that “providers may elect to vaccinate children aged 2 – 10 years who are infected with human immunodeficiency virus (HIV).”(48) There are no data, however, about the safety or immunogenicity of MCV4 in this age group of HIV-infected patients. (See Section 1.4 for updated information on this topic.)

1.2 Rationale

The degree to which HIV-infected youth are responsive to new conjugate vaccines is still largely undefined. The recent approval by the FDA of MCV-4 has led to a recommendation to vaccinate 11-12 year-old individuals at a pre-adolescent visit, individuals entering high school (approximately 15 years of age) and incoming college freshman living in dormitories, in recognition of the increased meningococcal disease risk during adolescence. As the majority of children with perinatally acquired HIV infection have aged into
adolescence, and the majority of new pediatric HIV infections in the US are occurring in the adolescent age group, the new age-based recommendations for meningococcal immunization patients will lead to most HIV-infected youth being age-eligible for a vaccine for which there are no safety or immunogenicity data available from HIV-infected populations. The data from use of other conjugated vaccines in HIV infection has concentrated mostly on younger children and has revealed incomplete understanding of the clinical and immunologic factors that correspond to vaccine safety, immunogenicity and benefit of additional doses. This proposal represents an important opportunity to examine explicitly the safety and immunogenicity of conjugated meningococcal vaccine in HIV-infected youth, including youth with all degrees of immunosuppression, whether or not on ART, with all modes of HIV acquisition and of variable duration of HIV infection.

Although meningococcal disease in HIV-infected patients is not a major problem in the United States, the data from the study of the safety and immunogenicity of meningococcal conjugate vaccine in this population can be applied to use of the vaccine in areas of the world, such as sub-Saharan Africa, in which meningococcal disease and HIV infection (see Figure 1) occur within the same population at alarmingly high rates. In particular, the inclusion of youth representing all degrees of immunosuppression will yield safety and immunogenicity data that is relevant to the large number of untreated and immunosuppressed HIV-infected African youth.

This study will evaluate the safety and immunogenicity of MCV-4 in HIV-infected youth between ≥11 and <25 years of age. This study is also designed to answer several important questions related to immunization of HIV-infected youth including both short-term and long-term immunogenicity. Answers to these questions will determine whether these youth are likely to be protected against different serotypes of meningococcus and whether routine second doses of this vaccine are necessary in this special population. Because previous studies of PCV, Hib, hepatitis A and varicella vaccines have indicated potential benefit from additional doses in HIV-infected children, we think that it is important to evaluate a 2-dose arm of the MCV4 vaccine in this patient population. In the absence of specific data for a 2-dose series of MCV4, and based on hepatitis A vaccination data, a 24 week interval between vaccinations was chosen for this study.

Subjects with CD4 less than 15% will be included in the study. They will be given 2 doses of MCV4 at 24 week intervals. Dosing this population with a single dose may result in a poor immune response. This study will ideally evaluate both safety and immunogenicity of 2 doses in this population of moderate to severely immune compromised subjects. However, if there are
insufficient numbers of eligible patients in this immunologic category to reach statistical power for a precise immunogenicity estimate, the safety data and exploratory data about immunogenicity derived from a small number of these patients will be important, as we anticipate that providers will otherwise be immunizing this group without any available safety and immunogenicity information.

As for many meningococcal vaccine studies, we do not expect there to be high enough rates of meningococcal infection or colonization to be able to study vaccine efficacy in protecting against invasive disease or nasal colonization.

Figure 1: Overlapping distributions of areas with high prevalence of HIV infection and of meningococcal infection

1.3 Rationale for Addition of Group 3

HIV infection can lead to T-cell dependent B-cell dysfunction which increases the risk of invasive disease due to encapsulated organisms, such as pneumococcus. This immune dysfunction may increase the risk of invasive meningococcal disease in HIV-infected patients as well, though few cases
have been reported. (7-11) In a case-control study during a meningococcal A outbreak in Uganda, the prevalence of HIV infection was no more common among meningococcal cases than a cohort of pregnant women selected as controls. In a retrospective cohort study of a population of 2900 HIV-infected patients followed over 10 years in London(9), only two cases of invasive meningococcal disease were identified, but this annualized rate of 6.9/100,000 was substantially higher than population-based studies of meningococcal disease in similar areas. In a population-based study of invasive meningococcal disease in Atlanta, Georgia(11), there was, as expected, a higher annual rate of disease among ≥18 to <25 years old (1.17 per 100,000) compared to that of all adults (0.5 per 100,000), but the estimated annual rate among HIV-infected adults was substantially higher (11.2 per 100,000). These data are suggestive but not definitive of an increased risk of invasive meningococcal disease in HIV-infected populations.

Menactra (MCV4) is a tetravalent meningococcal polysaccharide-protein conjugate vaccine. The vaccine contains Neisseria meningitidis serogroup A, C, Y, and W-135 capsular polysaccharide antigens individually conjugated to diphtheria toxoid protein. The vaccine was approved by the FDA on January 18, 2005 for 11-55 year olds. On October 17, 2007 the FDA approved this vaccine for children between ≥2 to <11 years of age. Immunization against meningococcal disease using MCV4 is recommended by the CDC ACIP for all ≥11 and <25 year olds, microbiologists who are routinely exposed to isolates of N. meningitidis; military recruits; persons who travel to or reside in countries in which N. meningitidis is hyperendemic or epidemic, particularly if contact with the local population will be prolonged; persons who have terminal complement component deficiencies; and persons who have anatomic or functional asplenia.

Based on the routine recommendation for ≥11 to ≤18 year olds and likely increased susceptibility of HIV-infected patients to meningococcal disease, a Phase I/II trial of MCV-4 in HIV-infected youth (≥11 to ≤18 years old) is underway and fully accrued as Protocol P1065 in the IMPAACT network. This protocol will examine safety and comparative immunogenicity of 1- vs. 2-dose MCV4 in youth with CD4 T-lymphocyte (CD4) ≥15% and safety and immunogenicity of 2-dose MCV4 in youth with CD4 <15%. The study of 2 doses in this population is based on the need for additional doses of other vaccines in HIV-infected children to achieve higher response rates.

In ≥2 to <11 year-old healthy children MCV-4 had a safety profile similar to that of MPSV-4 and elicited significantly higher and more persistent serum bactericidal antibody responses against meningococcal serogroups A, C, Y and W-135 than did the licensed polysaccharide vaccine. On October 18,
2007, the FDA approved MCV4 for $\geq 2$ to $<11$ year olds. Based on the concern that HIV-infected children in the $\geq 2$ to $<11$ year old range are likely at increased risk of meningococcal disease, this will be an important group who could benefit from routine use of the vaccine. There are no data, however, about the safety or immunogenicity of MCV4 in this population. In addition, the response rate even in healthy children in this age group is lower than it is in older children. The majority (83%) of $\geq 2$ to $<11$ year old HIV-infected children in this country have CD4 values 25% or higher (based on IMPAACT and CDC Legacy data). Based on 219C data, only 30% of HIV-infected $\geq 2$ to $<11$ year olds would be expected to have documentation of previous immunosuppression (CD4<25% on at least 2 specimens), and only 20% of $\geq 2$ to $<11$ year olds are under 6 years old. Thus, this study will specifically examine the safety and immunogenicity of a series of 2 doses of MCV4 in the group of HIV-infected $\geq 2$ to $<11$ year olds who represent the majority of HIV-infected U.S. children in this age range, namely those who currently have CD4 $\geq 25%$.

### Table 3: Numbers and Percentages of Healthy $\geq 2$ to $<11$ year old Subjects With No Detectable SBA(<8) at Day 0 Who Seroconverted (Titer $\geq 32$) by Day 28

<table>
<thead>
<tr>
<th>Serogroup</th>
<th>MCV-4</th>
<th>MPSV-4</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N %</td>
<td>n/N %</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>275/279 98.6</td>
<td>266/281 94.7</td>
<td>0.005</td>
</tr>
<tr>
<td>C</td>
<td>297/338 87.9</td>
<td>298/366 80.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Y</td>
<td>75/87 86.2</td>
<td>72/96 75.0</td>
<td>0.026</td>
</tr>
<tr>
<td>W-135</td>
<td>384/400 96.0</td>
<td>360/402 89.6</td>
<td>0.001</td>
</tr>
</tbody>
</table>

n indicates the number of subjects with $\geq 4$-fold increase over baseline titer; N, total number of subjects with titer <8 at baseline.

### Table 4: Comparison of Percentages of Healthy $\geq 2$ to $<11$ year old Subjects and Healthy $\geq 11$ to $\leq 18$ year old Subjects Who Seroconverted (4-fold titer increase) by Day 28 and Who Achieved a Titer $\geq 1:128$ by Day 28

<table>
<thead>
<tr>
<th></th>
<th>Healthy $\geq 2$ to $&lt;11$ year olds$^{(49)}$</th>
<th>Healthy $\geq 11$ to $\leq 18$ year old Subjects$^{(17)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4-fold increase (&lt;8 at baseline)</td>
<td>4-fold increase (variable baseline)</td>
</tr>
<tr>
<td></td>
<td>4-fold increase (≥1:128)</td>
<td>4-fold increase (≥1:128)</td>
</tr>
<tr>
<td>A</td>
<td>98.6</td>
<td>97</td>
</tr>
<tr>
<td>C</td>
<td>87.9</td>
<td>81</td>
</tr>
<tr>
<td>Y</td>
<td>86.2</td>
<td>93</td>
</tr>
<tr>
<td>W-135</td>
<td>96.0</td>
<td>91</td>
</tr>
</tbody>
</table>

*98.2-100% for all serotypes; serotype-specific data not provided in publication.

1.4 Background and Rationale for Step 3 (Version 4.0)

The Advisory Committee for Immunization Practices (ACIP) of the Centers for Disease Control (CDC) has updated its recommendations for use of meningococcal conjugate vaccine (MCV4) in children and youth (50). ACIP now recommends that subjects previously vaccinated with
MCV4 who remain at “increased risk for meningococcal disease” should be revaccinated with MCV4. For those who received their first MCV4 at age 7 or older, it is now recommended that MCV4 be administered at 5-year intervals for as long as the child is at increased risk of meningococcal disease. As before, HIV infection is not specified on the list of conditions definitively associated with increased risk of meningococcal disease, but ACIP acknowledges that HIV-infected patients are likely at increased risk.

HIV-infected youth are also at increased risk of lower immunogenic response to MCV4 compared to healthy adolescents, based on the results from P1065 (47). P1065 data show that HIV-infected youth have significantly higher immunogenicity following an initial 2-dose series of MCV4 (6 months apart) compared to a single MCV4 dose. At Week 28, a positive response (4-fold rise in titer) to MCV4 was observed for 45% of subjects with 1 dose vs. 73% with 2 doses for Neisseria meningitidis serogroup A (SG-A), 33% for 1 dose vs. 68% for 2 doses for SG-C, 60% for 1 dose vs. 74% for 2 doses for SG W135, and 73% for 1 dose vs. 84% for 2 doses for SG-Y (51).

Even among those who received two MCV4 doses, however, antibody titers declined substantially by 72 weeks from initial MCV4 dose. At Week 72, a positive response (4-fold rise in titer) to MCV4 was observed for 33% of subjects with 1 dose vs. 54% with 2 doses for SG-A, 18% for 1 dose vs. 41% for 2 doses for SG-C, 53% for 1 dose vs. 62% for 2 doses for SG W135, and 56% for 1 dose vs. 60% for 2 doses for SG-Y. These data demonstrate that HIV infected youth who have received a single dose of MCV4 would likely benefit from receiving a second MCV4 dose before the general 5-year interval in the ACIP recommendations; they also demonstrate that HIV-infected youth who received an initial 2-dose series may benefit from an additional booster to maintain or reattain protective immunity. Based on comparison of GMT’s in P1065 there was a booster response to the MCV4 in the 2-dose group for meningococcal serogroups C, Y and W-135 (51).

Based on a multivariable logistic regression model adjusting for CD4%, viral load, and CDC Class at study entry, the adjusted odds ratio for 4-fold response at Week 28 for 2 vs. 1 doses of MCV4 was 3.67 for SG-A, 5.63 for SG-C, 2.24 for SG-Y, and 2.55 for SG-W135. At Week 72, the adjusted odds ratios were 2.96 for SG-A, 3.45 for SG-C, 1.56 for SG-Y, and 2.48 for SG-W135. All odds ratios were statistically significant with the exception of Week 72 for SG-Y (51).
The protocol team proposes approaching the children and youth who were in Groups 1 and 3 in P1065 versions 2.0 and 3.0, respectively, for participation in this follow-up study at about 3 years +/- 6 months from their initial MCV4 study vaccine.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives (Groups 1 and 2)

2.11 To compare the immunogenicity of the quadrivalent meningococcal conjugate vaccine (MCV4) in HIV-1 infected youth at 28 weeks between a single-dose regimen vs. a two-dose regimen, where an immunogenic response is defined as a 4-fold or greater increase in serum bactericidal antibody titers;

2.12 To estimate the short-term (4 and 24 weeks) immunogenicity of the MCV4 vaccine in HIV-1 infected youth for those in Group 1 (CD4% >15);

2.13 To estimate the long-term (at 72 weeks) immunogenicity of the MCV4 vaccine in HIV-1 infected youth;

2.14 To evaluate the safety of the MCV4 vaccine in HIV-1 infected youth, including short-term local and systemic reactions following administration of the vaccine.

2.2 Primary Objectives (Group 3)

2.21 To estimate the immunogenic response to MCV4 in HIV-1 infected ≥2 to <11 year old children with CD4% ≥25, after two doses of MCV4, where an immunogenic response is defined as a 4-fold or greater increase in serum bactericidal antibody titers at Week 28 compared to baseline;

2.22 To estimate the short-term (4 and 24 weeks) immunogenicity of the MCV4 vaccine in HIV-1 infected ≥2 to <11 year old children with CD4≥25%;

2.23 To estimate the long-term (at 72 weeks) immunogenicity of 2 doses of the MCV4 vaccine in HIV-1 infected ≥2 to <11 old children with CD4≥25%;

2.24 To evaluate the safety of a two-dose series of MCV4 in HIV-1 infected ≥2 to <11 old children with CD4≥25%.
2.3 Primary Objectives (Groups 1 and 3 – Step 3)

2.31 To assess the level of protective antibody titers (rSBA≥1:128) 3 years +/- 6 months post-initial immunization with MCV4.

2.32 To estimate the proportion of subjects who have evidence of immunologic memory (7-8 days) to a booster dose of MCV4 3 years +/- 6 months after initial immunization with MCV4.

2.33 To estimate the rates of immunologic primary response (4 weeks) to a booster dose of MCV4 3 years +/- 6 months after initial immunization with MCV4 in children who lack evidence of immunologic memory to the initial immunization.

2.34 To estimate the short-term (4 and 24 weeks) immunogenicity of the booster dose of MCV4.

2.4 Secondary Objectives (Groups 1 and 2)

2.41 To examine whether the short and long-term immunogenicity of the MCV4 in HIV-1 infected youth varies as a function of the study subjects’ immune status at the time of vaccination;

2.42 To compare the long-term immunogenicity (at 72 weeks) of the MCV4 in HIV-1 infected youth between a 1-dose vs. 2-dose regimen for those in Group 1 (CD4% ≥ 15);

2.43 To evaluate whether the safety of the MCV4 vaccine varies by immune status based on CD4% at the time of vaccination;

2.44 To evaluate whether, in subjects with CD4% < 15%, 2 doses of MCV4 can produce an immunogenic response (defined as a 4-fold or greater increase in serum bactericidal antibody titers reaching at least 1:8);

2.45 To identify host genetic determinants of immunity that may affect the response to MCV4.

2.5 Secondary Objectives (Group 1 – Step 3)

2.51 To compare long-term (3 years +/- 6 months) antibody levels as evidence of long-term immunogenicity of 1 dose vs. 2 doses of meningococcal conjugate vaccine.

2.52 To compare rates of immunologic memory response 7-8 days after a booster dose of MCV4 between HIV-infected youth who have previously received 1 dose vs. 2 doses of MCV4.
2.53 To compare rates of immunologic response 4 weeks after a booster dose of MCV4 between HIV-infected youth who have previously received 1 dose vs. 2 doses of MCV4.

2.54 To compare the short-term (4 and 24 weeks) immunogenicity of the booster dose of MCV4 between HIV-infected youth who have previously received 1 dose vs. 2 doses of MCV4.

2.55 To evaluate the safety of the booster dose of MCV4.

3.0 STUDY DESIGN

3.1 STUDY DESIGN FOR STEPS 1 AND 2 (VERSIONS 1.0 – 3.0)

This is a phase I/II randomized study of the safety and immunogenicity of conjugate quadrivalent meningococcal vaccine (MCV4) in HIV-infected children and youth. The study population is HIV-infected children and youth ≥2 to <25 years of age (see specific inclusion and exclusion criteria). All subjects will be receiving one dose of (open label) conjugated meningococcal vaccine, while subjects in Groups 1A and 1B will be randomized to receive vs. not receive a second dose of vaccine.

STEP 1: All subjects will be administered MCV4 vaccines at study entry.

STEP 2: At week 24, subjects ≥11 to <25 years of age with CD4% ≥ 15 at study entry who did not have adverse reactions meriting vaccine discontinuation will be randomized to either Group 1A or 1B. At week 24, subjects with CD4%< 15 at study entry, and all subjects ≥2 to <11 years of age who are eligible will also be registered to Step 2. Study participants will fall into four groups as outlined in Table 5.

<table>
<thead>
<tr>
<th>Group</th>
<th>CD4 %</th>
<th>Arm</th>
<th>MCV4 Immunization</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>≥15</td>
<td>1-dose</td>
<td>Entry</td>
</tr>
<tr>
<td>1B</td>
<td></td>
<td>2-dose</td>
<td>Entry and 24 weeks</td>
</tr>
<tr>
<td>2</td>
<td>&lt;15</td>
<td>2-dose only</td>
<td>Entry and 24 weeks</td>
</tr>
<tr>
<td>3</td>
<td>≥25</td>
<td>2-dose only</td>
<td>Entry and 24 weeks</td>
</tr>
</tbody>
</table>

For the subjects who are ≥11 to <25 years of age, accrual will be stratified so that there are equal numbers of subjects with 15% ≤ CD4% <25% and CD4% ≥ 25%. All subjects who are ≥2 to <11 years of age will receive 2 vaccines (one at entry and one at 24 weeks). Subjects in all four groups will be followed for 72 weeks after enrollment. Vaccines will be administered at
entry for all participants and, again at 24 weeks for all participants in Group 1B, and those in Groups 2 and 3 who did not have adverse reactions meriting vaccine discontinuation. One-dose arm subjects (Group 1A) will receive study vaccine only at study entry. Subjects enrolled in this study will remain in the clinic for at least 30 minutes (½ hour) after each vaccine administration, so that clinic personnel can observe any potential adverse reactions to the vaccine. Reactions to the vaccines will be monitored three days after each vaccine, and again at 7 days after each vaccine. The team will review any safety issues during each of its monthly conference calls.

The schedule of laboratory and clinical evaluations for this study is outlined in Appendix IA, “Schedule of Evaluations for Steps 1 and 2 (Versions 1.0 – 3.0).”

The study visits and laboratory testing have been designed to coincide with the timing of visits and testing in usual clinical care practice and to minimize additional visits in order to make the study feasible for most children and youth. For this reason, we have not included an extra visit and serology one week after second dose of vaccine, which while scientifically desirable for demonstrating evidence of an anamnestic response, would be more burdensome to adolescent participants.

3.2 STUDY DESIGN FOR STEP 3 (VERSION 4.0)

Open label study of a booster dose of MCV4 provided to all eligible participants from Groups 1 (enrolled at 11-24 years old, CD4% \(\geq 15\%\) at the time of enrollment) and 3 (enrolled at 2-10 years old, CD4% \(\geq 25\%\) at time of enrollment) of P1065 versions 2.0 and 3.0, respectively. The proposed study would be an immunogenicity study examining the duration of protection and the response to a booster dose of MCV4 three years +/- 6 months after initial vaccination in HIV-infected children and youth, and comparing the immunogenic response to the booster dose between those originally randomized to receive 2 doses vs. 1 dose. Study end-points would be based on immunogenicity, including a four-fold rise in rSBA titer and achieving a protective titer on the rSBA assay (1:128).

The study design in terms of study visits would be similar to the booster study of MCV4 in healthy adolescents (17); and the booster study for hepatitis B virus vaccine in HIV-infected children receiving highly active antiretroviral therapy (52). Study visits would take place at baseline, 7-8 days, 4 weeks and 24 weeks from entry. This would allow the protocol team to have data to compare the booster response in HIV-infected
children and youth to the booster response to MCV4 available for healthy adolescents from the Keyserling study (17).

The schedule of laboratory and clinical evaluations for this study is outlined in Appendix IB, “Schedule of Evaluations for Step 3 (Version 4.0).”

