

CLINICAL STUDY PROTOCOL

V98_05 Ver 5.0

**A Phase II Open-Label, Multi-Center Study of a Group B Streptococcus Vaccine in HIV
Positive and HIV Negative Pregnant Women**

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Name of Sponsor Novartis Vaccines and Diagnostics (NVD)	Protocol number: V98_05	Eudract number: N/A	Date of Synopsis: 18AUG10
Title of Study: A Phase II Open-Label, Multi-Center Study of a Group B Streptococcus Vaccine in HIV Positive and HIV Negative Pregnant Women			
Detailed Title of Study: A Phase II Open-Label, international Multi-Center Study of a Group B Streptococcus polysaccharide conjugate Vaccine administered intramuscularly to HIV Positive and HIV Negative Pregnant Women			
Publication (reference): N/A			
Study Period: <i>approx.</i> 4-6 months		Clinical Phase: Phase II	
Rationale: Group B streptococcus (GBS) is a leading cause of newborn bacterial infection worldwide. No vaccine exists to prevent this infection. Antibody (Ab) against the capsular polysaccharide (CPS) of GBS is known to be protective. Furthermore, pre-clinical and large epidemiologic studies have shown that maternal Ab against GBS CPS confers newborn protection. A GBS vaccine capable of inducing protective levels of circulating anti-CPS antibodies in maternal blood prior to delivery is expected to protect infants from invasive GBS disease. Protection of the newborn is dependent on trans-placental transfer of maternal Ab to the infant which occurs predominantly in the third trimester of pregnancy. Ab levels in the newborn infant are determined in part by Ab level in maternal serum and by placental transfer efficiency ^{1,2} which is likely influenced by gestational age and birth weight. ³ Previous studies of measles susceptibility of infants have shown potential impact of maternal HIV infection on placental Ab transfer ⁴ . Given the high incidence of HIV infection in pregnant women in South Africa ¹ and Malawi and the high rates of newborn GBS disease in these same regions ^{5,6} , understanding placental transfer of maternal anti-GBS Ab in HIV ⁺ and HIV ⁻ women will be important to vaccine development. The current study is intended to investigate placental transfer of serotype-specific GBS Ab following vaccination with a CPS-based vaccine among HIV ⁺ and HIV ⁻ women. HIV ⁺ women will be stratified according to CD4 ⁺ T cell count using the threshold defined by the WHO (≤ 350 cells/ μ l) at which to begin anti-retroviral therapy. ⁷ Analysis of data from a phase Ib (V98_06) study (trivalent GBS, serotypes Ia, Ib and III vaccine) have shown an increase in overall serotype specific anti-GBS antibody serum concentrations but no significant differences in the serotype-specific Ab responses in healthy non-pregnant women injected with doses of 20 and 5 μ g of each glycoconjugate. No additional contribution from a higher dosage, inclusion of adjuvant (aluminum hydroxide) and administration of 2 versus 1 injection was observed, therefore the lowest dose (5 μ g) will be evaluated in the present study (V98_05).			
Study Agent/Intervention Description: Trivalent GBS CRM ₁₉₇ -glycoconjugate vaccine delivered as one injection by an intramuscular (IM) route in a volume of 0.5 mL at a dose of 5 μ g each (serotypes Ia, Ib and III).			

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Immunogenicity Objectives:

Primary:

- To compare placental transfer of serotype-specific GBS maternal polysaccharide Ab among infants born to HIV⁺ and HIV⁻ mothers

Secondary:

To study the kinetics of the maternal vaccine-induced serotype specific GBS Ab among HIV⁺ and HIV⁻ women

Exploratory:

- To study the transplacental serotype specific GBS Ab transfer in subjects who test positive for malaria.
- To investigate the relation between time from vaccination to delivery and antibody concentration in both mothers (at delivery) and infants (at birth)
- To investigate the decay of maternal serotype specific GBS Abs in infants in the first 6 weeks of life

Safety Objectives:

Pregnant Women:

- To assess safety and tolerability of a GBS trivalent vaccine in HIV⁺ and HIV⁻ women by assessing the incidence of local and systemic reactogenicity, adverse events, serious adverse events, and pregnancy outcome.
- To compare the paired (pre-vaccination, day of delivery), viral loads and CD4⁺ cell counts for the women in the HIV⁺ group.