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

Eligibility criteria have been developed to be minimally restrictive in order to maximize the proportion of age-eligible patients at participating sites who can participate and in recognition of the expected use in clinical practice of this vaccine in infected children and youth comprising the full range of HIV-related clinical and immunologic impairment. The inclusion criterion for the ≥2 to <11 year old children is limited to those with CD4 ≥25% which is representative of the vast majority of HIV-infected children in this age group.

4.1 Inclusion Criteria for Step 1

4.11 HIV-infected children and youth ≥2 to <25 years of age at study entry.

4.12 HIV infection, defined as 2 positive test results obtained from 2 different samples. Tests may include two of the same type OR two different types of tests listed below, as long as there are 2 positive test results obtained from 2 different samples:
- HIV antibody (ELISA + WB), obtained at age >18 months
- HIV culture, any age
- HIV DNA PCR, any age
- HIV RNA PCR >10,000 copies/mL, any age
- Neutralizable HIV p24 antigen obtained >28 days of age

4.13 CD4 % documented within 120 days of study entry (result has to be available and known before enrollment).

4.14 Patients who are on HAART must have been on a stable regimen of antiretrovirals for 90 days prior to vaccine.

4.15 Ability to complete all study immunizations and evaluations, in the opinion of the investigator.

4.16 Females of child-bearing potential must have a negative pregnancy test within 72 hours prior to enrollment. NOTE: “Female of child-bearing potential” is defined as girls who have reached menarche or women who have not been post-menopausal for at least 24 consecutive months (i.e., who have had menses within the preceding 24 months) or have not undergone surgical sterilization (e.g., hysterectomy, or bilateral
oophorectomy, or bilateral salpingotomy or tubal ligation). Acceptable
documentation of a child or adolescent lack of reproductive potential
include documentation that the child is prepubescent, (i.e. onset of
menses for girls or onset of puberty for boys) has not occurred, by
participant or care giver reported history or physical examination
Acceptable documentation of lack of reproductive potential for a
woman for this trial is the woman’s self-reported history of surgical
sterilization, menopause, or male partner’s azoospermia.

4.17 Subjects (and/or their partners) who are participating in sexual activity
that could lead to pregnancy must agree to use at least one of the
following methods of contraception as long as they are in this study:
- hormonal birth control drugs (oral, injectable or transdermal)
- male or female condoms with or without a spermicide
- diaphragm/cervical cap with spermicide
- intrauterine device (IUD).
Condoms are recommended because their appropriate use is the only
contraception method effective for preventing HIV-1 transmission.

4.18 Subjects must agree to avoid all methods of reproduction, including in vitro fertilization and sperm donation.

4.19 Adult subjects (≥18 to <25 years of age), parent or legal guardian, or
subjects who are emancipated minors able and willing to provide
signed informed consent.

4.2 Inclusion Criteria for Step 2

4.21 Continue to meet criteria 4.15 through 4.18 above.

4.3 Inclusion Criteria for Step 3 (Version 4.0)

4.31 Continue to meet criteria 4.15 through 4.19 above.

4.32 Subject must have been enrolled in previous versions of P1065 and
stratified into Group 1 or 3.
Note: Subjects do not have to be <25 years of age to participate in
Step 3 (Version 4.0). This age inclusion criterion applied only to
entry of Group 1 participants into Version 2.0.

4.33 Subject must have serology data from weeks 0, 4 and 28 from their
previous participation in P1065.
Note: Participating sites will be provided with a list of potentially
eligible subjects who meet this inclusion criterion. However, sites
should still check that the subject meets all other inclusion criteria
and does not meet any exclusion criteria (see Section 4.6).
4.4 Exclusion Criteria for Step 1

4.41 Receipt of any non-study vaccine on study entry day, inactive vaccine within the 2 weeks preceding study entry or other vaccine administration expected within the 2 weeks after study entry.

4.42 Receipt of any live non-study vaccine within the 4 weeks preceding study entry.

4.43 Prior receipt of meningococcal conjugate vaccine at any time or prior receipt of meningococcal polysaccharide vaccine within the 2 years prior to study entry.

4.44 Known hypersensitivity to any component of the MCV-4 vaccine including diphtheria toxoid.

4.45 Known hypersensitivity to dry natural rubber latex. (Although latex is not a component of the vaccine, the stopper of the vial contains dry natural rubber latex).

4.46 Life-threatening reaction after previous administration of a vaccine containing similar components.

4.47 Family history (in parent, sibling, or son/daughter) or personal history of GBS.

4.48 Breastfeeding.

4.49 Any clinically significant diseases (other than HIV infection) or clinically significant findings during the screening medical history or physical examination that, in the investigator’s opinion, would compromise the outcome of this study.

4.410 Current immunomodulatory therapy, including IL-2, any interferon product, GM-CSF, or thalidomide. [Note: G-CSF and erythropoietin are allowed.]

4.411 Current immunosuppressive therapy, including the equivalent of ≥ 1 mg/kg/per day of prednisone in the 2 weeks preceding study entry. Subjects for whom long-term corticosteroid therapy (≥ 2 weeks) is anticipated are excluded. [Note: non-steroidal anti-inflammatory agents and inhaled corticosteroids are allowed.]

4.412 Presence of malignancy within 12 weeks of study entry or treatment for malignancy currently or within 12 weeks of study entry.

4.413 Loss of strength in lower extremity or extremities within 24 weeks prior to study entry.
4.414 Presence of a known bleeding diathesis or patients taking anticoagulant therapy prior to study entry.

4.415 Absent ankle and patellar Deep Tendon Reflexes (DTRs) (all four).

4.416 Recent receipt of IGIV or any blood or immunoglobulin product (except washed red blood cells). Interval within which participant would be excluded will correspond to intervals used between IG/blood product and measles vaccine, as outlined in Table 6 below. Even though these intervals were developed for preventing interference with immune response to live vaccines, the same intervals will be used to help ensure that residual passive antibody will not affect meningococcal serologic assays.

4.417 Other acute or chronic medical or surgical conditions or contraindications that in the opinion of the investigator may interfere with the evaluation of the protocol objectives.

4.418 Any new and unresolved grade ≥3 laboratory toxicity within the past 120 days.

4.419 Any new and unresolved grade ≥3 clinical toxicity within the past 120 days.

4.5 Exclusion Criteria for Step 2

4.51 New occurrence or new awareness of GBS in the patient or patient’s family since the time of study entry.

4.52 Loss of strength in lower extremity or extremities since the last vaccination.

4.53 Absent ankle and patellar Deep Tendon Reflexes (DTRs) (all 4).

4.54 New diagnosis of an active malignancy, or chemotherapy treatment of an established diagnosis since study entry.

4.55 New diagnosis or suspected disease of the immune system, or receiving immunosuppressive therapy since study entry.

4.56 The subject or legal guardian refuses further vaccine.

4.57 The subject requires treatment with medications that are disallowed while on this study (see section 4.7).

4.58 Any Grade 4 toxicity since the last vaccination, unless judged by the site investigator and the Protocol Team to be unrelated to the vaccine.

4.59 Selected Grade 3 toxicities (for example, Grade 3 seizure or allergic reaction) meriting vaccine discontinuation, as determined by the IMPAACT P1065 Protocol Team and the site principal investigator.
4.510 Treatment with immunosuppressive or immunomodulation therapy (other than inhaled, intranasal, or topical corticosteroid) within 60 days of planned receipt of the second vaccine.

4.511 A severe allergic reaction (e.g., swelling of the mouth and throat, difficulty breathing, hypotension, or shock) that required medical intervention, occurring within 24 hours of the first vaccine and potentially attributable to that first vaccine.

4.512 New diagnosis of any coagulation disorder that would contraindicate IM injections.

4.513 The subject experiences toxicity as defined in Section 6.1.

4.514 Positive urine pregnancy test within 72 hours prior to receiving the second vaccine. Pregnancies will be followed to outcome. (Groups 1 and 2 only)

4.515 Breastfeeding. Breastfeeding subjects will be followed to outcome. (Groups 1 and 2 only)

4.516 Any new diseases which the investigator judges to be clinically significant (other than HIV infection) or clinically significant findings since the first dose that, in the investigator’s opinion, would compromise the outcome of this study.

4.517 Any new clinical grade ≥3 clinical toxicity that has not resolved within 2 weeks before vaccine receipt.

4.6 Exclusion Criteria for Step 3 (Version 4.0)

4.61 Receipt of any dose of non-study meningococcal vaccine since initial enrollment into P1065.

4.62 New occurrence or new awareness of GBS in the patient or patient’s family since the last P1065 study visit.

4.63 Loss of strength in lower extremity or extremities since the last MCV4 vaccination.

4.64 Absent ankle and patellar Deep Tendon Reflexes (DTRs) (all 4).

4.65 New diagnosis of an active malignancy, or chemotherapy treatment of an established diagnosis since the last P1065 study visit.

4.66 New diagnosis or suspected disease of the immune system since the last P1065 study visit.

4.67 The subject or legal guardian refuses further vaccine.
4.68 The subject requires treatment with medications that are disallowed while on this study (see Section 4.7).

4.69 Grade 3 or higher toxicities (for example, Grade 3 seizure or allergic reaction) secondary to receipt of vaccine in previous version of P1065 meriting vaccine discontinuation, as determined by the IMPAACT P1065 Protocol Team and the site principal investigator.

4.610 Current immunomodulatory therapy, including IL-2, any interferon product, GM-CSF, or thalidomide. [Note: G-CSF and erythropoietin are allowed.]

4.611 Current immunosuppressive therapy, including the equivalent of ≥ 1 mg/kg/per day of prednisone in the 2 weeks preceding study entry. Subjects for whom long-term corticosteroid therapy (≥ 2 weeks) is anticipated are excluded. [Note: non-steroidal anti-inflammatory agents and inhaled, intranasal and topical corticosteroids are allowed.]

4.612 A severe allergic reaction (e.g., swelling of the mouth and throat, difficulty breathing, hypotension, or shock) that required medical intervention, occurring within 24 hours of the first vaccine and potentially attributable to that first vaccine.

4.613 New diagnosis of any coagulation disorder that would contraindicate IM injections since the last P1065 study visit.

4.614 Breastfeeding.

4.615 Any new diseases which the investigator judges to be clinically significant (other than HIV infection) or clinically significant findings since enrollment into P1065 that, in the investigator’s opinion, would compromise the outcome of this study.

4.616 Any new grade ≥3 clinical toxicity that is not related to vaccine and has not resolved within 2 weeks before entry into Step 3.
Table 6: Suggested Intervals Between Immune Globulin Administration and Measles Immunization (MMR or Monovalent Measles Vaccine) (Table 3.32, Red Book 2006)

<table>
<thead>
<tr>
<th>Indication for Immunoglobulin</th>
<th>Route</th>
<th>U or mL</th>
<th>Mg IgG/kg</th>
<th>Interval, month (^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus (as TIG)</td>
<td>IM</td>
<td>250 U</td>
<td>approx 10</td>
<td>3</td>
</tr>
<tr>
<td>Hepatitis A prophylaxis (as IG)</td>
<td>IM</td>
<td>0.02 mL/kg</td>
<td>3.3</td>
<td>3</td>
</tr>
<tr>
<td>Contact prophylaxis</td>
<td>IM</td>
<td>0.06 mL/kg</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>International travel</td>
<td>IM</td>
<td>0.06 mL/kg</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Hepatitis B prophylaxis (as HBIG)</td>
<td>IM</td>
<td>0.25 mL/kg</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>Rabies prophylaxis (as RIG)</td>
<td>IM</td>
<td>20 IU/kg</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>Measles prophylaxis (as IG)</td>
<td>IM</td>
<td>125 U/10 kg (maximum 625 U)</td>
<td>20–39</td>
<td>5</td>
</tr>
<tr>
<td>Standard</td>
<td>IM</td>
<td>0.25 mL/kg</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>Immunocompromised host</td>
<td>IM</td>
<td>0.50 mL/kg</td>
<td>80</td>
<td>6</td>
</tr>
<tr>
<td>Varicella prophylaxis (as VZIG)</td>
<td>IM</td>
<td>...</td>
<td>15 mg/kg</td>
<td>None</td>
</tr>
<tr>
<td>RSV prophylaxis (palivizumab monoclonal antibody)</td>
<td>IM</td>
<td>...</td>
<td>15 mg/kg</td>
<td>None</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Washed RBCs</td>
<td>IV</td>
<td>10 mL/kg</td>
<td>Negligible</td>
<td>0</td>
</tr>
<tr>
<td>RBCs, adenine-saline added</td>
<td>IV</td>
<td>10 mL/kg</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Packed RBCs</td>
<td>IV</td>
<td>10 mL/kg</td>
<td>20–60</td>
<td>5</td>
</tr>
<tr>
<td>Whole blood</td>
<td>IV</td>
<td>10 mL/kg</td>
<td>80–100</td>
<td>6</td>
</tr>
<tr>
<td>Plasma or platelet products</td>
<td>IV</td>
<td>10 mL/kg</td>
<td>160</td>
<td>7</td>
</tr>
<tr>
<td>Replacement (or therapy) of immune deficiencies (as IGIV)</td>
<td>IV</td>
<td>...</td>
<td>300–400</td>
<td>8</td>
</tr>
<tr>
<td>ITP (as IGIV)</td>
<td>IV</td>
<td>...</td>
<td>400</td>
<td>8</td>
</tr>
<tr>
<td>RSV-IGIV</td>
<td>IV</td>
<td>...</td>
<td>750</td>
<td>9</td>
</tr>
<tr>
<td>ITP</td>
<td>IV</td>
<td>...</td>
<td>1000</td>
<td>10</td>
</tr>
<tr>
<td>ITP or Kawasaki syndrome</td>
<td>IV</td>
<td>...</td>
<td>1600–2000</td>
<td>11</td>
</tr>
</tbody>
</table>

MMR indicates measles-mumps-rubella; IgG, immunoglobulin G; TIG, Tetanus Immune Globulin; IG, Immune Globulin; IM, intramuscular; HBIG, Hepatitis B IG; RIG, Rabies IG; VZIG, Varicella-Zoster IG; RBCs, Red Blood Cells; IV, intravenous; IGIV, IG intravenous; ITP, immune (formerly termed "idiopathic") thrombocytopenic purpura; RSV-IGIV, Respiratory Syncytial Virus IGIV.

\(^1\) These intervals should provide sufficient time for decreases in passive antibodies in all children to allow for an adequate response to measles vaccine. Physicians should not assume that children are fully protected against measles during these intervals. Additional doses of IG or measles vaccine may be indicated after exposure to measles (see text).
4.7 Disallowed Medications

4.71 Any inactive vaccines received within 2 weeks prior to study entry or vaccine administration expected within the 2 weeks after study entry (per 4.41).

4.72 Any live vaccine within 4 weeks prior to study entry (per 4.42).

4.73 Any current immunomodulatory therapy, including IL2 (per 4.410).

4.74 Any current immunosuppressant therapy (per 4.411).

4.8 Enrollment Procedures

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL be reviewed or approved by the DAIDS PRO, and sites will receive an Initial Registration Notification when the DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification indicates successful completion of the protocol registration process. Sites will not receive any additional notifications from the DAIDS PRO for the initial protocol registration. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) WILL NOT be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.
For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

4.9 Co-enrollment Guidelines

4.91 Steps 1 and 2 (Versions 1.0 – 3.0)

Subjects may co-enroll in non-treatment trials such as PACTG 1036B, 1055, and 1058.

Subjects who are enrolled in antiretroviral treatment trials who have been on their current antiretroviral treatment at least 24 weeks would be eligible for co-enrollment, including but not limited to PACTG 1034 and 1053. Co-enrollment requires approval of the Chair(s) of the other studies.

Subjects enrolled in immunization studies (non-HIV immunizations) would be eligible for co-enrollment 4 weeks after completion of the final immunization in that study, including ATN 024, ATN 048, and ATN 052.

4.92 Step 3 (Version 4.0)

Subjects may co-enroll in non-treatment trials such as IMPAACT P1058A and P1074.

Subjects enrolled in immunization studies (non-HIV immunizations) would be eligible for co-enrollment 4 weeks after completion of the final immunization in that study.

Co-enrollment into other protocols not listed should be discussed with the chairs of both protocols.

5.0 STUDY TREATMENT

5.1 Drug Regimens, Administration, and Duration

5.11 Regimen

STEP 1:

All eligible subjects will receive a single dose of Meningococcal Polysaccharide Diphtheria Toxoid Conjugate Vaccine (MCV4)
administered as 0.5 mL intramuscularly (IM) at study entry.

**STEP 2:**

At week 24, \( \geq11 \) to \(<25\) year old subjects with CD4\% \( \geq 15 \) at study entry who did not have adverse reactions meriting vaccine discontinuation will be randomized to either Group 1A or 1B.

Subjects randomized to group 1A will NOT receive a dose of MCV4 at week 24.

Subjects randomized to group 1B will receive a second dose of MCV4 administered as 0.5 mL IM at week 24.

Eligible subjects in Groups 2 (\( \geq11 \) - \(<25\) year olds) and 3 (\( \geq2 \) - \(<11\) year olds) will receive a second dose of MCV4 administered as 0.5 mL IM at week 24.

A new prescription must be written for the site pharmacist to dispense the second dose of MCV4 at the week 24 visit.

<table>
<thead>
<tr>
<th>Groups</th>
<th>At Entry</th>
<th>24 weeks</th>
<th>Step 3 Entry (Week 0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>0.5 mL IM</td>
<td></td>
<td>0.5 mL IM</td>
</tr>
<tr>
<td>1B</td>
<td>0.5 mL IM</td>
<td>0.5 mL IM</td>
<td>0.5 mL IM</td>
</tr>
<tr>
<td>2</td>
<td>0.5 mL IM</td>
<td>0.5 mL IM</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.5 mL IM</td>
<td>0.5 mL IM</td>
<td>0.5 mL IM</td>
</tr>
</tbody>
</table>

**STEP 3 (VERSION 4.0):**

Eligible subjects in Groups 1 (Groups 1A and 1B) and 3 will receive an additional dose of MCV4 administered as 0.5 mL IM at Step 3 Entry (Week 0).

A new prescription must be written for the site pharmacist to dispense the dose of MCV4 at Step 3 Entry (Week 0) visit.

5.12 Administration

MCV4 vaccine should be administered as a single 0.5 mL injection by the intramuscular route, preferably in the deltoid region.

Do not administer this product intravenously, subcutaneously, or intradermally.
Parenteral drug products should be inspected visually for container integrity, particulate matter and discoloration prior to administration, whenever solution and container permit.

5.13 Duration

The total duration of the study will be 72 weeks in Steps 1 and 2. Vaccines will be administered at entry for all participants, again at 24 weeks for all participants in Groups 1B, 2 and 3.

The total duration of the study in Step 3 will be an additional 24 weeks. The vaccine will be administered at entry in Step 3 for all subjects in Groups 1A, 1B and 3.

5.2 Drug Formulation

MCV4 is a meningococcal polysaccharide diphtheria toxoid conjugate vaccine. The vaccine contains Neisseria meningitidis serogroup A, C, Y, and W-135 capsular polysaccharide antigens individually conjugated to diphtheria toxoid protein. The vaccine is administered intramuscularly. The four meningococcal components, present as individual serogroup-specific glycoconjugates, compose the final formulated vaccine. No preservative or adjuvant is added during the manufacturing process. The vaccine is manufactured as a sterile, clear to slightly turbid liquid. Each 0.5 mL dose of vaccine is formulated in sodium phosphate buffered isotonic sodium chloride solution to contain 4 µg each of meningococcal A, C, Y, and W-135 polysaccharides conjugated to approximately 48 µg of diphtheria toxoid protein carrier. MCV-4 is available only in single-dose vials. Store the vaccines at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Product that has been exposed to freezing should not be used. Protect from light. Do not use after expiration date. For additional information, please refer to the Menactra® package insert, now available on the Regulatory Support Center's home page: http://rsc.tech-res.com/CS10/.

5.3 Drug Supply, Distribution, and Pharmacy

Meningococcal Polysaccharide Diphtheria Toxoid Conjugate Vaccine (A/C/Y and W-135, MCV-4, Menactra®) will be provided by Sanofi Pasteur, Inc., Swiftwater, PA.

Study vaccines will be available through the NIAID Clinical Research Products Management Center (CRPMC). The IMPAACT pharmacist can obtain the study agents for the protocol by following the instructions in the
manual “Pharmacy Guidelines and Instructions for AIDS Clinical Trials Networks” in the section entitled Study Product Control.

The NIAID CRPMC will not provide antiretroviral therapy, syringes, or supplies for administration of vaccines as part of this study.

The IMPAACT pharmacist is required to maintain complete records of all study vaccine received from the NIAID CRPMC and subsequently dispensed. All unused study vaccine must be returned to the NIAID CRPMC after the study is completed or terminated. The procedures to be followed are given in the manual, “Pharmacy Guidelines and Instructions for AIDS Clinical Trials Networks” in the section entitled Study Product Control.

6.0 SUBJECT MANAGEMENT

6.1 Toxicity Management

As a result of the October 2005 report to VAERS of five cases of GBS in persons after receipt of MCV4 vaccination, with a total number of 17 cases reported by September 2006, HIV-infected subjects receiving MCV4 will be closely monitored for GBS.(13;22) Subjects who have previously experienced GBS, who have a close family member with a history of GBS, who are areflexic in all four extremities, or who have had recent changes in neurologic symptoms or exam will be excluded from the protocol.

Subjects enrolled in this study will remain in the clinic for at least 30 minutes (½ hour) after each vaccine administration, so that clinic personnel can observe any potential adverse reactions to the vaccine. In addition, subjects will be monitored at 3 days, 7 days and 42 days after receiving the vaccine by phone communication, at 24 weeks after second vaccine dose by phone communication, and at other intervals during scheduled clinic visits (see Appendix I) for signs and symptoms of GBS. A standardized questionnaire used at the 3 and 7 day intervals will ascertain the following signs and symptoms:

- Redness or swelling at the injection site
- Lump or hardness at the injection site
- Pain or tenderness at the injection site
- Itching at the injection site
- Temperature elevation
- Cough
- Runny nose/congestion
- Sore throat
- Irritableness
- Headache
- Chills
- Vomiting
- Muscle aches
- Tiredness
- Itching separate from injection site
- Weakness of legs
- Tingling of hands and/or feet
- Other reactions
- Unplanned visits related to vaccination

The standardized questionnaire used at the 42 day interval and the 24 week post second vaccine dose interval will solicit symptoms related to GBS, medically attended adverse events, and other serious adverse events occurring since the last vaccine dose as follows:
- Death
- Life threatening adverse drug experience
- Hospitalization
- Persistent or significant disability/incapacity
- Weakness of legs
- Tingling of hands and/or feet
- New difficulty walking

In Step 3 (Version 4.0), subjects will remain in the clinic for at least 30 minutes (½ hour) after vaccine administration so that clinic personnel can observe any potential adverse reactions to the vaccine. Subjects will also be evaluated at Week 1 for vaccine adverse reactions. In addition, subjects will be evaluated for signs and symptoms of GBS using the standardized questionnaire at the Week 4 and Week 24 visits.

The GBS monitoring tool questionnaire that is completed at the clinic may be accessed by going to the www.fstrf.org website and clicking on the QUALITY OF LIFE link. Anti-pyretics should not be routinely given in anticipation of adverse events after vaccination, such as fever or discomfort; however neither should anti-pyretics be withheld when symptoms are present. If these events occur, they should be recorded and then antipyretics given.

A clinic visit is also required within 24 hours if there is any positive response about weakness of legs, tingling of hands and/or feet, or new difficulty walking. Also, other serious adverse events (death, life threatening adverse drug experience, hospitalization, persistent or significant disability/incapacity)
will be reviewed expeditiously by the protocol team who will decide whether referral to the SMC is warranted.

It is anticipated that vaccine-associated adverse events (AEs) will occur frequently, but that these will be minor local reactions and side effects that will rarely necessitate interruption of the immunization schedule. Toxicities will be graded by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December, 2004, Clarification August 2009, which is available on the RSC web site (http://rsc.tech-res.com/safetyandpharmacovigilance/).

All IMPAACT investigators will perform appropriate clinical management of AEs according to the situation. The Protocol Team should be contacted if the investigator is unsure of the relationship of the toxicities to the study vaccine, or feels that abnormal values or events may be due to intercurrent infection or another drug. The Protocol Team will make a judgment about whether the adverse event is vaccine related. A clinic visit is required within 24 hours for all unexplained or unexpected adverse reactions ≥ Grade 3 as assessed by study staff and as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December, 2004, Clarification August 2009. A clinic visit is also required within 24 hours if there is any positive response about weakness of legs, tingling of hands and/or feet, or new difficulty walking.

All vaccine-related Grade ≥ 3 toxicities must be discussed as soon as possible (within 72 hours) via email with the protocol team. In addition, any new Grade 2 or higher neuromuscular weakness occurring within 42 days of vaccination will initiate a team safety review. Grade 3 abnormal laboratory values should be repeated within 72 hours. If the repeat assay verifies that the abnormality was not spurious, the toxicity is considered to be “confirmed”. Clinical and confirmed laboratory abnormalities ≥ Grade 3 must be evaluated and followed to determine etiology and resolution to ≤ Grade 2. If the repeat assay proves the abnormality to be spurious (not confirmed), the site must notify the study team as such.

6.2 Study Management Plan

Baseline viral loads and T-cell subsets will be established on all study subjects at entry into the study. Laboratory information for hematology will be obtained on all study subjects, prior to the second dose of vaccine to detect unexpected vaccine-related reactions. Any ≥ Grade 3 hematological abnormalities that are detected in vaccinees, tested approximately four weeks
after the first vaccine dose, must be demonstrated to have improved to \( \leq \) Grade 2 prior to receiving the second dose.

Refer to Section 8.712 for the specific early stopping algorithm. The IMPAACT P1065 team, as well as an independent Study Monitoring Committee (SMC), will review the data to decide if vaccination can proceed in the other strata.

6.3 Criteria for Deferral of Second Dose of Vaccine (Versions 1.0 – 3.0)

If a subject meets any of the following criteria the second dose of vaccine may be deferred. If deferred, the patient will have a two week window (up to four weeks with protocol Chair’s approval) to receive the second vaccine. If the second dose is not received, he/she will continue to be followed for the duration of the study according to Appendix I.

6.31 Body temperature \( \geq 101^\circ F \) or \( \geq 38.3^\circ C \), orally determined, within 72 hours prior to vaccination.

6.32 Presence of an acute opportunistic non-bacterial or bacterial infection within seven days of injection.

6.33 Treatment with systemic (oral or parenteral) prednisone or prednisone-equivalents \( (\geq 2.0 \text{ mg/kg or } \geq 20 \text{ mg total dose for } \geq 3 \text{ days}) \) within 30 days of receiving the second vaccine.

6.34 Vaccinations with inactivated vaccines received within two weeks of any dose of study vaccine, and no other vaccinations may be planned for two weeks after a dose of study vaccine.

6.35 Vaccinations with live vaccines received within four weeks of any dose of study vaccine, and no other vaccinations may be planned for two weeks after a dose of study vaccine.

6.36 Grade \( \geq 3 \) clinical toxicity expected to be transient and resolve at least 2 weeks before vaccine dose.

6.4 Criteria for Permanent Exclusion from Second Dose of Vaccine (Versions 1.0 – 3.0)

6.41 Family history (in parent, sibling, or son/daughter) or personal history of GBS. [For instances in which there is a new occurrence or new awareness of GBS in the patient or patient’s family since the time of study entry].
6.42 Loss of strength in lower extremity or extremities within the past 24 weeks.

6.43 Absent ankle and patellar Deep Tendon Reflexes (DTRs) (all 4).

6.44 New diagnosis of an active malignancy, or chemotherapy treatment of an established diagnosis since study entry.

6.45 New diagnosis or suspected disease of the immune system, or receiving immunosuppressive therapy since study entry.

6.46 The subject or legal guardian refuses further vaccine.

6.47 The subject requires treatment with medications that are disallowed while on this study (see section 4.7).

6.48 Any Grade 4 toxicity will preclude additional doses of vaccine, unless judged by the site investigator and the Protocol Team to be unrelated to the vaccine.

6.49 Selected Grade 3 toxicities (for example, Grade 3 seizure or allergic reaction) meriting vaccine discontinuation, as determined by the IMPAACT P1065 Protocol Team and the site principal investigator.

6.410 Treatment with immunosuppressive or immunomodulation therapy (other than corticosteroid) within 60 days of planned receipt of the second vaccine.

6.411 A severe allergic reaction (e.g., swelling of the mouth and throat, difficulty breathing, hypotension, or shock) that required medical intervention, occurring within 24 hours of the first vaccine and potentially attributable to that first vaccine.

6.412 Positive urine pregnancy test within 7 days prior to receiving the second vaccine. Pregnancies will be followed to outcome. (This applies to Groups 1 and 2).

6.413 Breastfeeding. Subjects who had enrolled in the study and subsequently began breastfeeding will be followed to study outcome. (This applies to Groups 1 and 2).

6.414 New diagnosis of any coagulation disorder that would contraindicate IM injections.

6.415 The subject experiences toxicity as defined in Section 6.1.

6.416 Any new diseases which the investigator judges to be clinically significant (other than HIV infection) or clinically significant findings since the first dose that, in the investigator’s opinion, would compromise the outcome of this study.
6.417 Any new clinical grade $\geq 3$ clinical toxicity that has not resolved within 2 weeks before vaccine receipt.

6.5 Criteria for Discontinuation from the Study

Subjects who discontinue from the study early will have a physical examination, HIV symptoms assessment, and use of clinically ordered HIV RNA and Hematology results (as indicated in Appendix IA and IB).

6.51 The subject or legal guardian refuses follow-up evaluations.

6.52 The site principal investigator determines that further participation would be detrimental to the subject's health or well-being.

6.53 The subject fails to comply with the study requirements, so as to cause harm to him/herself or seriously interfere with the validity of the study results.

6.54 Any subject in any of the study groups who receives any non-study meningococcal vaccine will be discontinued from further study treatment but will remain on study for scheduled visits for the purpose of safety evaluations.

7.0 EXPEDITED ADVERSE EVENT REPORTING

7.1 Expedited Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Where DAERS has not been implemented, sites will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/. For questions about EAE
reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

7.2 Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.

The study agents for which expedited reporting are required are: Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine, (MCV-4, Menactra®, Sanofi Pasteur, Inc.).

7.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0 December 2004, Clarification August 2009, must be used and is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

7.4 Expedited AE Reporting Period

The expedited AE reporting period for this study is the entire study duration for an individual subject (from study enrollment until study completion or discontinuation of the subject from study participation for any reason).

After the protocol-defined AE reporting period, unless otherwise noted, only SUSARs as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This is a Phase I/II randomized study that will evaluate the safety and immunogenicity of MCV-4 in HIV-infected children and youth between \( \geq 2 \) and \( < 25 \) years of age. It will be open label for those subjects between \( \geq 2 \) and \( < 11 \) years of age and for those with entry CD4% \( < 15 \). This study is also designed to answer several important questions related to immunization of HIV-infected children and youth, including both short-term and long term
immunogenicity and the effect of immune status at time of vaccination on immunogenic response. Answers to these questions will provide information on whether these youths are likely to be protected against different serotypes of meningococcus and whether a routine second dose of this vaccine is necessary in this special population. Because previous studies of PCV, Hib, hepatitis A and varicella vaccines have indicated potential benefit from additional doses in HIV-infected children, we think that it is important to evaluate a 2-dose arm of the MCV4 vaccine in this patient population. In the absence of specific data for a 2-dose series of MCV4, and based on Hepatitis A vaccination data, a 24 week interval between vaccinations was chosen for this study.

Since the Advisory Committee for Immunization Practices (ACIP) of the Centers for Disease Control (CDC) has updated its recommendations for use of meningococcal conjugate vaccine to recommend revaccination in those with ongoing, increased risk, Step 3 (Version 4.0) of this study is designed to assess immunogenicity and response to revaccination at 3-years after the initial vaccination in subjects ≥2 years of age with CD4% ≥15.

8.2 Outcome Measures

The primary outcomes will be estimates of the immunogenic response rates to the MCV4 vaccine in the 1-dose and 2-dose arms, and the corresponding odds ratio (OR) between study arms (one dose vs. two doses of MCV4) for positive response to vaccination at 28 weeks (4-fold rise in meningococcal serum bactericidal titers). Other primary outcomes will be estimates of the immunogenic response rates within strata defined by CD4% (<15%, ≥15%) after the first dose (weeks 4 and 24), and estimates of response rates at later time points (weeks 28 and 72) by treatment arm. The outcome measures for safety objectives will include the number and percent of subjects with documented reactions to the vaccine, and with ≥grade 3 adverse events and with suspected or proven GBS.

For Step 3 (Version 4.0), the primary outcome will be immunogenicity, defined as follows:

- **Seropositivity:**
  Ab levels will be measured at days 0, 7, and 28. Positive assays will be defined as Ab titers ≥1:128.

  [Note: for all assays, day 0, 7, and 28 specimens from each subject will be tested concurrently.]
• Immunologic Memory:

Evidence of immunologic memory will be analyzed separately, according to each of the following definitions:

(a) Secondary (anamnestic) response defined as a four-fold rise in Ab titers between day 0 (booster dose) and day 7;

OR

(b) Seropositivity on day 0 or change from seronegative to seropositive between day 0 and day 7.

• Immunologic Primary Response:

Evidence of a primary response (suggestive of a response to the booster vaccine dose, but not suggestive of immunologic memory) will be analyzed separately according to each of the following definitions:

(a) A four-fold rise in Ab concentration between day 0 and day 28, but not between day 0 and day 7;

OR

(b) A change from seronegative on day 0 to seropositive on day 28, but not between day 0 and day 7.

8.3 Randomization and Stratification (Versions 1.0 – 3.0)

Accrual will be stratified so that there are equal numbers of subjects with 15% ≤ CD4% < 25% and CD4% ≥ 25%. Because prior studies of immunizations in severely immunocompromised HIV-infected patients have demonstrated poor response to vaccination, all patients in Group 2 (CD4% < 15%) will receive the 2-dose regimen of MCV4 in this study. (Refer to Table 5 in Section 3.0, Study Design.) Because all subjects in Groups 2 and 3 will receive 2 doses of MCV4, they will be excluded from analyses comparing the 1-dose and 2-dose arms. Participants with CD4% ≥ 15% will be randomly assigned to one of two vaccine treatment arms: participants in the first arm (Group 1A) will receive one dose of MCV4 as per currently recommended guidelines and participants in second arm (Group 1B) and Groups 2 (CD4% < 15) and 3 (≥2 and <11 year olds) will receive two doses of MCV4. Randomization will be stratified by CD4% group to insure balance between the study arms among the subjects in Group 1 (≥11 and <25 age).

8.4 Sample Size and Accrual (Groups 1 and 2)

Based on current numbers and ages of children enrolled in PACTG 219C at existing sites and data from existing ATN sites (personal communication), we believe most children will meet the minimally restrictive inclusion and
exclusion criteria, and we thus expect to be able to accrue sufficient participants within a 52 week time frame.

In the study of healthy patients of the same age, 92% demonstrated a 4-fold or greater increase in meningococcus serogroup C titers following vaccination. Since some studies of other vaccines in HIV-infected patients have shown a somewhat lower seroconversion rate compared to healthy patients, we examined the ability to detect an odds ratio (OR) of 2.5 or greater between arms with response rates of 0.60 – 0.80 in the one-dose arm for our sample size calculations (see Table 7).

Table 7: Sample size needed to detect an odds ratio of 2.5 or greater with three hypothetical ‘true proportions’ of seroconverters in the 1-dose arm.

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>Response Rate in 1-Dose Arm</th>
<th>Response Rate Detectable with 80% power in 2-Dose Arm</th>
<th>Required Sample Size per Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>0.60</td>
<td>0.79</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>0.70</td>
<td>0.85</td>
<td>119</td>
</tr>
<tr>
<td></td>
<td>0.80</td>
<td>0.91</td>
<td>156</td>
</tr>
</tbody>
</table>

Sample sizes are based on the goal of being able to detect an odds ratio of 2.5 between the two study arms in Step 2. If meningococcus group C seroconversion rates are 70% in the 1-dose arm, and assuming a power of 80% and two-sided significance level of 0.05, a sample size of 119 subjects per arm would be needed. We would recruit 128 subjects per group to account for an estimated 7% of subjects who fail to return for further study visits or are ineligible for Step 2 due to adverse reactions to the first dose of MCV4.

Table 8 shows the precision of point estimates for vaccination response rates for the 119 subject study arms (Groups 1A and 1B) and for the 40 subject CD4% < 15 group. Estimates of the response rate at early time points may have increased precision (smaller confidence intervals) since the assumed attrition rate of 7% corresponds to 72 weeks; thus almost all of the 128 subjects enrolled in each group (either treatment arm or CD4% stratum) may be evaluated at earlier time points.
Table 8: Precision of point estimates of proportions.

<table>
<thead>
<tr>
<th>True proportion</th>
<th>Sample size (per group)</th>
<th>Precision of estimate (95% binomial exact confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.60</td>
<td>40</td>
<td>[0.43,0.75]</td>
</tr>
<tr>
<td></td>
<td>119</td>
<td>[0.50,0.69]</td>
</tr>
<tr>
<td>0.70</td>
<td>40</td>
<td>[0.53,0.83]</td>
</tr>
<tr>
<td></td>
<td>119</td>
<td>[0.61,0.78]</td>
</tr>
<tr>
<td>0.80</td>
<td>40</td>
<td>[0.64,0.91]</td>
</tr>
<tr>
<td></td>
<td>119</td>
<td>[0.71,0.87]</td>
</tr>
</tbody>
</table>

Depending on the observed response rate in the study, this sample size target of 119 evaluable subjects per sub-group would allow detection of a difference between 1-dose and 2-dose groups in Step 2 of 12-16% (see Table 9). It will also allow the same precision of point estimates and 80% power for the secondary objective of detecting differences in short-term immunogenicity after 1 dose of MCV4 between subjects with $15 \leq CD4\% < 25$ and subjects with $CD4\% \geq 25$.

Table 9: Limits of detection for the difference in response rates between dosage arms at 28 & 72 weeks assuming 3 hypothetical response rates.

<table>
<thead>
<tr>
<th>Response Rate in 1-Dose Arm</th>
<th>Lower limit of detection with 80% power in 2-Dose Arm</th>
<th>Difference</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.60</td>
<td>0.76</td>
<td>0.16</td>
<td>2.1</td>
</tr>
<tr>
<td>0.70</td>
<td>0.85</td>
<td>0.15</td>
<td>2.5</td>
</tr>
<tr>
<td>0.80</td>
<td>0.92</td>
<td>0.12</td>
<td>2.9</td>
</tr>
</tbody>
</table>

*Power=0.8, $\alpha=0.05$, two-sample, two-sided, N=119 per comparison group.

Based on a sample size of 40 subjects for Group 2 (severely immunocompromised) and 128 subjects per all other sub-groups, the total anticipated sample size for this study would be 296 subjects as outlined in Table 10.

Table 10: Sample size requirements

<table>
<thead>
<tr>
<th>Group</th>
<th>CD4%</th>
<th>Arm</th>
<th># Study subjects*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\geq 15%$</td>
<td>1 dose</td>
<td>128*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 doses</td>
<td>128*</td>
</tr>
<tr>
<td>2</td>
<td>$&lt; 15%$</td>
<td>2 doses</td>
<td>40</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>296*</td>
</tr>
</tbody>
</table>

*number based on 7% loss to follow-up (final sample size estimate is 119/arm)
Based on the most recent numbers of study participants in PACTG 219C who would be eligible by age for participation in this trial (see Table 11), there are clearly ample potential study participants in the least immunosuppressed group, Group 1. The safety data and exploratory data about immunogenicity derived from a smaller number (40) of these patients will be important, as we anticipate that providers will otherwise be immunizing this group off-label.

Table 11: Eligible PACTG 219C Participants by CD4% Category (as of March 7, 2006)

<table>
<thead>
<tr>
<th>CD4%</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15%</td>
<td>86</td>
<td>12</td>
</tr>
<tr>
<td>≥15 - &lt;25%</td>
<td>157</td>
<td>22</td>
</tr>
<tr>
<td>≥25%</td>
<td>478</td>
<td>66</td>
</tr>
<tr>
<td>Total</td>
<td>721</td>
<td>100</td>
</tr>
</tbody>
</table>

In the last 3 years, the adolescent population has grown due to new horizontal cases (at a higher rate than patients turning 25 years old when they leave the program) and the aging of the perinatal population. Even for the <15% group we would expect to have adequate subjects.

8.5 Sample Size and Accrual (Group 3)

The sample size for Group 3 is calculated to provide a certain precision of estimated immunogenicity rates for the primary objective. The goal is to have the half-width of a 95% confidence interval on the observed immunogenicity rate not exceed 8-12%. Based on historical data from healthy ≥2 - <11 year olds, the average seroconversion rate was 92% for all 4 serotypes. A sample size of 50 subjects would permit an estimate of the true response rate to within +/- 8% of an observed rate of 92%, to within +/- 9% of an observed rate of 85% and to within +/- 12% of an observed rate of 70%. See Table 12 for additional sample size estimate information. We would recruit 56 subjects to account for an estimated 10% of subjects who fail to return for further study visits. In order to get a somewhat balanced age representation within the overall ≥2 to <11 year-old age range, at least 20% (11 subjects) of the 56 subjects must be in the ≥2 to <6 year-old age range and at least 20% (11 subjects) in the ≥6 to ≤10 year-old age range. These minimum requirements will be achieved by placing upper limits on the accrual within each of two separate age strata in Group 3; in other words, a maximum accrual of 45 within each of the ≥2 to <6 and ≥6 to ≤10 age strata.