Infants:

- To evaluate the health of newborns and infants of GBS vaccinated HIV⁺ and HIV⁻ mothers, by a clinical examination at birth and at 6 weeks of age.

Methodology:

HIV⁺ and HIV⁻ healthy pregnant women at 24-35 weeks gestation will be enrolled. HIV⁺ women will be stratified into 2 groups according to CD4⁺ count: ≤ 350 cells/ μ L but > 50 cells/ μ L and > 350 cells/ μ L. All study subjects will receive one intramuscular injection of a GBS trivalent vaccine.

Blood will be collected for serology: from mothers at day 1, 15 and 31, and at delivery. From infants blood will be collected at birth (or within 72 hours). Optimally, umbilical

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<p>cord blood will be collected from newborns if not available, newborn blood may be collected within 72 hours of birth. Mothers and infants will return 6 weeks after delivery / birth for the health status follow up. At this time point blood will be collected for serology from infants.</p>																		
<p>Number of Subjects Planned: Up to 270 pregnant women: up to 180 HIV⁺ stratified into 2 groups by CD4⁺ count [up to 90 subjects/group] and up to 90 HIV⁻ subjects. The sample size has been increased with the protocol amendment 2 from 180 to a maximum of 270 subjects to ensure a study population representative of both participating countries (Malawi and South Africa).</p>																		
<p>Subject Population: Pregnant women (24-35 weeks gestation) between 18-40 years of age.</p>																		
<table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th data-bbox="256 951 611 1058"></th> <th colspan="2" data-bbox="611 951 1254 1058">Number of Subjects Per Group</th> </tr> <tr> <th data-bbox="256 1058 611 1148">CD4⁺ Count</th> <th data-bbox="611 1058 935 1148">HIV⁺</th> <th data-bbox="935 1058 1254 1148">HIV⁻</th> </tr> </thead> <tbody> <tr> <td data-bbox="256 1148 611 1211"></td> <td data-bbox="611 1148 935 1211"></td> <td data-bbox="935 1148 1254 1211">up to 90</td> </tr> <tr> <td data-bbox="256 1211 611 1274">>350 cells/μL</td> <td data-bbox="611 1211 935 1274">up to 90</td> <td data-bbox="935 1211 1254 1274"></td> </tr> <tr> <td data-bbox="256 1274 611 1350">\leq350 cells/μL and > 50 cells/μL</td> <td data-bbox="611 1274 935 1350">up to 90</td> <td data-bbox="935 1274 1254 1350"></td> </tr> </tbody> </table>					Number of Subjects Per Group		CD4 ⁺ Count	HIV ⁺	HIV ⁻			up to 90	>350 cells/ μ L	up to 90		\leq 350 cells/ μ L and > 50 cells/ μ L	up to 90	
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>350 cells/ μ L	up to 90																	
\leq 350 cells/ μ L and > 50 cells/ μ L	up to 90																	
<p>Subject Characteristics and Main Criteria for Inclusion and Exclusion:</p> <p>Key Inclusions: Pregnant women between 24-35 weeks gestation and between 18-40 years of age inclusive.</p> <p>Key Exclusions: Women at risk for poor obstetrical outcome. Women who are severely immuno-compromised (CD4⁺ count \leq 50 cells/μL). Women who are HIV⁺ with WHO stage III or IV disease.</p>																		
<p>Investigational Test Vaccine:</p> <p>Each 3 mL vial contains 24 μg of each glycoconjugate. Before injection, the lyophilized vaccine will be re-suspended with 2.4 mL of saline solution. After re-suspension, the vial will contain each active substance at the final concentration (10 μg/mL). Injection of 0.5</p>																		

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mL of solution is used to deliver 5 µg of each glycoconjugate.