If the accrual in either age group has reached its maximum and the other age group remains unfilled for 2 months after the strata fills, the team may elect to allot accrual for the remaining slots to the filled age group.
Table 12: Precision of estimated immunogenicity rates for various observed rates and sample sizes from 50-100, based on an exact binomial 95% confidence interval

<table>
<thead>
<tr>
<th>Observed Rate</th>
<th>Sample Size (per group)</th>
<th>Precision of estimate (± %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>92%</td>
<td>50</td>
<td>± 8.0</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>± 6.7</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>± 5.0</td>
</tr>
<tr>
<td>85%</td>
<td>50</td>
<td>± 9.0</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>± 8.3</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>± 7.0</td>
</tr>
<tr>
<td>70%</td>
<td>50</td>
<td>± 12.0</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>± 10.0</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>± 9.0</td>
</tr>
</tbody>
</table>

8.6 Sample Size and Accrual (Step 3 – Version 4.0)

All 226 eligible Group 1 patients and 49 eligible Group 3 patients who participated in both Steps 1 and 2 and have serologic data from Weeks 0, 4 and 28 would be approached to enroll in this protocol amendment. Estimating a 20 to 30% rate of non-participation (based on loss to follow-up, transfer to another site, receipt of interim MCV4, or unwillingness to participate in another trial), the final group is estimated to be approximately 158 to 180 Group 1 subjects and 34 to 40 Group 3 subjects, for a total of 192 to 220 subjects. For the primary objectives, this sample size will provide relatively precise estimates of rates of protective antibody titers at Step entry and response rates after the booster dose of MCV4 (half-width of 95% confidence intervals ranging from 4.5%-6.8% for N=192 and 4.2%-6.7 % for N=220). If non-participation is greater than anticipated, precision will still be acceptable for a wide range of observed rates (see Table 12, above).

For the secondary objectives (Group 1 only), the anticipated sample size will provide 80% power to detect increases in response rates of 14-20% (ORs of 2.5-4.4) for the 2-dose vs. 1-dose arm, assuming response rates of 60-80% in the 1-dose arm (See table 13). If participation falls to 50%, there will be 80% power to detect increases in response rates of 17-23% (ORs of 3.3-7.3) for the 2-dose vs. 1-dose arm.
Table 13. Minimum detectable difference in response rates at 80% power between those originally randomized to 1-dose vs. 2-doses of MCV4 in P1065, based on sample sizes of 180 (20% loss to follow-up), 158 (30% loss to follow-up), and 114 (50% loss to follow-up); only including those in Group 1 (originally randomized to 1 or 2 doses)

<table>
<thead>
<tr>
<th>Response rate in those originally randomized to 1-dose MCV4 arm</th>
<th>Smallest Detectable Increased Response Rate in 2-dose Arm</th>
<th>Smallest Detectable Difference from 1-dose Arm</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>N= 180</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td>79%</td>
<td>19%</td>
<td>2.52</td>
</tr>
<tr>
<td>70%</td>
<td>87%</td>
<td>17%</td>
<td>2.88</td>
</tr>
<tr>
<td>80%</td>
<td>94%</td>
<td>14%</td>
<td>3.89</td>
</tr>
<tr>
<td>N= 158</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td>80%</td>
<td>20%</td>
<td>2.71</td>
</tr>
<tr>
<td>70%</td>
<td>88%</td>
<td>18%</td>
<td>3.15</td>
</tr>
<tr>
<td>80%</td>
<td>95%</td>
<td>15%</td>
<td>4.45</td>
</tr>
<tr>
<td>N= 114</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td>83%</td>
<td>23%</td>
<td>3.35</td>
</tr>
<tr>
<td>70%</td>
<td>91%</td>
<td>21%</td>
<td>4.15</td>
</tr>
<tr>
<td>80%</td>
<td>97%</td>
<td>17%</td>
<td>7.26</td>
</tr>
</tbody>
</table>

8.7 Monitoring

The protocol team will monitor accrual and safety (and any other aspects) on an ongoing basis, and interim safety reviews will be conducted at regular intervals (or as needed) by an independent Safety Monitoring Committee.

8.71 Routine Monitoring by Protocol Team

The Protocol Team, consisting of the Protocol Chair, investigators, data manager, and biostatistician, will monitor accrual and safety. Close cooperation among team members will be necessary in order to evaluate and respond to occurrences of toxicity in a timely manner. Accrual and toxicity data should be available to the Protocol Team on a monthly basis, or as needed.
8.711 Accrual (Versions 1.0 – 3.0)

We expect to accrue full sample size over a 24 to 52 week period beginning at the time the tenth site has been officially registered to the protocol, but no later than three months after the study has been opened to enrollment and the first site has been officially registered to the protocol.

Expected and minimum recruitment goals by each subgroup are outlined in Table 14 for 8 week, 16 week, 24 week, 36 week and 52 week time periods. If minimum recruitment goal is not met for any time period, the Protocol Team will review and analyze recruitment status and barriers at the sites. If minimum recruitment goals are not met for two consecutive time periods, then the Protocol Team will additionally make a formal assessment in writing to the Scientific Oversight Committee (SOC) within two weeks of second accrual report showing failure to meet minimum recruitment goals, outlining how recruitment can be improved and how target sample sizes are still feasible in order to continue the study. The SOC will consider whether sufficient accrual to yield evaluable data can be achieved in a reasonable time. If sufficient accrual is not expected, the SOC may decide on a review to be scheduled earlier at the SOC’s discretion. The SOC may also decide that it is futile to continue further enrollment and take a number of actions that include discontinuing further accrual to the study or referring the study to the SMC or to CSRC. N.B: If minimum recruitment goals are being met in all subgroups except Group 2, then the study will be considered to be meeting its minimum recruitment goals, since it has already been acknowledged that this subgroup may not fully accrue.
Table 14: Recruitment Monitoring Plan

<table>
<thead>
<tr>
<th>Group</th>
<th>CD4%</th>
<th># Study subjects PLANNED</th>
<th>8 week accrual</th>
<th>16 week accrual</th>
<th>24 week accrual</th>
<th>36 week accrual</th>
<th>52 week accrual</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15% to &lt; 25%</td>
<td>128</td>
<td>44 (22)</td>
<td>88 (44)</td>
<td>128 (64)</td>
<td>128 (96)</td>
<td>128 (128)</td>
</tr>
<tr>
<td></td>
<td>≥25%</td>
<td>128</td>
<td>44 (22)</td>
<td>88 (44)</td>
<td>128 (64)</td>
<td>128 (96)</td>
<td>128 (128)</td>
</tr>
<tr>
<td>2*</td>
<td>&lt;15%</td>
<td>40*</td>
<td>10 (5)*</td>
<td>20 (10)*</td>
<td>30(15)*</td>
<td>40(25)*</td>
<td>40 (40)*</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>296</td>
<td>98 (49)</td>
<td>196 (98)</td>
<td>286 (143)</td>
<td>296 (217)</td>
<td>296 (296)</td>
</tr>
</tbody>
</table>

*Group 2 is less likely to meet recruitment goals

Based on population estimates and level of site interest, we expect accrual of group 3 to be complete within 6 months (and likely 3 months) of opening.

8.712 Safety

All Grade 3/4 toxicities will be evaluated on monthly conference calls. The extent to which AEs are over-represented in particular immunologic strata will also be monitored. Studies of this vaccine in HIV-uninfected youth were associated with rates of moderate reactions as high as 12.8% (pain) but rates of severe reactions no higher than 1.1% (headache, fatigue, malaise.) We expect that the HIV infected participants in this study, who will range from severely immunocompromised to immunologically intact, will experience a higher rate of apparent adverse events at baseline that are a feature of their illness, not of a reaction to the vaccine. Thus, a priori, we will set a rate of 10% of new grade 3 or higher adverse events occurring within Group 1 or within Group 2 for triggering a safety review by the protocol team. If the protocol team observes any pattern which suggests that subject safety may be jeopardized, further accrual will be stopped pending a thorough investigation and the study will not resume unless the Protocol Team determines that it is safe to do so. A new Grade 2 or higher neuromuscular weakness occurring within 42 days of vaccination will initiate a team safety review. If GBS occurs within 42 days after a vaccine dose, this will be considered a potentially life threatening toxicity, and such occurrences will be discussed by the team. Two or more GBS cases occurring within 42 days of
vaccination will trigger an immediate Safety Monitoring Committee (SMC) review. All further study enrollment and vaccinations will be suspended pending the outcome of the SMC discussion; in addition, a summary of the SMC discussion and basis for recommendations will be submitted to the FDA as an amendment to the protocol.

For Step 3 (Version 4.0), there will be 28 days post-vaccination follow-up for safety endpoints and a 20% threshold of new grade 3 or higher adverse events for triggering a safety review by the protocol team. We expect to continue to see low rates of toxicities on Step 3, based on results from Steps 1 and 2.

8.72 Interim Monitoring by Independent Safety Monitoring Committee

The study will be monitored by a Safety Monitoring Committee (SMC) who will review safety and accrual using the accrual goals outlined in Table 14. The SMC members will be independent of the study (except for the protocol statistician and the non-voting, ex officio protocol medical officers) and have no financial or perceived conflict of interest. Given the accrual targets, we recommend that the SMC meet at 8 months after the first subject has enrolled and at least yearly thereafter. The committee will meet via teleconference. The IMPAACT P1065 Team may request additional ad hoc reviews if deemed necessary. In addition to the protocol team members mentioned above, the SMC will comprise a pediatrician, a pediatric infectious diseases specialist, an independent designate of Sanofi Pasteur, and other experts as appropriate. The Chair of the SMC will have primary responsibility for reporting the Committee’s comments to the IMPAACT Leadership and to the P1065 team. The group is required to commit to the duration of the study but replacements are permitted.

8.8 Analysis

8.81 Primary Objectives for Groups 1 and 2

8.811 Primary Objective #1 (single dose vs. two doses at 28 weeks):

This primary objective will only consider subjects in Group 1 (baseline immunologic category of CD4%≥15%). Immunogenic response (seroconversion) is defined as a 4-fold or greater increase in serum bactericidal antibody titers. For the 28-week time point, the proportion of seroconverters for
serogroup C will be calculated and compared between treatment arms (1 vs. 2 doses) based on the odds ratio for response between the two arms and its corresponding 95% confidence interval. Estimates will also be made for the other three serogroups (A, Y, and W-135), but the sample size and power considerations were conducted for a single primary endpoint and thus will be assumed to focus on serogroup C, with other serogroups as secondary endpoints. A logistic regression model will also be fit to calculate the odds ratio for the 2-dose arm versus the 1-dose arm for serogroup C, adjusting for baseline immunologic category. Further adjustment by other potential confounders may be considered, such as CDC class, viral load, and age of subject. The primary assessment of this objective will be conducted as an intent-to-treat analysis; that is, assignment to the 1-dose or 2-dose arm will be used regardless of the actual number of doses received. Since randomization to the 1-dose or 2-dose arms will be conducted at the time the second dose is administered, it is expected that few subjects will be randomized to the 2-dose arm but not receive a second dose. However, if needed, an additional “as treated” analysis will be conducted; for this analysis, those subjects in the 2-dose arm who only receive a single dose will be considered to fall in the 1-dose arm.

8.812 Primary Objective #2 (short-term immunogenicity):
For the 4-week and 24 week time points, the proportion of seroconverters (those with at least a 4-fold rise in meningococcal serum bactericidal titers from baseline) will be calculated along with corresponding 95% confidence intervals and reported for serogroup C, both overall and within the 2 immunologic groups (CD4% < 15% and CD4% ≥ 15%). Estimates will also be made for the other three serogroups (A, Y, and W-135).

8.813 Primary Objective #3 (long-term immunogenicity):
For the 72-week time point, the proportion of seroconverters (those with at least a 4-fold rise in meningococcal serum bactericidal titers from baseline) will be calculated along with corresponding 95% confidence intervals and reported for serogroup C by treatment arm. Estimates will also be made for the other three serogroups (A, Y, and W-135) within each of
the 6 subgroups defined by treatment arm (1 vs. 2 doses for CD4% ≥15) and vaccine serogroup (A, Y, and W-135).

8.814 Primary Objective #4 (safety):

The safety of the vaccine will be evaluated by summarizing the number and percent of subjects with documented reactions to the vaccine, and with new grade 3 or higher adverse events; each summary will be conducted overall, by first vs. second dose, and with Group 2 (CD4%<15%, all receive 2-doses) examined separately. These summaries will be prepared and distributed to team members on a routine basis during the course of the study (monthly during the first 6 months, and as recommended by the SMC thereafter). To specifically evaluate the safety of the second dose, we will compare those subjects randomized at step 2 who received 1 vs. 2 doses, to examine any increase in grade 3 or higher adverse events for those receiving the second immunization.

8.82 Primary Objectives for Group 3

8.821 Primary Objective #1 (immunogenicity after two doses at 28 weeks):

For the 28-week time point, the proportion of seroconverters in Group 3 (those with at least a 4-fold rise in meningococcal serum bactericidal titers from baseline) will be calculated along with corresponding 95% confidence intervals and reported for serogroup C. Estimates will also be made for the other three serogroups (A, Y, and W-135).

8.822 Primary Objective #2 (short-term immunogenicity):

For the 4-week and 24 week time points, the proportion of seroconverters (those with at least a 4-fold rise in meningococcal serum bactericidal titers from baseline) will be calculated along with corresponding 95% confidence intervals and reported for serogroup C. Estimates will also be made for the other three serogroups (A, Y, and W-135).

8.823 Primary Objective #3 (long-term immunogenicity):

For the 72-week time point, the proportion of seroconverters (those with at least a 4-fold rise in meningococcal serum bactericidal titers from baseline) will be calculated along with corresponding 95% confidence intervals and reported for
serogroup C. Estimates will also be made for the other three serogroups (A, Y, and W-135.)

8.824 Primary Objective #4 (safety):
The safety of the vaccine will be evaluated by summarizing the number and percent of subjects in Group 3 with documented reactions to the vaccine, and with new grade 3 or higher adverse events; each summary will be conducted overall, by first vs. second dose. These summaries will be prepared and distributed to team members on a routine basis during the course of the study (monthly during the first 6 months, and as recommended by the SMC thereafter).

8.83 Primary Objectives for Step 3 (Version 4.0)

8.831 Primary Objective #1 (immunogenicity after 3 years):
For the 3-year time point, GMTs, median titers, and the proportion of subjects with protective antibody levels (titers ≥1:128) will be calculated along with corresponding 95% confidence intervals and reported for all serogroups.

8.832 Primary Objective #2 (memory response at Week 1):
The rates of subjects with evidence of immunologic memory as defined in Section 8.2 at Week 1 post-vaccination and associated 95% CIs will be calculated and reported for all serogroups.

8.833 Primary Objective #3 (primary response at Week 4):
The rates of subjects with evidence of a primary response as defined in Section 8.2 at Week 4 post-vaccination and associated 95% CIs will be calculated and reported for all serogroups.

8.834 Primary Objective #4 (immunogenicity at Weeks 4 & 24):
For the 4-week and 24-week time points, the proportion of subjects with protective levels of antibody (titers ≥1:128) will be calculated along with corresponding 95% confidence intervals and reported for serogroup C. Estimates will also be made for the other three serogroups (A, Y, and W-135.)
8.84 Secondary Objectives

8.841 Secondary Objective #1a (short-term immunogenicity by immunologic strata at baseline):

For each of the Step 1 time points (4 and 24 weeks), the proportion of seroconverters to serogroup C in Groups 1 and 2 will be calculated and reported overall and by baseline immunologic category (CD4% <15%, 15 to <25%, and ≥25%). At each time point, a logistic regression model will be fit to calculate the estimated odds ratio and corresponding 95% confidence intervals for the CD4%<15% and 15 to <25% immunologic categories versus the ≥25% category. Potential confounders such as CDC class, viral load, and age will also be considered and evaluated for all logistic regression models. These models will also be estimated for the other three serogroups (A, Y, and W-135). Given the large number of models involved (8 models for 4 serogroups and 2 time points), we will also conduct additional analyses using a repeated measures approach under a generalized estimating equation model. First, a single model will be fit for each serogroup which includes responses over time for each subject, taking into account the correlation on multiple responses for the same subject. This model will allow a direct estimate of the effect of time on the odds of seroconversion, and will also provide estimates for the effect of baseline immunological status. Second, a unified model will be fit taking into account responses from all 4 serogroups simultaneously; this model will allow an estimate of the difference in responses across serogroups and will also have greater power than the 8 individual models to assess immunological effects on response.

8.842 Secondary Objective #1b (long-term immunogenicity by immunologic strata at baseline):

For each of the later time points (28 and 72 weeks), the proportion of seroconverters to serogroup C in Groups 1 and 2 will be calculated and reported overall and by baseline immunologic category (CD4% <15%, 15 to <25%, and ≥25%), broken down by treatment arm (1 vs. 2 doses). At each time point, a logistic regression model will be fit to calculate the estimated odds ratio and corresponding 95% confidence intervals for the CD4%<15% and 15 to <25% immunologic categories versus the ≥25% category, adjusted for treatment arm. Potential confounders such as CDC class and age will
also be considered and evaluated for all logistic regression models. These models will also be estimated for the other three serogroups (A, Y, and W-135). Given the large number of models involved (8 models for 4 serogroups and 2 time points), we will also conduct additional analyses using a repeated measures approach under a generalized estimating equation model. First, a single model will be fit for each serogroup which includes responses at all four time points (4, 24, 28, and 72 weeks) for each subject, taking into account the correlation on multiple responses for the same subject. This model will allow a direct estimate of the effect of time on the odds of seroconversion, and will also provide estimates for the effect of both treatment arm (1 vs. 2 dose) and baseline immunological status. Second, a unified model will be fit taking into account responses from all 4 serogroups simultaneously; this model will allow an estimate of the difference in responses across serogroups and will also have greater power than the 8 individual model to assess treatment and immunological effects on response.

Secondary Objective #2 (single dose vs. two doses at 72 weeks):

This secondary objective will only consider subjects in Group 1 (baseline immunologic category of CD4% >15%). For the 72-week time point, the proportion of seroconverters for serogroup C will be calculated and compared between treatment arms (1 vs. 2 doses), based on the odds ratio for response between the two arms and corresponding 95% confidence interval. Estimates will also be made for the other three serogroups (A, Y, and W-135). A logistic regression model will be fit to calculate the odds ratio for the 2-dose arm versus the 1-dose arm for serogroup C, adjusting for baseline immunologic category. Further adjustment by other potential confounders may be considered, such as CDC class, viral load, and age of subject. The primary assessment of this objective will be conducted as an intent-to-treat analysis; that is, assignment to the 1-dose or 2-dose arm will be used regardless of the actual number of doses received. Since randomization to the 1-dose or 2-dose arms will be conducted at the time the second dose would be administered, it is expected that few subjects would be randomized to the 2-dose arm but not receive a second dose. However, if needed, an additional analysis will be conducted using an “as treated” analysis; for
this analysis, those subjects in the 2-dose arm who only receive a single dose will be considered to fall in the 1-dose arm. We will also evaluate whether earlier responses observed at 4 and 28 weeks are maintained at 72 weeks.

8.844 Secondary Objective #3 (association of safety with immune status):

To evaluate in Groups 1 and 2 whether safety varies as a function of immune status at the time of vaccination, a logistic regression model for occurrence of new grade 3 or higher adverse events will be fit to calculate the estimated odds ratio and corresponding 95% confidence intervals for the CD4%<15% and 15 to <25% immunologic categories versus the ≥25% category. The models will be adjusted for potential covariates as appropriate.

8.845 Secondary Objective #4 (response in subjects with CD4% < 15%):

This secondary objective will only consider subjects in Group 2 (baseline immunologic category of CD4% < 15%). Immunogenic response (seroconversion) is defined for this group as a 4-fold or greater increase in serum bactericidal antibody titers reaching at least 1:8. For the 4, 28, and 72-week time points, the proportion of seroconverters for serogroup C will be calculated along with corresponding 95% confidence intervals. Estimates will also be made for the other three serogroups (A, Y, and W-135).

8.846 Secondary Objective #5 (genetic determinants of immune response):

For all time points (4, 24, 28, and 72 weeks), the proportion of seroconverters (4-fold rise in meningococcal serum bactericidal titers from baseline) will be compared to non-responders by the host genetic determinants including those listed below, with control for baseline immune status and treatment arm as appropriate.

TLR4-Asp299Gly, FcγRIIa-His131Arg, FcγRIIb-NA1/NA2 (codon 65 and 82), properdin-C2061T, C2726T and C3041G, interleukin-1β–C511T, TNFα–G308A, IL10–A1082G, IL6-G174C and IL1β–C511T
8.85 Secondary Objectives for Step 3 (Version 4.0)

Due to the possibility of differential drop-out between the 1-dose and 2-dose arms of Group 1, we will compare the Step 3 subjects on the two arms on demographic and clinical characteristics to assess whether they differ significantly on characteristics that might affect reaction to the booster dose, using Kruskal-Wallis, Fisher’s exact test, or chi-square tests as appropriate. Characteristics that vary significantly will be included in the models used to compare the two arms in the secondary objectives.

8.851 Secondary Objective #1 (1 dose vs. 2 doses after 3 years):

For the 3-year time point, the proportion of Group 1 subjects with protective antibody titers for serogroup C will be calculated and compared between treatment arms (1 vs. 2 doses). Estimates will also be made for the other three serogroups (A, Y, and W-135). For the 3-year time point, a logistic regression model will be fit to calculate the odds ratio for the 2-dose arm versus the 1-dose arm for serogroup C, adjusting for baseline immunologic stratum. Further adjustment by other potential confounders may be considered, such as CDC class, viral load, and age of subject reported for serogroup C. Models will also be made for the other three serogroups (A, Y, and W-135).

8.852 Secondary Objective #2 (memory response):

For the 1-week post-booster vaccination time point, the proportion of Group 1 subjects with memory response for serogroup C will be calculated and compared between treatment arms (1 vs. 2 doses). Estimates will also be made for the other three serogroups (A, Y, and W-135). A logistic regression model will be fit to obtain estimated ORs for 2 doses vs. 1 dose adjusting for confounders as noted above in 8.851.

8.853 Secondary Objective #3 (response at Week 4):

For the 4-week post-booster vaccination time point, the proportion of Group 1 subjects with any response (memory or primary) for serogroup C will be calculated and compared between treatment arms (1 vs. 2 doses). Estimates will also be made for the other three serogroups (A, Y, and W-135). A logistic regression model will be fit to obtain estimated ORs for 2 doses vs. 1 dose adjusting for confounders as noted above in 8.851.
8.854 Secondary Objective #4 (immunogenicity at Weeks 4 & 24):

For the 4-week and 24-week post-booster vaccination time points, the proportion of Group 1 subjects with protective levels of antibody (titers $\geq 1:128$) for serogroup C will be calculated and compared between treatment arms (1 vs. 2 doses). Estimates will also be made for the other three serogroups (A, Y, and W-135). A logistic regression model will be fit to obtain estimated ORs for 2 doses vs. 1 dose adjusting for confounders as noted above in 8.851.

8.855 Secondary Objective #5 (safety):

The safety of the booster vaccine will be evaluated by summarizing the number and percent of subjects with documented reactions to the vaccine, and with new grade 3 or higher adverse events; each summary will be conducted overall, by first vs. second dose. These summaries will be prepared and distributed to team members on a routine basis during the course of the study.

9.0 HUMAN SUBJECTS

9.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol, the informed consent documents (Appendix IV, V, VI, VII), and any subsequent modifications must be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. Written informed consent must be obtained from the subject (or parents or legal guardians of subjects who cannot consent for themselves, such as those below the legal age). The subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks of the study. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject (or parent or legal guardian).

Each site which receives US HHS funding and follows the United States Code of Federal Regulations Title 45 – Public Welfare, Part 46 – Protection of Human Subjects (also known as the Common Rule) should have on record at the site a plan that detects and addresses any change in guardianship occurring in pediatric subjects and determines when a study subject must have a consent process which involves a legally authorized representative (LAR) other than a
family member with guardianship. The plan will include how the site determines when a LAR is initially or no longer needed and how frequently the LAR resigns the consent. The plan should follow all IRB, local, and state guidelines. Confirmation of such a plan at a site should be submitted with protocol registration materials.

9.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain subject confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject (or his/her parent or legal guardian), except as necessary for monitoring by the FDA, the local IRB, NIH study staff, study monitors, Sanofi Pasteur Laboratories, and their designees.

9.3 Disposition of Subject Specimens

Once the study has closed, all study tests have been completed and confirmed, and results have been analyzed and finalized for publication, sites, laboratories and repositories will receive notification from the IMPAACT Laboratory Steering Committee (ILSC), requiring them to destroy any residual blood specimens within 30 days of being notified. Specimens must be disposed of in accordance with the institution’s environmental safety guidelines for the disposal of infectious substances. It is recommended that specimens be sterilized by autoclaving and discarded in a manner specified by the respective institution’s policy.

For subjects that will be participating in Step 3 (Version 4.0), blood samples that are left over after testing will be stored instead of being destroyed. This includes samples that are collected during Step 3 (Version 4.0) and samples that may be left over from the subject’s participation in earlier parts of the study. The stored left-over samples will be used for future IMPAACT-approved, HIV-related research. They will not be used for future genetic testing.

9.4 Study Discontinuation

The study may be discontinued at any time by the National Institute of Allergy and Infectious Diseases (NIAID), the Food and Drug Administration (FDA), the local Institutional Review Board (IRB) or other government agencies, such as the Office for Human Research Protections (OHRP), as part
of their duties to ensure that research subjects are protected, or Sanofi Pasteur Laboratories.

10.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by IMPAACT policies. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical sponsors prior to submission.

11.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other bloodborne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the CDC and the National Institutes of Health.

All dangerous good materials, including diagnostic specimens and infectious substances, must be transported according to the instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.
12.0 REFERENCES

Ref Type: Report


Ref Type: Catalog


Ref Type: Report


(44) Feikin DR, Elie CM, Goetz MB et al. Randomized trial of the quantitative and functional antibody responses to a 7-valent pneumococcal conjugate vaccine and/or


(50) Updated recommendation from the Advisory Committee on Immunization Practices (ACIP) for revaccination of persons at prolonged increased risk for meningococcal disease. MMWR Morb Mortal Wkly Rep 2009; 58(37):1042-1043.


## APPENDIX IA – SCHEDULE OF EVALUATIONS FOR STEPS 1 AND 2 (VERSIONS 1.0 – 3.0)

(DO NOT USE FOR STEP 3, VERSION 4.0)

<table>
<thead>
<tr>
<th>Event</th>
<th>Screen</th>
<th>Entry</th>
<th>On Treatment: Study Week/Visit</th>
<th>Early Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>x</td>
<td>x</td>
<td>1 4 6 24</td>
<td>x</td>
</tr>
<tr>
<td>Physical exam</td>
<td>x</td>
<td></td>
<td>25 28 30 48 72</td>
<td>x</td>
</tr>
<tr>
<td>Assessment of HIV-related symptoms</td>
<td>x</td>
<td>x</td>
<td>1 25 28 30 48 72</td>
<td>x</td>
</tr>
<tr>
<td>GBS Monitoring Tool</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Telephone Interview/Questionnaire</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Vaccination</td>
<td>x</td>
<td>Group 1A</td>
<td>1 4 6 24</td>
<td>25 28 30 48 72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Group 1B</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Group 2</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Group 3</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Hematology</td>
<td>1mL</td>
<td></td>
<td>1mL</td>
<td>1mL</td>
</tr>
<tr>
<td>Pregnancy Test (Groups 1A, 1B and 2)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>HIV RNA</td>
<td>2 mL</td>
<td></td>
<td>2 mL</td>
<td>2 mL</td>
</tr>
<tr>
<td>PBMC</td>
<td>2 mL</td>
<td></td>
<td>2 mL</td>
<td>2 mL</td>
</tr>
<tr>
<td>Lymphocyte subsets</td>
<td>1 mL</td>
<td></td>
<td>1 mL</td>
<td>1 mL</td>
</tr>
<tr>
<td>(CD4/CD8 % and absolute counts)</td>
<td>1 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal serology specimen</td>
<td>5 mL</td>
<td></td>
<td>5 mL</td>
<td>5 mL</td>
</tr>
<tr>
<td>TOTAL BLOOD VOLUME (mL)</td>
<td>4 mL</td>
<td></td>
<td>9 mL</td>
<td>10 mL (5mL for Group 3)</td>
</tr>
</tbody>
</table>
APPENDIX IA (cont.)

Footnotes:

1. Only those eligible subjects in groups 1B, 2 and 3 will receive a second vaccination at week 24. If at week 24 a subject is deferred from receiving the vaccine, he/she will have 2 weeks (or 4 weeks, with protocol chair/designee approval) to receive the vaccine. All subsequent visits will be adjusted based on the date the second vaccine is given.

2. Screening evaluations should be completed within 120 days prior to study entry. Screening visit may take place on the same day as entry visit, as long as all screening results are obtained prior to study enrollment.

3. Height, weight, vital signs, including body temperature, pulse and blood pressure.

4. Includes CDC classification.

5. The GBS Monitoring Tool is a Case Report Form (CRF) that will be used to assess symptoms and status of any neurological changes and/or family history of GBS. Site personnel will complete this form based on interviewing and physically evaluating each subject.

6. Telephone interviews for adverse effect reporting will take place 72 hours, 1 week and 6 weeks after each MCV4 vaccine dose, and at 24 weeks after the second vaccine. There are 2 standardized telephone questionnaires; one for the 72 hour and 1 week contact, and another for the 6 week and 24 week post second vaccine contact. Study sites will contact subjects to conduct interviews, which should take approximately 15 minutes.

At each vaccination visit, subjects will be given a standard CDC Vaccine Information Sheet for Meningococcal Vaccine. [Refer to the Centers for Disease Control’s vaccine website: (http://www.cdc.gov/vaccines/pubs/vis/downloads/vis-mening.pdf) for the most current version of this document.]

7. After each vaccine administration, subjects will remain in the clinic for at least 30 minutes (½ hour) so that clinic personnel can observe any potential adverse reactions to the vaccine.

8. Immunization should take place as soon as possible but less than 7 days from enrollment. If immunization does not take place on the same day as randomization, the following guidelines must be followed:
   - the pregnancy test needs to be repeated if the most recent negative pregnancy test is more than 72 hours old,
   - other entry labs, such as T-cell subsets, viral load and meningococcal serology do NOT need to be repeated, and
   - the subject must still meet study inclusion/exclusion criteria.

9. Complete blood count, cell differential, platelet count; blood will be drawn before administering vaccine.

10. Females of childbearing potential must have a negative pregnancy test within 72 hours prior to receiving either the first or second vaccine dose. Either a blood or urine pregnancy test is acceptable. Pregnancy test is not required at 24 weeks for those not receiving second vaccine.

11. Primary physician should obtain HIV quantitative RNA using assay that is locally available and appropriate for clinical care needs. The lymphocyte subsets will be performed locally at laboratories that are at least CLIA certified, and preferably IQA certified as well. Although the HIV RNA and lymphocyte subsets may not be performed at the exact time in the schema; the investigator should supply the results of these tests closest in time to the time indicated in the schedule.

12. See Appendix II. If unable to obtain a blood draw at this visit, it may be obtained at a subsequent visit.

13. See Appendix III.

For insufficient blood draws, list priority order: Safety (hematology); Immunology; Virology
### APPENDIX IB – SCHEDULE OF EVALUATIONS FOR STEP 3 (VERSION 4.0)

<table>
<thead>
<tr>
<th>Event</th>
<th>Screen</th>
<th>Step 3 Entry</th>
<th>Follow-up Study Week/Visit</th>
<th>Early Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1,2,3</td>
<td>1,2,4</td>
<td>4,5</td>
</tr>
<tr>
<td>History</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Physical exam</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Assessment of HIV-related symptoms</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>GBS Monitoring Tool</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccination</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine injection observation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td>1mL</td>
<td>1mL</td>
<td></td>
<td>1mL</td>
</tr>
<tr>
<td>Pregnancy Test</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA</td>
<td>5 mL</td>
<td>5 mL</td>
<td></td>
<td>5 mL</td>
</tr>
<tr>
<td>Lymphocyte subsets (CD4/CD8 % and absolute counts)</td>
<td>1 mL</td>
<td>1 mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBMC/DNA Storage (Group 3 only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal serology specimen</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
<td>5 mL</td>
</tr>
<tr>
<td>TOTAL BLOOD VOLUME (mL)</td>
<td>7 mL</td>
<td>12 mL</td>
<td>5 – 10 mL</td>
<td>5 – 10 mL</td>
</tr>
</tbody>
</table>

**Footnotes:**

1. Screening evaluations should be completed within 90 days prior to Step 3 Entry. Screening visit may take place on the same day as entry visit, as long as all specimens are obtained prior to Step 3 Entry and vaccination. Results do not have to be received prior to vaccination, except for the pregnancy test (see footnote 14).
2. Study week resets to Week 0 at Entry to Step 3.
3. Visit window for Step 3 Entry is 3 years +/- 6 months from the first study vaccine dose in previous version of P1065.
4. Week 1 visit window is -1 day and +2 days.
5. Week 4 visit window is +/- 4 days.
6. Week 24 visit window is +/- 4 weeks.
7. Subjects who received meningococcal vaccine outside of the study (i.e. period between completion of prior version of P1065 and entry into Step 3 - Version 4.0) are not eligible.
8. Height, weight, vital signs, including body temperature, pulse and blood pressure.
9. Includes CDC classification.
10. The GBS Monitoring Tool is a Case Report Form (CRF) that will be used to assess symptoms and status of any neurological changes and/or family history of GBS. Site personnel will complete this form based on interviewing and physically evaluating each subject.
APPENDIX IB (cont.)

11. Immunization should take place as soon as possible but less than 7 days from enrollment. If immunization does not take place on the same day as enrollment, the following guidelines must be followed:
   • the pregnancy test needs to be repeated if the most recent negative pregnancy test is more than 72 hours old,
   • other entry labs, such as T-cell subsets, viral load and meningococcal serology do NOT need to be repeated, and
   • the subject must still meet study inclusion/exclusion criteria.

12. After vaccine administration, subjects will remain in the clinic for at least 30 minutes (½ hour) so that clinic personnel can observe any potential adverse reactions to the vaccine. Vaccine adverse reactions will also be evaluated at Week 1. The Injection Vaccine Observation form should be completed.

13. Complete blood count, cell differential, platelet count; blood will be drawn before administering vaccine.

14. Females of childbearing potential must have a negative pregnancy test within 72 hours prior to receiving the booster vaccine dose. Either a blood or urine pregnancy test is acceptable.

15. Primary physician should obtain HIV quantitative RNA using assay that is locally available and appropriate for clinical care needs. The lymphocyte subsets will be performed locally at laboratories that are at least CLIA certified, and preferably IQA certified as well. Although the HIV RNA and lymphocyte subsets may not be performed at the exact time in the schema, the investigator should supply the results of these tests closest in time to the time indicated in the schedule.

16. See Appendix II. PBMC/DNA storage will be done for Group 3 subjects only. It needs to be obtained only once, at either Week 1, 4 or 24.

17. See Appendix III. Meningococcal serology specimen at entry must be collected before administering booster vaccine.

For insufficient blood draws, list priority order: Safety (hematology); Immunology; Virology; Storage
APPENDIX II

STORAGE SPECIMEN COLLECTION AND SHIPPING INSTRUCTIONS

GENETICS
(PBMC Pellet for DNA Analysis)

DO NOT USE FOR GROUP 1 IN STEP 3 (VERSION 4.0)

5 mL of blood in EDTA anti-coagulated should be processed as soon as possible within 48 hours of collection. Standard procedures as outlined in the ACTG Laboratory Manual should be followed for isolation of PBMC.

PBMC should be resuspended at a concentration of 1-2 X 10^6 cells/mL in PBS per cryovial. Centrifuge vials for 3 minutes at the highest speed in a microfuge (typically >10,000g). Optimally prepare at least 2-4 vials. Aspirate supernatant without disturbing the pellet. Store at -70°C.

Specimens should be logged into the LDMS at laboratories where this is available. The specimens should be identified with the patient ID#, study ID#, visit ID#, date and time of collection, primary, derivative, additive and sub/additive derivative codes.

Specimens should be shipped on dry ice to Dr. Stephen Spector’s laboratory (address below) when requested by protocol team; specific shipping instructions will be given at that time.

SHIPPING ADDRESS:

Stephen A. Spector, M.D.
University of California, San Diego
Department of Pediatrics
Division of Infectious Diseases
Stein Clinical Research Bldg, Room 430
Attn: Joseph Sanding
9500 Gilman Dr., Mail Code 0672
La Jolla, CA  92093-0672
Office Phone:  (858) 534-7055
Fax: (858) 534-7411
# APPENDIX III

## IMMUNOLOGY COLLECTION AND SHIPPING INSTRUCTIONS

<table>
<thead>
<tr>
<th>ASSAY</th>
<th>SPECIMEN</th>
<th>COLLECTION CONTAINER</th>
<th>IMMEDIATE SPECIMEN HANDLING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional meningococcal antibody activity against serogroups A, C, Y, and W-135</td>
<td>Serum</td>
<td>Red top collection tubes with no additives</td>
<td>Follow collection and handling instructions as described in this Appendix.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Collect 5mL of whole blood</td>
<td></td>
</tr>
</tbody>
</table>

**PROCESSING INSTRUCTIONS:**

1. After collection, the tube should be stored at room temperature for a minimum of 60 minutes and a maximum of 2 hours before centrifugation. The tube must be stored vertically and must not be shaken.

2. Beyond 2 hours, the sampling tube is placed at +2° to +8°C and must be centrifuged within a maximum of 24 hours.

3. After being allowed to clot for a minimum of 60 minutes to a maximum of 2 hours at room temperature, blood samples for serum antibody response assessment will be centrifuged before being divided into appropriate aliquots of serum.

4. Samples will then be handled one subject at a time to avoid the mix-up of subjects' blood tubes. Serum will be transferred to the appropriate number of tubes after having labeled the tubes with self-adhesive labels that clearly identify the subject number and sampling stage or visit number.

5. The first 1.0 mL of sera will be placed in a cryotube (primary sample). Retention vial(s) are prepared with remaining sera in 1.0 mL aliquots (if possible) capturing all residual sera.

6. Primary and retention samples will be stored in separate cryoboxes, identified with labels indicating primary and retention samples.

7. Sample collection and number of derivatives that are stored must be logged into the LDMS.

8. The subject's current study identification number, the date of sampling, and the number of aliquots obtained will be specified on a sample identification list. Comments may be made on this list regarding the quality of samples.

9. Serum tubes must be stored frozen in a non-frost-free freezer. The temperature should be set and maintained at -20°C. If a particular freezer cannot be set at -20°C, the temperature should be set to its lowest possible temperature, in order to maintain a temperature as close to -20°C as possible. The use of a non-frost-free -70°C freezer is also acceptable.

10. Once receipt of the primary samples is confirmed and any discrepancies resolved, the sponsor will request that retention samples be shipped.

**DESIGNATED LABORATORY:**
Sample Receipt, B53 Global Clinical Immunology, Attention: Receiving Department, Sanofi Pasteur, Discovery Drive, Swiftwater, PA 18370, USA
Phone: 570-895-3488, 570-895-2850    Fax: 570-895-3013

**SHIPPING:** sera samples should be collected until the end of the study and shipped frozen in bulk, using dry ice to maintain them in a frozen state.
APPENDIX IV

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC AND ADOLESCENT CLINICAL TRIALS GROUP
(IMPAACT)
SAMPLE INFORMED CONSENT

For Protocol: P1065

Phase I/II Study of Safety and Immunogenicity of Quadrivalent Meningococcal Conjugate Vaccine in HIV-Infected Children and Youth, Version 3.0
Groups 1 and 2 (Ages ≥11 – <25)
July 21, 2008


INTRODUCTION
You/your child or youth is being asked to take part in this research study because you/your child or youth is infected with the human immunodeficiency virus (HIV), the virus that causes AIDS. In addition, you/your child or youth is at the age when the recently FDA approved vaccine for the prevention of meningitis, called MCV-4, is being routinely offered to children and youth. At this time, however, there is no exact information on the best way to use this vaccine in HIV infected children or youth at the age when immunization is recommended. There is no available safety or immune response information for children or youth who receive this vaccine and have HIV. The “immune response” is how your body recognizes and defends itself against bacteria, viruses, and substances that appear foreign and harmful to the body. This study presents an opportunity to study and follow closely the safety and immune responses of children and youth with HIV who receive the meningococcal vaccine. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want yourself or your child to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you/your child agree to take part in this study, or to allow your child to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.
APPENDIX IV

WHY IS THIS STUDY BEING DONE?

Meningococci are bacteria that can cause meningitis. Meningitis is a disease that may be severe and even life-threatening. Research has shown that 15-24 year olds are at high risk for infection from meningococci, and that HIV-infected people may be at greater risk for this infection than healthy people. For more information about meningitis, please ask the study coordinator for a copy of the current version of the Vaccine Information Sheet on Meningococcal Vaccine, available on the Centers for Disease Control’s website (http://www.cdc.gov/nip/publications/VIS/vis-mening.pdf).