Immunogenicity Endpoints

The primary study endpoint is placental transfer (%) of serotype-specific GBS Ab measured as [newborn blood Ab concentration/maternal Ab concentration x 100] for each woman-infant pair.

The secondary immunogenicity endpoints are vaccine-induced maternal serotype-specific GBS Ab levels at baseline, study day 15 and 31 and at the time of delivery.

Sample Size Justification

The dropout rate is expected to be approximately 15%, which provides for about 50 evaluable women per HIV status group out of the 60 enrolled per group. The two HIV positive groups are defined by CD4 cell counts at screening. Assuming that about 80% of the women will deliver infants that are at ≥ 37 wks gestation or weight ≥ 2500 g at birth, this reduces the primary immunogenicity set to approximately 40 subjects. With a sample size of 40 per group, we have about 95% power to detect 8% difference in the % of placental transfer between any two study groups, i.e. about $0.95^3=85\%$ power for all three serotypes at once. The power calculation stipulates that the serotype-specific GBS Ab levels present in newborn blood relative to maternal antibody concentrations are uniformly distributed between 80% and 110% among HIV⁻ mothers³. The significance level alpha is set to $0.05/3 \sim 0.016$.

In addition, if the maximum number of subjects per group (i.e.90) is reached, holding true the same assumptions for the dropout rate and for the percentage of babies born at ≥ 37 wks gestation or weight ≥ 2500 g at birth, the number of evaluable subjects may increase up to 60 per group. With that sample size, the study will have about 95% power to detect 6.5% difference in the % of placental transfer between any two study groups, i.e. about $0.95^3=85\%$ power for all three serotypes at once.

Safety Endpoints

Vaccine safety will be assessed by measuring the incidence of local and systemic reactogenicity for 7 days post vaccination. All reported adverse events, serious adverse events throughout the study participation, including obstetrical outcome will be recorded as well.

The CD4 counts and HIV load measured at baseline, at day 31, at the day of delivery, and 6 weeks post -delivery.

Infants will be monitored for general safety including newborn outcome at birth and at 6 weeks of age.

Scheduled Interim Immunogenicity Analysis:

Interim Immunogenicity Analysis:

An interim immunogenicity analysis will be performed on data collected at the time of delivery to evaluate the proportion of maternal antibodies transferred to the newborns in either of the three study groups. The analysis will be carried out at the time when data up to delivery become available for at least 60 subjects per group, in each of the 3 groups (HIV⁻, HIV⁺ CD4^{>350}, HIV⁺ CD4^{≤350}) have delivered. The aim of the interim analysis is to give guidance on the population of interest for the phase III efficacy study.

Data Monitoring Committee:

A Data Monitoring Committee (DMC) will be available for reviewing safety signals in either vaccinated subjects or their infants.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Ab	Antibody
AE	Adverse Event
AP	(Statistical) Analysis Plan
ART	Antiretroviral Therapy
BCDM	Biostatistics and Clinical Data Management
B&SR	Biostatistics and Statistical Reporting
CFR	Code of Federal Regulations
CPS	Capsular polysaccharide
CRF	Case Report Form
CRM	Modified diphtheria toxoid
DMC	Data Monitoring Committee
ELISA	Enzyme-Linked Immunosorbent Assay
EDC	Electronic Data Capture
EDT	Electronic Data Transfer
EC	Ethics Committee
FAS	Full Analysis Set
GBS	Group B Streptococcus
GC	Glycoconjugate
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GMP	Good Manufacturing Practice
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IM	Intramuscular
IMP	Investigational Medicinal Product
IWR	Interactive Web Randomization
ITT	Intention-To-Treat
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intention-To-Treat
NVD	Novartis Vaccines and Diagnostics
mL	Milliliter
PP	Per Protocol
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
WHO	World Health Organization