A vaccine, called MCV4, was developed to protect people against meningococcal infections. A single dose of this vaccine is recommended for people beginning at 11 years old. We do not have any information about how well MCV4 works in people with HIV infection or how safe it is for people with HIV infection. The purpose of this study is to test how well MCV4 works in 2 to 24 year old people with HIV infection and to test how safe MCV4 is in 2-24 year old people with HIV infection.

The full name of the vaccine is Quadrivalent Meningococcal Conjugate Vaccine (MCV4). The brand name of the vaccine is Menactra®. The vaccine used in this study will be provided by Sanofi-Pasteur Laboratories. This vaccine cannot cause meningococcal infection. The study will look at five things:

- The safety of the MCV4 vaccine;
- To see if the body’s defense system produces antibodies (substances the body makes in response to an infection or vaccination to help fight off disease) in response to the vaccination;
- To see if 1 dose or 2 doses of the vaccine work better to stimulate the body’s defense system to form antibodies to the meningococcal bacteria. Children or youth in the group with the lowest immune function will all be assigned to receive two vaccine doses. For all other children, there is a 50% chance of being assigned to receive either one dose or two doses of vaccine (like flipping a coin);
- To see how long the antibodies will last;
- To conduct genetic testing to see if people’s own genes affect the way they respond to this vaccine.

WHAT DO MY CHILD OR I HAVE TO DO IF MY CHILD OR I AM IN THIS STUDY?

Before Starting the Study (‘‘Screening Visit’’, this will take approximately 1½ hours)

Once you agree/allow your child to participate in this study, you/your child will have some basic blood tests done and be asked some questions to be sure you/your child can participate in this study.
APPENDIX IV

- The study staff will ask you some questions about your/your child’s medical history, including immunizations, and use of any past or present anti-HIV drugs. You/your child may be asked for permission to review your/your child’s medical records.
- About 1 teaspoon of blood will be taken to measure the levels of HIV and T cells, and to perform basic blood tests.
- Girls/women who have had their first menstrual period will have a pregnancy test. A small amount of urine or blood (less than 1 teaspoon) will be taken for this test. You/your child will be informed of the test result as soon as it is available. If you/your child are pregnant, you/your child cannot be in this study.
- If you or your child is breastfeeding, you/your child cannot be in this study.

During the Study

At the “Enrollment Visit” (which can occur on the same day as the screening visit, although it is not required, and will take approximately 1½ hours) the following will take place:

- You/your child will be assigned to a study group depending on your level of CD4 (cells that help fight HIV) as follows:
  - If the level of CD4 is equal to or greater than 15%, you/your child will be assigned to a group that will receive either one dose of vaccine to be given at entry (Group 1A), or two doses of vaccine, one to be given at entry, and one to be given six months later (Group 1B);
  - If the CD4 level is less than 15%, you/your child will be assigned to Group 2, and will receive 1 dose of vaccine at entry and one dose of vaccine at 24 weeks.
- If you/your child’s CD4 level is equal to or greater than 15%, you/your child has an equal chance of being assigned to getting 1 dose or getting 2 doses of vaccine. We will find out the assignment 24 weeks after the first vaccine dose.
- About 2 teaspoons of blood will be drawn for laboratory tests to look for antibodies for meningitis, to measure the levels of HIV and T cells, and to perform basic blood tests.
- You/your child will have a physical exam and review of symptoms, medications, and medical history.
- Girls/women who have had their first menstrual period will have a pregnancy test. A small amount of urine or blood (less than 1 teaspoon) will be taken for this test. A negative pregnancy test result must be obtained before you/your child can receive the vaccine.
- Study staff will check to make sure there is no reason that you/your child should not get the vaccine. If so, you/your child will be given his/her first dose of vaccine at this visit.
APPENDIX IV

- After vaccine administration, you/your child will remain in the clinic for at least 30 minutes (½ hour) so that clinic personnel can observe you/your child to make sure that no reactions to the vaccine develop.
- You/your child will be instructed to report any unusual reactions that occur.
- The clinic will call you three days after you/your child received the vaccine, and again four days later (one week after receiving the vaccine) and six weeks later to see if there are any problems. These phone calls should last for about 15 minutes each. A clinic visit would be required within 24 hours of vaccination for any positive response about weakness of legs, tingling of hands and/or feet, or new difficulty walking.

One month after you/your child receives the vaccine (this visit will take approximately ½ hour to complete):
- You/your child will return to the clinic for a physical examination to find out your/your child’s height, weight, vital signs (such as blood pressure), and symptoms.
- A small amount of blood (2 teaspoons) will be taken to measure the level of antibodies against the meningitis bacteria and to store for DNA analysis.

Six months after you/your child receives the vaccine (this visit will take approximately one and ½ hours to complete):
- You/your child will be re-examined at the clinic.
- About 2 teaspoons of blood will be drawn for the same tests described for the Enrollment visit.
- You/your child will have a physical exam and review of symptoms, medications, and medical history.
- If you/your child are a woman/girl who is already having her period (menstruating), and are in the study group that will receive a second vaccine, another blood or urine sample will be collected for a pregnancy test. If you/your child are pregnant or breastfeeding, you/your child will not receive the second dose of vaccine, but you/your child will still be followed in the study. If you/your child are not pregnant or breastfeeding, you/your child will be given the second dose of vaccine during this visit.
- If you/your child are in the group that will receive a second vaccine, and have a negative pregnancy test as discussed above, the study staff will check to make sure it is safe for you/your child to get the vaccine. If so, you will receive the second vaccine. After vaccine administration, you/your child will remain in the clinic for at least 30 minutes (½ hour) so that clinic personnel can observe you/your child to make sure that no reactions to the vaccine develop.
- The clinic will call you/your child at the following time points after you/your child received the second vaccine to see if there are any problems:
APPENDIX IV

- three days
- one week
- 6 weeks
- 6 months

These phone calls should last for about 15 minutes each. A clinic visit would be required within 24 hours of vaccination for any positive response about weakness of legs, tingling of hands and/or feet, or new difficulty walking.

Seven (7) months after you/your child receives the first vaccine (this visit will take approximately ½ hour to complete):
- You/your child will have a physical exam and review of symptoms, medications, and medical history.
- A small amount of blood (1 teaspoon) will be taken to measure the level of antibodies against the meningitis bacteria, just like at the one month visit.

Eighteen (18) months after receiving the first vaccine (This will be your/your child’s final study visit and will take approximately ½ hour to complete):
- You/your child will have a physical examination
- About 1 to 2 teaspoons of blood will be drawn for some, or all, of the laboratory tests previously described for the Enrollment visit
- Study staff will review symptoms, medications and medical history.

Off-Treatment Study Visits (Follow-up Period), and Early Discontinuation Study Visit

If you/your child stop taking part in receiving study vaccine at any time, you/your child will be asked to continue with study visits. If you/your child no longer want to be in this study, or no longer can be in this study, you/your child will be asked to come to the clinic one last time. At this last visit, some or all the laboratory tests described before will be done if tests have not been done at a recent study visit. About 2 teaspoons of blood will be drawn for these tests. No vaccine will be given at this early discontinuation study visit. You/your child will have a physical exam and review of symptoms and medications at this visit. This visit will take about ½ hour to complete. If you or your child become pregnant while on study, you/your child can not get any more doses of study vaccine but will still be followed on the study.

OTHER INFORMATION:

You/your child will be given the results of your/your child’s routine lab tests when they become available. The information and knowledge that comes out of doing this study may be used for other research related to HIV disease and approved by IMPAACT. The summaries and conclusions about the different things looked at by this study may be used in designing future research studies about vaccinations and HIV disease that are similar.
APPENDIX IV

to the problems studied in this research. No individual information in the IMPAACT study records will be looked at or used for this purpose. Any blood samples that remain after tests are run for this study will be destroyed. The results of blood tests for measuring antibody response to MCV4 will not be provided to you or your doctor. These tests will not be run at the time they are received. Instead they will be run in batches or at the end of the study.

GENETIC TESTING

At the one month visit, about 1 teaspoon of blood will be drawn and stored while you/your child are taking part in this study and while the samples are still being studied. This sample will be used for genetic testing, which is a study of your/your child’s genes (DNA). This will help researchers understand how different people may respond in different ways to the MCV4 vaccine. The researchers do not plan to contact you, your child, or the study doctor with the results of these studies. This is because research studies are often done with experimental procedures, and these results should not be used to make decisions about your/your child’s HIV care.

However, in case researchers learn new information that makes them believe that a certain study result is important for your/your child’s HIV care, then your/your child’s study doctor will be informed. If you would like the researchers to also tell you this information in a case like this, then, you/your child will need to tell the study staff if your/your child’s address or phone number change. You/your child may decide that you/your child do not want blood used for genetic testing. You/your child can still be in this study even if you/your child make this decision. Please read the statement below, and mark your initials in the spaces.

I agree to have my blood used for genetic testing as part of this study.

__________ Yes  ____________ No  ____________ Date

I agree to have my child’s blood used for genetic testing as part of this study.

__________ Yes  ____________ No  ____________ Date

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
About 352 participants will take part in this study.

HOW LONG WILL I/MY CHILD BE IN THIS STUDY?
You/your child will be in this study for 18 months.
WHY WOULD THE DOCTOR TAKE ME/MY CHILD OFF THIS STUDY EARLY?

The study doctor may need to take you/your child off the study early without your permission if:

- The study is cancelled by the US Food and Drug Administration (FDA), National Institutes of Health (NIH), Sanofi Pasteur Laboratories, Office of Human Research Protections (OHRP), or the site’s Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research subjects)
- You/your child are not able to attend the study visits as required by the study
- The Safety Monitoring Committee (SMC), who oversees the safety of this trial, recommends that the study be stopped.

The study doctor may also need to take you/your child off the study vaccine(s) without your permission if:

- Continuing the study vaccine may be harmful to you/your child
- You/your child is not able to take the study vaccine as required by the study
- You/your child need treatment not allowed in the study.
- You/your child become pregnant.
- You/your child are breastfeeding.

If you/your child must stop taking the study vaccine(s) before the study is over, the study doctor may ask you/your child to continue to be part of the study and return for some study visits and procedures. If you/your child must stop taking the study vaccine because you/your child become pregnant or are breastfeeding, you/your child will still be followed in the study.

WHAT ARE THE RISKS OF THIS STUDY?

Risk of Blood Draws

You/your child may feel faint or may feel some discomfort while having blood taken. There may be some swelling, bleeding, or bruising where the needle goes into the skin, or a small blood clot may develop. There is a small risk of infection forming where the needle goes into the skin to take blood.

Risks Related to the Vaccine

Approximately 7642 people aged 11-55 years of age have been enrolled in MCV4 vaccine clinical studies conducted by Sanofi Pasteur. Subjects were monitored for 28 days for both local and general clinical complaints, and for 6 months after the vaccination for visits to an emergency room, unexpected visits to a doctor’s office, and serious
APPENDIX IV

adverse experiences. About 7000 participants completed the 6 month follow-up evaluation. It is not known if receiving two doses of vaccine is more effective or more risky than receiving one dose of vaccine.

In these studies, MCV4 vaccine has been generally well-tolerated. The most common side effects that may occur as a result of the MCV4 injection in this study, which are similar to those observed with other commonly used vaccines, include skin redness, pain, tenderness, soreness, and swelling at the site of injection. You/your child may also experience headache and low energy.

A few cases of Guillain-Barré Syndrome (GBS), a rare but serious nervous system inflammatory disease of the peripheral nerves, have been reported among some people who received MCV4. The peripheral nerves send sensory information (e.g., pain, temperature) from the body to the brain and motor (i.e., movement) signals from the brain to the body. Symptoms of GBS include weakness and numbness or tingling in the legs and arms, and possible loss of movement and feeling in the legs, arms, upper body, and face. The frequency of GBS is about 1 to 2 cases in every 100,000 people per year in the United States. Men and women, young and old, are equally likely to contracting GBS.

There is not enough evidence yet to tell whether the reported cases of GBS in people who received MCV4 were caused by the vaccine. This is being investigated by health officials. It is also not known if GBS cases would be more likely, as likely or less likely in HIV infected people who get this vaccine.

The following side effects have been reported by people who received MCV4:

- Headache
- Fever
- Chills
- Diarrhea
- Loss of appetite
- Vomiting
- Joint pain
- Flu symptoms
- Common cold symptoms
- Abdominal pain
- Dizziness
- Feeling tired
- Pain, itching, redness, bruising or swelling at the injection site
APPENDIX IV

There are other less common side effects that your/your child’s study doctor can identify for you. The study doctor or staff will discuss these with you/your child. There can be other side effects that are not presently known about the MCV4 vaccine.

ARE THERE RISKS RELATED TO PREGNANCY?

This section applies to you/your child only if you/your child can become pregnant. It is not known if the vaccine used in this study can harm unborn babies. If you/your child are having sex that can lead to pregnancy, you/your child or your/your child’s partner must agree to use one of the methods of birth control listed below as long as you/your child are in this study. You/your child may discuss these choices with the study staff.

- Hormonal birth control drugs that prevent pregnancy given by pills, shots, or placed on or under the skin.
- Male or female condoms with or without a cream or gel that kills sperm.
- Diaphragm or cervical cap with a cream or gel that kills sperm.
- Intrauterine device (IUD).

Condoms are recommended because their appropriate use is the only contraception method effective for preventing HIV-1 transmission.

Whether you/your child are randomized into Group 1 or Group 2, you/your child or your/your child’s partner must use the chosen method of contraception as long as you/your child are in this study. If you/your child can become pregnant, you/she must have a pregnancy test before you/she enters this study. The test must be negative. If you think you/your child may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you/your child about her choices. You/your child must have a negative pregnancy test before the second dose of vaccine may be given.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you/your child take part in this study, there may be a direct benefit to you/him/her, but no guarantee can be made. Participants may develop antibodies (protective part of the blood to fight infections) against meningococcal infection and this may help prevent infection. It is also possible that you/your child may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DOES MY CHILD HAVE BESIDES THIS STUDY?

Instead of being in this study, you/your child may continue to be followed by your/your child’s regular doctor. A single dose of this vaccine is FDA approved for use in the age groups included in the study, and HIV is not a contraindication. It is possible that you/your child or youth could receive the vaccine off study. Please talk to your doctor about these and other choices available to you/your child. Your doctor will explain the risks and benefits of these choices.
APPENDIX IV

WHAT ABOUT CONFIDENTIALITY?

To help us protect your/your child’s privacy, we have obtained a Certificate of Confidentiality from the NIH. With this Certificate, the researchers cannot be forced to disclose information that may identify you/your child, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you/your child, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the US Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the Federal Food and Drug Administration (FDA).

People who may review your/your child’s records include: the FDA, (insert Name of Site) IRB, NIH, study staff, study monitors, Sanofi Pasteur Laboratories., and their designees.

You/your child should understand that a Certificate of Confidentiality does not prevent you/your child or a member of your/your child’s family from voluntarily releasing information about your or your child’s participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify your child as a participant in the research project under the following circumstances: possible child abuse and/or neglect or risk of harm to you, your child, or others.

WHAT ARE THE COSTS TO ME?

You/your child will not be expected to pay for any study vaccinations, study related visits, or study procedures. Anti-HIV drugs will not be provided through this study.

Taking part in this study may lead to added costs to you/your child and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because you are/your child is taking part in a research study.
APPENDIX IV

WHAT HAPPENS IF I AM/MY CHILD IS INJURED?
If you or your child are injured as a result of being in this study, you/your child will be given immediate treatment for you/his/her injuries. The cost for this treatment will be charged to your or your child’s insurance company. There is no program for compensation either through this institution or the NIH. You/your child will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY/MY CHILD’S RIGHTS AS A RESEARCH SUBJECT?
Taking part in this study is completely voluntary. You may choose not to take part in or allow your child to take part in this study, or you may remove yourself or your child from the study at any time. You/your child will be treated the same no matter what you decide.

We will tell you/your child about new information from this or other studies that may affect your/your child’s health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?
For questions about this study or a research-related injury, contact:
- name of the investigator or other study staff
- telephone number of above

For questions about your/your child’s rights as a research subject, contact:
- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above
APPENDIX IV

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to let your child take part in this study, please sign your name below.

<table>
<thead>
<tr>
<th>Participant’s Name (print)</th>
<th>Participant’s Signature and Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant’s Legal Guardian (print)</td>
<td></td>
</tr>
<tr>
<td>(As appropriate)</td>
<td>Legal Guardian’s Signature and Date</td>
</tr>
<tr>
<td>Study Staff Conducting Consent Discussion (print)</td>
<td>Study Staff Signature and Date</td>
</tr>
<tr>
<td>Witness’ Name (print)</td>
<td></td>
</tr>
<tr>
<td>(As appropriate)</td>
<td>Witness’s Signature and Date</td>
</tr>
</tbody>
</table>
APPENDIX V

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC AND ADOLESCENT CLINICAL TRIALS GROUP
(IMPAACT)
SAMPLE INFORMED CONSENT

For Protocol: P1065

Phase I/II Study of Safety and Immunogenicity of Quadrivalent Meningococcal Conjugate Vaccine in HIV-Infected Children and Youth, Version 3.0
Group 3 (Ages ≥2 to <11)
July 21, 2008


INTRODUCTION

Your child is being asked to take part in this research study because you/your child is infected with the human immunodeficiency virus (HIV), the virus that causes AIDS. In addition, your child is at the age when the recently FDA approved vaccine for the prevention of meningitis, called MCV-4, is being routinely offered to children. At this time, however, there is no exact information on the best way to use this vaccine in HIV infected children at the age when immunization is recommended. There is no available safety or immune response information for children who receive this vaccine and have HIV. The “immune response” is how your body recognizes and defends itself against bacteria, viruses, and substances that appear foreign and harmful to the body. This study presents an opportunity to study and follow closely the safety and immune responses of children with HIV who receive the meningococcal vaccine. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want yourself or your child to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you allow your child to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.
APPENDIX V

WHY IS THIS STUDY BEING DONE?

Meningococci are bacteria that can cause meningitis. Meningitis is a disease that may be severe and even life-threatening. Research has shown that 15-24 year olds are at high risk for infection from meningococci, and that HIV-infected people may be at greater risk for this infection than healthy people. While this study is already examining the safety and effectiveness of the MCV4 vaccine for 11 to 24 year old HIV-infected youth, there are also concerns that HIV-infected children in the 2-10 year old age range are more likely to get meningitis than healthy children, and that they are less likely to respond to a single dose of the vaccine than healthy children of the same age. Therefore, the study will also now look at the safety and effectiveness of giving 2-10 year old children two doses of the vaccine. For more information about meningitis, please ask the study coordinator for a copy of the current version of the Vaccine Information Sheet on Meningococcal Vaccine, available on the Centers for Disease Control’s website (http://www.cdc.gov/nip/publications/VIS/vis-mening.pdf).

A vaccine, called MCV4, was developed to protect people against meningococcal infections. A single dose of MCV4 has been recommended for people beginning at 11 years old, and has recently been approved for children 2 to 11 years of age as well. We do not have any information about how well MCV4 works in people with HIV infection or how safe it is for people with HIV infection. MCV4 has been approved for routine use as a single dose and we have very little information about using a 2-dose series of MCV4. The purpose of this study is to test how well a 2-dose series of MCV4 works in 2-10 year old children with HIV infection and to test how safe a 2-dose series of MCV4 is in 2-10 year old children with HIV infection.

The full name of the vaccine is Quadrivalent Meningococcal Conjugate Vaccine (MCV4). The brand name of the vaccine is Menactra®. The vaccine used in this study will be provided by Sanofi-Pasteur Laboratories. This vaccine cannot cause meningococcal infection. The study will look at four things:

- The safety of the MCV4 vaccine;
- To see if the body’s defense system produces antibodies (substances the body makes in response to an infection or vaccination to help fight off disease) in response to the vaccination;
- To see 2 doses of the vaccine will work to stimulate the body’s defense system to form antibodies to the meningococcal bacteria.
- To see how long the antibodies will last;

WHAT DO MY CHILD OR I HAVE TO DO IF MY CHILD OR I AM IN THIS STUDY?

Before Starting the Study (“Screening Visit”; this will take approximately 1½ hours)
APPENDIX V

Once you agree/allow your child to participate in this study your child will have some basic blood tests done and be asked some questions to be sure your child can participate in this study.
- The study staff will ask you some questions about your child’s medical history, including immunizations, and use of any past or present anti-HIV drugs. You/your child may be asked for permission to review his/her medical records.
- About 1 teaspoon of blood will be taken to measure the levels of HIV and T cells, and to perform basic blood tests.

During the Study

At the “Enrollment Visit” (which can occur on the same day as the screening visit, although it is not required, and will take approximately 1½ hours) the following will take place:
- About 2 teaspoons of blood will be drawn for laboratory tests to look for antibodies for meningitis, to measure the levels of HIV and T cells, and to perform basic blood tests.
- Your child will have a physical exam and review of symptoms, medications, and medical history.
- Study staff will check to make sure there is no reason that your child should not get the vaccine. If so, your child will be given his/her first dose of vaccine at this visit.
- After vaccine administration, your child will remain in the clinic for at least 30 minutes (½ hour) so that clinic personnel can observe your child to make sure that no reactions to the vaccine develop.
- You will be instructed to report any unusual reactions that occur.
- The clinic will call you three days after your child received the vaccine, and again four days later (one week after receiving the vaccine) and six weeks later to see if there are any problems. These phone calls should last for about 15 minutes each. A clinic visit would be required within 24 hours of vaccination for any positive response about weakness of legs, tingling of hands and/or feet, or new difficulty walking.

One month after your child receives the vaccine (this visit will take approximately ½ hour to complete):
- Your child will return to the clinic for a physical examination to find out your child’s height, weight, vital signs (such as blood pressure), and symptoms.
- About 1 teaspoon of blood will be taken to look for level of antibodies against the meningitis bacteria.
Six months after your child receives the vaccine (this visit will take approximately one and ½ hours to complete):

- Your child will be re-examined at the clinic.
- About 2 teaspoons of blood will be drawn for the same tests described for the Enrollment visit.
- Your child will have a physical exam and review of symptoms, medications, and medical history.
- The study staff will check to make sure it is safe for your child to get the vaccine. If so, your child will receive the second vaccine. After vaccine administration, your child will remain in the clinic for at least 30 minutes (½ hour) so that clinic personnel can observe your child to make sure that no reactions to the vaccine develop.
- The clinic will call you at the following time points after your child received the second vaccine to see if there are any problems:
  - three days
  - one week
  - 6 weeks
  - 6 months

These phone calls should last for about 15 minutes each. A clinic visit would be required within 24 hours of vaccination for any positive response about weakness of legs, tingling of hands and/or feet, or new difficulty walking.

Seven (7) months after your child receives the first vaccine (this visit will take approximately ½ hour to complete):

- Your child will have a physical exam and review of symptoms, medications, and medical history.
- About 1 teaspoon of blood will be taken to look for level of antibodies against the meningitis bacteria.

Eighteen (18) months after receiving the first vaccine (This will be your child’s final study visit and will take approximately ½ hour to complete):

- Your child will have a physical examination
- About 1 to 2 teaspoons of blood will be drawn for some, or all, of the laboratory tests previously described for the Enrollment visit
- Study staff will review symptoms, medications and medical history.
APPENDIX V

Off-Treatment Study Visits (Follow-up Period), and Early Discontinuation Study Visit

If your child stops taking part in receiving study vaccine at any time, your child will be asked to continue with study visits. If your child no longer wants to be in this study, or no longer can be in this study, your child will be asked to come to the clinic one last time. At this last visit, some or all the laboratory tests described before will be done if tests have not been done at a recent study visit. About 2 teaspoons of blood will be drawn for these tests. No vaccine will be given at this early discontinuation study visit. Your child will have a physical exam and review of symptoms and medications at this visit. This visit will take about ½ hour to complete.

OTHER INFORMATION:

You will be given the results of your child’s routine lab tests when they become available. The information and knowledge that comes out of doing this study may be used for other research related to HIV disease and approved by IMPAACT. The summaries and conclusions about the different things looked at by this study may be used in designing future research studies about vaccinations and HIV disease that are similar to the problems studied in this research. No individual information in the IMPAACT study records will be looked at or used for this purpose. Any blood samples that remain after tests are run for this study will be destroyed. The results of blood tests for measuring antibody response to MCV4 will not be provided to you or your doctor. These tests will not be run at the time they are received. Instead they will be run in batches or at the end of the study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 352 subjects in the study, of whom about 56 are in the 2 – 10 year old age range.

HOW LONG WILL I/MY CHILD BE IN THIS STUDY?

Your child will be in this study for 18 months.

WHY WOULD THE DOCTOR TAKE MY CHILD OFF THIS STUDY EARLY?

The study doctor may need to take your child off the study early without your permission if:

- The study is cancelled by the US Food and Drug Administration (FDA), National Institutes of Health (NIH), Sanofi Pasteur Laboratories, Office of Human Research Protections (OHRP), or the site’s Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research subjects)
- Your child is not able to attend the study visits as required by the study
APPENDIX V

- The Safety Monitoring Committee (SMC), who oversees the safety of this trial, recommends that the study be stopped.

The study doctor may also need to take your child off the study vaccine(s) without your permission if:
- Continuing the study vaccine may be harmful to your child
- Your child is not able to take the study vaccine as required by the study
- Your child needs treatment not allowed in the study.

If your child must stop taking the study vaccine(s) before the study is over, the study doctor may ask your child to continue to be part of the study and return for some study visits and procedures.

WHAT ARE THE RISKS OF THIS STUDY?

Risk of Blood Draws
Your child may feel faint or may feel some discomfort while having blood taken. There may be some swelling, bleeding, or bruising where the needle goes into the skin, or a small blood clot may develop. There is a small risk of infection forming where the needle goes into the skin to take blood.

Risks Related to the Vaccine
Approximately 7642 people aged 11-55 years of age and 700 children 2-10 years of age have been enrolled in MCV4 vaccine clinical studies conducted by Sanofi Pasteur. Subjects were monitored for 28 days for both local and general clinical complaints, and for 6 months after the vaccination for visits to an emergency room, unexpected visits to a doctor’s office, and serious adverse experiences. About 7000 of the 11-55 year old participants and 650 of the 2-10 year old participants completed the 6 month follow-up evaluation. It is not known if receiving two doses of vaccine is more effective or more risky than receiving one dose of vaccine.

In these studies, MCV4 vaccine has been generally well-tolerated. The most common side effects that may occur as a result of the MCV4 injection in this study, which are similar to those observed with other commonly used vaccines, include skin redness, pain, tenderness, soreness, and swelling at the site of injection. Your child may also experience headache and low energy.

A few cases of Guillain-Barré Syndrome (GBS), a rare but serious nervous system inflammatory disease of the peripheral nerves, have been reported among some of the 11-55 year old people who received MCV4. The peripheral nerves send sensory information (e.g., pain, temperature) from the body to the brain and motor (i.e.,...
APPENDIX V

movement) signals from the brain to the body. Symptoms of GBS include weakness and numbness or tingling in the legs and arms, and possible loss of movement and feeling in the legs, arms, upper body, and face. The frequency of GBS is about 1 to 2 cases in every 100,000 people per year in the United States. Men and women, young and old, are equally likely to contract GBS.

There is not enough evidence yet to tell whether the reported cases of GBS in people who received MCV4 were caused by the vaccine. This is being investigated by health officials. It is also not known if GBS cases would be more likely, as likely or less likely in HIV infected people who get this vaccine.

The following side effects have been reported by people who received MCV4:
- Headache
- Fever
- Chills
- Diarrhea
- Loss of appetite
- Vomiting
- Joint pain
- Flu symptoms
- Common cold symptoms
- Abdominal pain
- Dizziness
- Feeling tired
- Pain, itching, redness, bruising or swelling at the injection site

There are other less common side effects that your child’s study doctor can identify for you. The study doctor or staff will discuss these with you and your child. There can be other side effects that are not presently known about the MCV4 vaccine.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If your child takes part in this study, there may be a direct benefit to him/her, but no guarantee can be made. Participants may develop antibodies (protective part of the blood to fight infections) against meningococcal infection and this may help prevent infection. It is also possible that your child may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DOES MY CHILD HAVE BESIDES THIS STUDY?
APPENDIX V

Instead of being in this study, your child may continue to be followed by your/your child’s regular doctor. A single dose of this vaccine is FDA approved for use in the age groups included in the study, and HIV is not a contraindication. It is possible that your child could receive the vaccine off study. Please talk to your doctor about these and other choices available to your child. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

To help us protect your child’s privacy, we have obtained a Certificate of Confidentiality from the NIH. With this Certificate, the researchers cannot be forced to disclose information that may identify your child, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify your child, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the US Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the Federal Food and Drug Administration (FDA).

People who may review your child’s records include: the FDA, (insert Name of Site) IRB, NIH, study staff, study monitors, Sanofi Pasteur Laboratories., and their designees.

You/your child should understand that a Certificate of Confidentiality does not prevent you/your child or a member of your/your child’s family from voluntarily releasing information about your child’s participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify your child as a participant in the research project under the following circumstances: possible child abuse and/or neglect or risk of harm to you, your child, or others.

WHAT ARE THE COSTS TO ME?

Your child will not be expected to pay for any study vaccinations, study related visits, or study procedures. Anti-HIV drugs will not be provided through this study.

Taking part in this study may lead to added costs to your child and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because your child is taking part in a research study.
APPENDIX V

WHAT HAPPENS IF MY CHILD IS INJURED?
If your child is injured as a result of being in this study, your child will be given immediate treatment for his/her injuries. The cost for this treatment will be charged to your child’s insurance company. There is no program for compensation either through this institution or the NIH. You/your child will not be giving up any legal rights for you and your child by signing this consent form.

WHAT ARE MY CHILD’S RIGHTS AS A RESEARCH SUBJECT?
Taking part in this study is completely voluntary. You may choose not to allow your child to take part in this study, or you may remove your child from the study at any time. Your child will be treated the same no matter what you decide.

We will tell you about new information from this or other studies that may affect your child’s health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?
For questions about this study or a research-related injury, contact:
- name of the investigator or other study staff
- telephone number of above

For questions about your child’s rights as a research subject, contact:
- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above
SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to let your child take part in this study, please sign your name below.

Participant’s Legal Guardian (print) (As appropriate)  Legal Guardian’s Signature and Date

Study Staff Conducting Consent Discussion (print)  Study Staff Signature and Date

Witness’ Name (print) (As appropriate)  Witness’s Signature and Date
APPENDIX VI

DIVISION OF AIDS
INTERNATIONAL MATERNAL PEDIATRIC AND ADOLESCENT CLINICAL TRIALS GROUP (IMPAACT)
SAMPLE INFORMED CONSENT

For Protocol: P1065

PHASE I/II STUDY OF SAFETY AND IMMUNOGENICITY OF QUADRIVALENT MENINGOCOCCAL CONJUGATE VACCINE (MCV4) IN HIV-INFECTED CHILDREN AND YOUTH (VERSIONS 1.0 – 3.0)

And

OPEN LABEL IMMUNOGENICITY STUDY OF A BOOSTER DOSE OF MCV4 IN PREVIOUSLY IMMUNIZED HIV INFECTED CHILDREN AND YOUTH (VERSION 4.0)

November 24, 2010


This SIC should be used for subjects enrolling on Step 3, OPEN LABEL IMMUNOGENICITY STUDY OF A BOOSTER DOSE OF MCV4 IN PREVIOUSLY IMMUNIZED HIV INFECTED CHILDREN AND YOUTH (VERSION 4.0)

INTRODUCTION

You/your child is being asked to take part in this research study extension because you/your child is infected with the human immunodeficiency virus (HIV), the virus that causes AIDS, and you/your child is at the age when the FDA approved vaccine for the prevention of meningitis, called MCV-4, is being routinely offered to children and youth. In addition, you/your child participated in Group 1 of P1065 Version 2.0 and Group 3 of P1065 Version 3.0, and completed at least 28 weeks of the study.

At this time, however, there is no exact information on the best way to use this vaccine in HIV infected children or youth. Based on the information obtained from Versions 2.0 and 3.0 of this trial we know that this vaccine appears to be safe in HIV-infected children/youth. We also know from this trial that most children and
youth with HIV infection make an immune response to this vaccine. The “immune response” is how your body recognizes and defends itself against bacteria, viruses, and substances that appear foreign and harmful to the body. This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want yourself or your child to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study extension. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you/your child agree to take part in this study, or to allow your child to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

Meningococci are bacteria that can cause meningitis. Meningitis is a disease that may be severe and even life-threatening. Research has shown that 15-24 year olds are at high risk for infection from meningococci, and that HIV-infected people may be at greater risk for this infection than healthy people. For more information about meningitis, please ask the study coordinator for a copy of the current version of the Vaccine Information Sheet on Meningococcal Vaccine, available on the Centers for Disease Control’s website (http://www.cdc.gov/nip/publications/VIS/vis-menin.pdf).

A vaccine, called MCV4, was developed to protect people against meningococcal infections. A single dose of this vaccine is recommended for people beginning at 11 years old. In 2009, the Advisory Committee for Immunization Practices (ACIP) of the Centers for Disease Control (CDC) updated its recommendations for use of MCV-4 in children and youth. The new recommendation for those who previously received this vaccine, and continue to be at increased risk for meningitis, is that they should receive another dose of the vaccine every 5 years.

The results from Version 2.0 of this study in which you/your child or youth already participated showed that the MCV4 appears to be safe in HIV-infected children and youth. The majority of people were able to make an immune response to the vaccine. However, we do not know how long that response lasts. The CDC is recommending a booster dose of MCV 5 years after the initial dose. We do not know how HIV-infected children and youth will respond to a booster dose of MCV4.

The full name of the vaccine is Quadrivalent Meningococcal Conjugate Vaccine (MCV4). The brand name of the vaccine is Menactra®. The vaccine used in this
study will be provided by Sanofi-Pasteur Laboratories. This vaccine cannot cause meningococcal infection. The purpose of this study extension is to look at the following things:

- To see how well the antibodies (substances the body makes in response to an infection or vaccination to help fight off disease) lasted 3 years +/- 6 months after the original dose of the vaccine;
- To see how the booster vaccine will work in stimulating the body’s defense system to produce antibodies to the meningococcal bacteria;
- To see the antibodies that are produced after receiving the booster vaccine in those who produced very low or no antibodies after the original dose of the vaccine;
- To see the short-term (up to 24 weeks) antibodies produced after receiving the booster vaccine;
- To compare all of the information above between those who originally received one dose and two doses of the vaccine.

WHAT DO MY CHILD OR I HAVE TO DO IF MY CHILD OR I AM IN THIS STUDY?

Before Starting the Study Extension (“Screening Visit”; this will take about 1½ hours to complete)

Once you agree/allow your child to participate in this study, you/your child will have some basic blood tests done and be asked some questions to be sure you/your child can participate in this study.

- The study staff will ask you some questions about your/your child’s medical history, including immunizations, and use of any past or present anti-HIV drugs. You/your child may be asked for permission to review your/your child’s medical records. If you/your child received the MCV-4 vaccine outside of the P1065 study (after completing participation in a previous version of the study), you/your child cannot be in the new version.
- You/your child will have a physical exam to check on your/your child’s height, weight, vital signs (such as blood pressure), and symptoms.
- About 1½ teaspoon (7 ml) of blood will be taken to measure the levels of HIV and T cells, and to perform basic blood tests.
- Girls/women who have had their first menstrual period will have a pregnancy test. A small amount of urine or blood (less than 1 teaspoon) will be taken for this test. You/your child will be informed of the test result as soon as it is available. If you/your child are pregnant, you/your child cannot be in this study.
- If you or your child is breastfeeding, you/your child cannot be in this study.
APPENDIX VI

During the Study Extension

At the “Enrollment Visit” (which can occur on the same day as the screening visit, although it is not required, and will take about 1½ hours to complete) the following will take place:

- About 2½ teaspoons (12 ml) of blood will be drawn for laboratory tests to look for antibodies for meningitis, to measure the levels of HIV and T cells, and to perform basic blood tests.
- You/your child will have a physical exam and review of symptoms, medications, and medical history.
- Girls/women who have had their first menstrual period will have a pregnancy test. A small amount of urine or blood (less than 1 teaspoon) will be taken for this test. A negative pregnancy test result must be obtained before you/your child can receive the vaccine.
- Study staff will check to make sure there is no reason that you/your child should not get the vaccine. If so, you/your child will be given his/her first dose of vaccine at this visit.
- After vaccine administration, you/your child will remain in the clinic for at least 30 minutes (½ hour) so that clinic personnel can observe you/your child to make sure that no reactions to the vaccine develop.
- You/your child will be instructed to report any unusual reactions that occur.

One week after you/your child receives the vaccine (this visit will take about ½ hour to complete):

- You/your child will return to the clinic for a physical examination to check on your/your child’s height, weight, vital signs (such as blood pressure), and symptoms. You/your child will also have a review of symptoms, medications, and medical history.
- A small amount of blood (1 teaspoon or 5 ml) will be taken to measure the level of antibodies against the meningitis bacteria.
- You/your child will be asked if you/your child had side effects after receiving the vaccine.

Four weeks after you/your child receives the vaccine (this visit will take about ½ hour to complete):

- You/your child will be re-examined at the clinic.
- A small amount of blood (1 teaspoon or 5 ml) will be taken to measure the level of antibodies against the meningitis bacteria.
- You/your child will have a physical exam and review of symptoms, medications, and medical history.
APPENDIX VI

Twenty four weeks after you/your child receives the vaccine (this will be your/your child’s final visit and will take about ½ hour to complete):

- You/your child will be re-examined at the clinic.
- A small amount of blood (1 teaspoon or 5 ml) will be taken to measure the level of antibodies against the meningitis bacteria.
- You/your child will have a physical exam and review of symptoms, medications, and medical history.

Early Discontinuation Study Visit

If you/your child stop taking part in receiving study vaccine at any time, you/your child will be asked to continue with study visits. If you/your child no longer want to be in this study, or no longer can be in this study, you/your child will be asked to come to the clinic one last time. At this last visit, some or all the laboratory tests described before will be done if tests have not been done at a recent study visit. A little over 2 teaspoons (11 ml) of blood will be drawn for these tests. No vaccine will be given at this early discontinuation study visit. You/your child will have a physical exam and review of symptoms and medications at this visit. This visit will take about ½ hour to complete.

OTHER INFORMATION:

You/your child will be given the results of your/your child’s routine laboratory tests when they become available. The information and knowledge that comes out of doing this study may be used for other research related to HIV disease and approved by IMPAACT. The summaries and conclusions about the different things looked at by this study may be used in designing future research studies about vaccinations and HIV disease that are similar to the problems studied in this research. No individual information in the IMPAACT study records will be looked at or used for this purpose. The results of blood tests for measuring antibody response to MCV4 will not be provided to you or your doctor. These tests will not be run at the time they are received. Instead they will be run in batches or at the end of the study.

GENETIC TESTING FOR THOSE WHO WERE IN GROUP 3 IN P1065 VERSION 3.0:

_____ Not applicable: Participated in Group 1 of P1065 Version 2.0.

At the visit one week after your child receives the vaccine, about 1 teaspoon (5 ml) of blood will be drawn and stored while your child are taking part in this study and
APPENDIX VI

while the samples are still being studied. This sample will be used for genetic
testing, which is a study of your child’s genes (DNA). In case that the sample cannot
be collected one week after your child receives the vaccine, the site will try to collect
the sample at 4 weeks or 24 weeks after. The sample will only be collected once and
your child will not be stuck separately to collect the sample. This will help
researchers understand how different people may respond in different ways to the
MCV4 vaccine. The researchers do not plan to contact you, your child, or the study
doctor with the results of these studies. This is because research studies are often
done with experimental procedures, and these results should not be used to make
decisions about your child’s HIV care.

However, in case researchers learn new information that makes them believe that a
certain study result is important for your child’s HIV care, then your child’s study
doctor will be informed. If you would like the researchers to also tell you this
information in a case like this, then, you will need to tell the study staff if your
child’s address or phone number change. You may decide that you do not want
your child’s blood used for genetic testing. Your child can still be in this study even
if you make this decision. Please read the statement below, and mark your initials
in the spaces.

Please indicate below whether you agree to allow your child’s blood to be used for
genetic testing as part of this study.

____________ Yes  ____________ No  ____________ Date

STORAGE OF BLOOD SAMPLES FOR FUTURE TESTING:

For NICHD Sites Only:

With your permission, samples of your/your child’s blood specimens collected as
part of this study that are left over after testing for this study will be stored instead
of being destroyed. The stored specimens will be used for future IMPAACT-
approved, HIV-related research. The left-over samples that will be stored will not
be used for future genetic testing. Limited information such as sex, age, ethnicity,
and health history may be linked to the stored samples. There is a separate consent
form to explain this and get your/your child's permission.

For NIAID Sites Only:

With your permission, samples of your/your child’s blood that are left over after
testing for this study will be stored (with usual protectors of identity) instead of
being destroyed and used for future IMPAACT-approved, HIV-related research.
This includes blood samples taken during this extension study and blood samples
APPENDIX VI

that may be left over from your/your child’s participation in earlier parts of this study. The left-over samples that will be stored will not be used for future genetic testing. Limited information such as sex, age, ethnicity, and health history may be linked to the stored samples.

Your/your child’s samples will be stored at a special laboratory facility. Only approved researchers will have access to them. People who work at the facility will also have access to your/your child’s samples to keep track of them. These people won’t have information that directly identifies you/your child. Your/your child’s samples will not be sold or directly used to produce commercial products. All proposed research studies using your/your child’s samples will be reviewed by the National Institutes of Health (NIH). There is no time limit on how long your/your child’s samples will be stored.

The researchers do not plan to contact you or your/your child’s regular doctor with the results of studies done using your/your child’s stored samples. This is because research studies are often done with experimental procedures. The results of such studies should not be used to make decisions about your/your child’s medical care. If the researchers decide that the result of a certain study provides important information for your/your child’s medical care, your/your child’s study doctor will be notified. If you would like to be contacted with this sort of information, you must notify the study staff of any changes in your address or phone number.

You may decide that you do not want your/your child’s samples stored for future research studies. You/your child can still participate in this study even if you make this decision.

You may withdraw your consent for the storage and use of your/your child’s samples at any time. If you withdraw your consent, these stored samples will be destroyed.

Please read the following statement carefully and then mark your initials in the appropriate space provided.

Please indicate below whether you agree to allow your/your child’s blood samples to be stored for use in future IMPAACT-approved, HIV-related research studies.

__________ Yes  __________ No  __________ Date
APPENDIX VI

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 192 – 220 participants will take part in this study extension. But if all those who can take part in the study are able and agree to participate, the most that is expected is 275 participants.

HOW LONG WILL I/MY CHILD BE IN THIS STUDY?

You/your child will be in this study extension for 24 weeks.

WHY WOULD THE DOCTOR TAKE ME/MY CHILD OFF THIS STUDY EARLY?

The study doctor may need to take you/your child off the study early without your permission if:

- The study is cancelled by the US Food and Drug Administration (FDA), National Institutes of Health (NIH), Sanofi Pasteur Laboratories, Office of Human Research Protections (OHRP), or the site’s Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research subjects)
- You/your child are not able to attend the study visits as required by the study
- The Safety Monitoring Committee (SMC), who oversees the safety of this trial, recommends that the study be stopped.

The study doctor may also need to take you/your child off the study vaccine(s) without your permission if:

- Continuing the study vaccine may be harmful to you/your child
- You/your child is not able to take the study vaccine as required by the study
- You/your child need treatment not allowed in the study.
- You/your child become pregnant.
- You/your child are breastfeeding.

If you/your child must stop taking the study vaccine(s) before the study is over, the study doctor may ask you/your child to continue to be part of the study and return for some study visits and procedures. If you/your child must stop taking the study vaccine because you/your child become pregnant or are breastfeeding, you/your child will still be followed in the study. The care related to pregnancy, delivery and care of the baby will not be provided during the follow-up visits for the study. You/your child may be contacted after you/your child completes participation in the study so that the study doctor will know the outcome of your/your child’s pregnancy.
APPENDIX VI

WHAT ARE THE RISKS OF THIS STUDY?

Risk of Blood Draws
You/your child may feel faint or may feel some discomfort while having blood taken. There may be some swelling, bleeding, or bruising where the needle goes into the skin, or a small blood clot may develop. There is a small risk of infection forming where the needle goes into the skin to take blood.

Risks Related to the Vaccine
Approximately 7642 people aged 11-55 years of age were enrolled in the MCV4 vaccine clinical studies conducted by Sanofi Pasteur. Subjects were monitored for 28 days for both local and general clinical complaints, and for 6 months after the vaccination for visits to an emergency room, unexpected visits to a doctor’s office, and serious adverse experiences. About 7000 participants completed the 6 month follow-up evaluation.

In these studies, MCV4 vaccine has been generally well-tolerated. The most common side effects that may occur as a result of the MCV4 injection in this study, which are similar to those observed with other commonly used vaccines, include skin redness, pain, tenderness, soreness, and swelling at the site of injection. You/your child may also experience headache and low energy.

A few cases of Guillain-Barré Syndrome (GBS), a rare but serious nervous system inflammatory disease of the peripheral nerves, have been reported among some people who received MCV4. The peripheral nerves send sensory information (e.g., pain, temperature) from the body to the brain and motor (i.e., movement) signals from the brain to the body. Symptoms of GBS include weakness and numbness or tingling in the legs and arms, and possible loss of movement and feeling in the legs, arms, upper body, and face. The frequency of GBS is about 1 to 2 cases in every 100,000 people per year in the United States. Men and women, young and old, are equally likely to contracting GBS.

In June of 2010, the CDC reviewed new information about GBS after MCV4 from a study of millions of youth. The CDC concluded that there was no increase in GBS risk after MCV4. It is also not known if GBS cases would be more likely, as likely or less likely in HIV infected people who get this vaccine.

The following side effects have been reported by people who received MCV4:

- Headache
- Fever
- Chills
APPENDIX VI

- Diarrhea
- Loss of appetite
- Vomiting
- Joint pain
- Flu symptoms
- Common cold symptoms
- Abdominal pain
- Dizziness
- Feeling tired
- Pain, itching, redness, bruising or swelling at the injection site

There are other less common side effects that your/your child’s study doctor can identify for you. The study doctor or staff will discuss these with you/your child. There can be other side effects that are not presently known about the MCV4 vaccine.

ARE THERE RISKS RELATED TO PREGNANCY?

This section applies to you/your child only if you/your child can become pregnant. It is not known if the vaccine used in this study can harm unborn babies. If you/your child are having sex that can lead to pregnancy, you/your child or your/your child’s partner must agree to use one of the methods of birth control listed below as long as you/your child are in this study. You/your child may discuss these choices with the study staff.

- Hormonal birth control drugs that prevent pregnancy given by pills, shots, or placed on or under the skin.
- Male or female condoms with or without a cream or gel that kills sperm.
- Diaphragm or cervical cap with a cream or gel that kills sperm.
- Intrauterine device (IUD).

Condoms are recommended because their appropriate use is the only contraception method effective for preventing HIV-1 transmission.

You/your child or your/your child’s partner must use the chosen method of contraception as long as you/your child are in this study. If you/your child can become pregnant, you/she must have a pregnancy test before you/she enters this study. The test must be negative. If you think you/your child may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you/your child about her choices. You/your child must have a negative pregnancy test before the second dose of vaccine may be given.

The manufacturer of the vaccine is keeping a record of females who are pregnant
APPENDIX VI

and receive the vaccine or those who become pregnant after receiving the vaccine. The record is called a pregnancy registry. If you/your child become pregnant while in the study, the study staff may ask if you/your child can be registered in the pregnancy registry for the vaccine.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you/your child take part in this study, there may be a direct benefit to you/him/her, but no guarantee can be made. Participants may develop antibodies (protective part of the blood to fight infections) against meningococcal infection and this may help prevent infection. It is also possible that you/your child may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DO I/DOES MY CHILD HAVE BESIDES THIS STUDY?

Instead of being in this study, you/your child may continue to be followed by your/your child’s regular doctor. A single dose of this vaccine is FDA approved for use in the age groups included in the study, and HIV is not a contraindication. It is possible that you/your child or youth could receive the vaccine off study. Please talk to your doctor about these and other choices available to you/your child. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

To help us protect your/your child’s privacy, we have obtained a Certificate of Confidentiality from the NIH. With this Certificate, the researchers cannot be forced to disclose information that may identify you/your child, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you/your child, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the US Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the Federal Food and Drug Administration (FDA).

People who may review your/your child’s records include: the FDA, (insert Name of Site) IRB, NIH, study staff, study monitors, Sanofi Pasteur Laboratories., and their designees.

You/your child should understand that a Certificate of Confidentiality does not prevent you/your child or a member of your/your child’s family from voluntarily
releasing information about your or your child’s participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify your child as a participant in the research project under the following circumstances: possible child abuse and/or neglect or risk of harm to you, your child, or others.

WHAT ARE THE COSTS TO ME?
You/your child will not be expected to pay for any study vaccinations, study related visits, or study procedures. Anti-HIV drugs will not be provided through this study.

Taking part in this study may lead to added costs to you/your child and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because you are/your child is taking part in a research study.

WHAT HAPPENS IF I AM/MY CHILD IS INJURED?
If you or your child are injured as a result of being in this study, you/your child will be given immediate treatment for you/his/her injuries. The cost for this treatment will be charged to your or your child’s insurance company. There is no program for compensation either through this institution or the NIH. You/your child will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY/MY CHILD’S RIGHTS AS A RESEARCH SUBJECT?
Taking part in this study is completely voluntary. You may choose not to take part in or allow your child to take part in this study, or you may remove yourself or your child from the study at any time. Your decision will not have any impact on your/your child’s participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you/your child are/is otherwise entitled.

We will tell you/your child about new information from this or other studies that may affect your/your child’s health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.
APPENDIX VI

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:
- name of the investigator or other study staff
- telephone number of above

For questions about your/your child’s rights as a research subject, contact:
- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above
APPENDIX VI

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to let your child take part in this study, please sign your name below.

_____________________                              ________________________________________
Participant’s Name (print)   Participant’s Signature and Date

____________________________                ________________________________________
Participant’s Legal Guardian (print) (As appropriate)  Legal Guardian’s Signature and Date

________________________                        _______________________________________
Study Staff Conducting Consent Discussion (print)  Study Staff Signature and Date

________________________                        _______________________________________
Witness’ Name (print) (As appropriate)  Witness’s Signature and Date
APPENDIX VII

FACT SHEET and TEMPLATE CONSENT FORM for
Specimen Storage at Repositories funded by the
National Institute of Child Health and Human Development (NICHD)

PARENT FACT SHEET

When your child joins this NICHD sponsored Study, you will be asked to give permission for having some specimens that the doctor or nurse will take from your child’s body saved in a repository. (A repository is a special laboratory with freezers where specimens like blood or tissue cells and body fluids that are taken from you during a study are kept. Your child’s name will not be on these specimens, only a special study number. The people who run the repository laboratory will not know your child’s name.)

Why have a repository?

Researchers can learn a lot from a study but as time goes by the tests that they used get better or new tests appear, and there is a need to learn more. When study volunteers consent to put specimens in the repository and consent to the researchers doing new tests on the specimens later after their time in the study is ended, these questions can be answered and more can be learned. None of these future studies would happen unless the Institutional Review Board overseeing the repository examines the study and makes sure that your child’s rights are being protected.

How will my child’s privacy be protected?

The only record that your child participated in this NICHD sponsored study is at the clinic where it is kept separate from your child’s health records and locked away.

Your child’s specimens in the repository will not have your child’s name on them. The specimens will have a special study code. It will be the same code that is on your child’s information in the NICHD sponsored Study from your child’s interviews and examinations. Again, none of this information will have your child’s name on it.

How would a researcher get to use the specimens in the repository?

If a researcher wants to do a test on specimens from the NICHD sponsored repository in the future, he or she will write up the idea and it will have to be approved by a committee to make sure the research is worthwhile. If the idea is approved, then coded specimens and coded information will be given to the researcher. The researcher will not know the names, addresses, or phone numbers of the people who gave the specimens to the repository.

Why wouldn’t I find out the results of the research using my child’s specimens?

You will not receive the results of research done with your child’s specimens. This is because research can take a long time and must use specimens from many people before results are known. Results from research using your child’s specimens may not be ready for
many years. Often when studies are first done, it is not always clear how to use the information from the study to change the health care that people receive. So none of these study results is likely to affect your child’s care right now, but they may be helpful to people like your child in the future. Your child’s specimens can last in the freezer for many years and there is no time limit to when studies could be done in the future.

Would I ever be contacted in the future about research using my child’s specimens?

All of the studies to be done in the future on your child’s specimens in the repository will be for the particular reasons that you agreed to. Every study that is planned to use specimens from your child and others from this NICHD sponsored Study has to be reviewed by a special committee of people known as an Institutional Review Board, who are not part of the Study. Their goal is to make sure that what is planned is the same kind of study that you had agreed to. If it is, then the research will go ahead since you would have agreed that these particular tests could be done without anyone contacting you to get your permission in the future.

If the study to be done is not like the kind of tests you agreed could be done, then the committee will decide if you need to be contacted to give permission for the new study.

I gave my permission to testing my child’s specimens in the repository, but what if I change my mind?

People always have the right to stop participating in research. So if you decide that you do not want researchers to be able to use the specimens from your child in the repository, you can contact the clinic staff. They will tell the repository that the specimens with the study code number linked to your child’s name in the clinic should not be studied. These specimens can be removed from the repository and destroyed if you tell us to do that.

What type of research will be done with my child’s specimens?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. If this would happen and these tests or drugs make money, there are no plans to share that money with the people who gave the specimens.

As part of this study (insert title), your child is being asked to have some (insert specimen source- blood, urine, tissue, genital fluid, saliva, etc.) taken. These specimens will go into the NICHD repository for research to be done at some time in the future so that more information can come from your child’s time in this NICHD sponsored Study.

You do not have to agree to store your child’s specimens for future tests for your child to take part in this study. Your child will not lose any benefits to which your child is entitled if you decide against storing your child’s specimens.
APPENDIX VII

You will also be asked to agree that these particular tests can be done without anyone contacting you to get your permission sometime in the future. No one doing these tests would know that these specimens came from your child and no one would contact you or your doctor or nurse with the results from these tests that might happen in the future.

TEMPLATE CONSENT FORM

What are the general HIV-related studies that can be done with the repository specimens?

Researchers would like to store your child’s specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications. They need specimens from people who have HIV and from those who do not. Sometimes, too, the specimens can be used to learn something about new problems that people with HIV have like liver disease, diabetes, and heart disease. These general studies would not include any genetic testing (looking at your child’s DNA).

Benefits: There are no direct benefits to your child. Your child will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your child’s study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your child’s name will not be available to the repository or to the scientists who may be doing any future test.

I give permission for the use of my child’s stored specimens for the purposes stated in the preceding section (general HIV-related tests).

___________________________  ___________________________  __________
Parent or Legal Guardian Signature  Witness Signature  Date

I give my assent to the use of my stored specimens for the purposes stated in the preceding section (general HIV-related tests).

___________________________  ___________________________  __________
Participant Signature  Witness Signature  Date

What are the special HIV-related studies that can be done with the repository specimens?

Researchers in this study would also like to store your child’s specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications through looking at how each person’s genetic makeup (your child’s DNA)
either protects them or puts them at greater risk. It may be that researchers use some of your child’s blood to make a “cell line”. That means the blood cells can keep dividing and give an endless supply of your child’s DNA for tests to be done in the future. This kind of information will be particularly important as scientists work toward a vaccine that could protect people from AIDS. They need specimens from people who have HIV and from those who do not.

Benefits: There are no direct benefits to your child. Your child will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your child’s study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your child’s name will not be available to the repository or to the scientists who may be doing any future test. Since there are no plans to give participants the results of the tests performed on their stored specimens, you will not receive any information on your child’s genetic makeup.

I give permission for the use of my child’s stored specimens for the purposes stated in the preceding section (special HIV-related tests).

<table>
<thead>
<tr>
<th>Parent or Legal Guardian Signature</th>
<th>Witness Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

I give my assent to the use of my stored specimens for the purposes stated in the preceding section (special HIV-related tests).

<table>
<thead>
<tr>
<th>Participant Signature</th>
<th>Witness Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

What if I have more questions?

If you have any questions about the repository, about storage, or the use of your child’s samples, contact (Study personnel) at (phone).

If you have questions about giving consent or your child’s rights as a research volunteer, contact the (Name of Institution) Institutional Review Board at (phone).

I refuse to have any specimen collected from my child stored in the repository.

<table>
<thead>
<tr>
<th>Parent or Legal Guardian Signature</th>
<th>Witness Signature</th>
<th>Date</th>
</tr>
</thead>
</table>
APPENDIX VIII

FACT SHEET and TEMPLATE CONSENT FORM for
Specimen Storage at the Repository of the National Institute of Child Health and Human Development (NICHD)
YOUTH FACT SHEET

When you join this NICHD sponsored Study, you will be asked to consent to having some specimens that the doctor or nurse will take from your body saved in a repository. (A repository is a special laboratory with freezers where specimens like blood or tissue cells and body fluids that are taken from you during the study are kept. Your name will not be on these specimens, only a special study number. The people who run the repository laboratory will not know your name.)

Why have a repository?

Researchers can learn a lot from a study but as time goes by the tests that they used get better or new tests appear, and there is a need to learn more. When study volunteers consent to put specimens in the repository and consent to the researchers doing new tests on the specimens later after their time in the study is ended, these questions can be answered and more can be learned. None of these future studies would happen unless the Institutional Review Board overseeing the repository examines the study and makes sure that your rights are being protected.

How will my privacy be protected?

The only record that you participated in this NICHD sponsored Study is at your clinic where it is kept separate from your health records and locked away.

Your specimens in the repository will not have your name on them, only a special study code. It will be the same code that is on your information in the NICHD sponsored Study from your interviews and examinations. Again, none of this information will have your name on it.

How would a researcher get to use the specimens in the repository?

If a researcher wants to do a test on specimens from the NICHD repository in the future, he or she will write up the idea and it will have to be approved by a committee to make sure the research is worthwhile. If the idea is approved, then coded specimens and coded information will be given to the researcher. The researcher will not know the names, addresses, or phone numbers of the people who gave the specimens to the repository.

Why wouldn’t I find out the results of the research using my specimens?

You will not receive the results of research done with your specimens. This is because research can take a long time and must use specimens from many people before results are known. Results from research using your specimens may not be ready for many years.
APPENDIX VIII

Often when studies are first done, it is not always clear how to use the information from the study to change the health care that people receive. So none of these study results is likely to affect your care right now, but they may be helpful to people like you in the future. Your specimens can last in the freezer for many years and there is no time limit to when studies could be done in the future.

Would I ever be contacted in the future about research using my specimens?

All of the studies to be done in the future on your specimens in the repository will be for the particular reasons that you agreed to. Every study that is planned to use specimens from you and others from this NICHD sponsored Study has to be reviewed by a special committee of people known as an Institutional Review board, who are not part of the Study. Their goal is to make sure that what is planned is the same kind of study that you agreed to. If it is, then the research will go ahead since you would have agreed that these particular tests could be done without anyone contacting you to get your permission in the future.

If the new study to be done is not like the kind of tests you agreed could be done, then the committee will decide if you need to be contacted to give consent for the new study.

I gave my consent to testing my specimens in the repository, but what if I change my mind?

People always have the right to stop participating in research. So if you decide that you do not want researchers to be able to use the specimens from you in the repository, you can contact the clinic staff. They will tell the repository that the specimens with the study code number linked to your name in the clinic should not be studied. These specimens can be removed from the repository and destroyed if you tell us to do that.

What type of research will be done with my specimens?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests or drugs. If this would happen and these tests or drugs make money, there are no plans to share that money with the people who gave the specimens.

As part of this study (insert title), you are being asked to have some (insert specimen source—blood, urine, tissue, genital fluid, saliva, etc.) taken from you. These specimens will go into the NICHD repository for research to be done at some time in the future so that more information can come from your time in this NICHD sponsored Study.

You do not have to agree to store your specimens for future tests to take part in this study. You will not lose any benefits to which you are entitled if you decide against storing your specimens.
APPENDIX VIII

TEMPLATE CONSENT FORM

What are the general HIV-related studies that can be done with the repository specimens?

Researchers would like to store your specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications. They need specimens from people who have HIV and from those who do not. Sometimes, too, the specimens can be used to learn something about new problems that people with HIV have like liver disease, diabetes, and heart disease. These general studies would not include any genetic testing (looking at your DNA).

Benefits: There are no direct benefits to you. You will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your name will not be available to the repository or to the scientists who may be doing any future test.

I consent to the use of my stored specimens for the purposes stated in the preceding section (general HIV-related tests).

___________________________ ___________________________   ___________________________
Participant Signature   Witness Signature       Date

What are the special HIV-related studies that can be done with the repository specimens?

Researchers in this study would also like to store your specimens to understand how HIV causes disease and complications, and how best to treat or prevent HIV infection and its complications through looking at how each person’s genetic makeup (your DNA) either protects them or puts them at greater risk. It may be that researchers use some of your blood to make a “cell line”. That means the blood cells can keep dividing and give an endless supply of your DNA for tests to be done in the future. This kind of information will be particularly important as scientists work toward a vaccine that could protect people from AIDS. They need specimens from people who have HIV and from those who do not.

Benefits: There are no direct benefits to you. You will be helping researchers learn more about how to help people with HIV or at risk of HIV infection.

Risks: The specimens would be collected as part of your study visits. (Insert text about collection procedures.) Once in the repository, there are few risks. Your name will not be available to the repository or to the scientists who may be doing any future test. Since there are no plans to give participants the results of the tests
APPENDIX VIII

performed on their stored specimens, you will not receive any information on your genetic makeup.

| I consent to the use of my stored specimens for the purposes stated in the preceding section (special HIV-related tests). |
| Participant Signature | Witness Signature | Date |

What if I have more questions?

If you have any questions about the repository, about storage, or the use of your samples, contact (Study personnel) at (phone).

If you have questions about giving consent or your rights as a research volunteer, contact the (Name of Institution) Institutional Review Board at (phone).

| I refuse to have any specimen collected for storage in the repository. |
| Participant Signature | Witness Signature | Date |