1.0 BACKGROUND AND RATIONALE

Group B streptococcus (GBS) is a leading cause of newborn bacterial infection worldwide. No vaccine exists to prevent this infection. Antibody (Ab) against the capsular polysaccharide (CPS) of GBS is known to be protective. Furthermore, pre-clinical and large epidemiologic studies have shown that maternal Ab against GBS CPS confers newborn protection. A GBS vaccine capable of inducing protective levels of circulating anti-CPS antibodies in maternal blood prior to delivery is expected to protect infants from invasive GBS disease. Protection of the newborn is dependent on trans-placental transfer of maternal Ab to the infant which occurs predominantly in the third trimester of pregnancy. Ab levels in the newborn infant are determined in part by Ab level in maternal serum and by placental transfer efficiency^{1,2}. Transplacental antibody transfer may be affected by a number of factors, including gestational age, malnutrition, malaria, maternal hypergammaglobulinemia and HIV infection. Malaria, caused by *Plasmodium falciparum*, is implicated in basement membrane thickening and antibody receptor damage in the placenta³.

Malaria is endemic in all parts of Malawi, with the majority of cases caused by *P. falciparum*. In contrast, in South Africa the risk for malaria is relatively low (<http://www.who.int/malaria/publications/country-profiles>).

Previous studies of measles susceptibility of infants have shown potential impact of maternal HIV infection on placental Ab transfer⁴. Understanding placental transfer of maternal anti-GBS Ab in HIV⁺ and HIV⁻ women will be important to vaccine development. The study will be performed in Malawi and South Africa because of the high prevalence of HIV infection in pregnant women in South Africa (15-36%)^{1,11} and Malawi (15-27%)^{8,11} and the high incidence rates of newborn GBS disease (0.8 to 3.0 per 1000 live births) in these same regions^{5,6}. Regional differences account for the high variability of HIV⁺ prevalence rates in pregnant women, mentioned above. The current study is intended to investigate placental transfer of serotype-specific GBS Ab following vaccination with a CPS-based vaccine among HIV⁺ and HIV⁻ women. HIV⁺ women will be stratified according to CD4⁺ T cell count using the threshold defined by the WHO (≤ 350 cells/ μ L) at which to begin anti-retroviral therapy.⁷

NVD GBS vaccine components have been examined in Phase I studies in healthy non-pregnant Swiss women (clinical protocols V98P1, V98P2). Over 150 women received one or two injections of 5, 10 or 20 μ g of a CRM₁₉₇ glycoconjugate. The NVD vaccine was uniformly well-tolerated with no serious vaccine-related effects and only minimal local reactogenicity. All doses were found to be immunogenic although no clear dose-response was evident. These data have been confirmed by results from a Phase Ib study (V98_06) showing no significant differences in the serotype-specific Ab responses in healthy non-pregnant women injected with a 20, and 5 μ g dose of the vaccine. Moreover, neither the presence of aluminum hydroxide, nor the use of a second injection resulted in an enhanced vaccine induced immune response.

The use of an established protein component such as the modified diphtheria toxoid (CRM) has been found to have potent adjuvant activity when conjugated to GBS CPS.⁹ CRM has a well established safety profile as a component of licensed Haemophilus influenzae type b, Meningococcal C and Pneumococcal conjugate vaccines. Substantial experience exists with other Novartis CRM₁₉₇ conjugated-polysaccharide vaccines and these have an excellent safety profile.¹⁰

Reproductive and developmental toxicity study showed that GBS trivalent vaccine did not lead to maternal toxicity, or effects on mating or the pregnancy rate in either species in rats and rabbits. In these animals maternal vaccination did not cause effects in the survival, clinical condition or body weight of offspring through to the end of the preweaning period¹².

The current study will examine a GBS trivalent vaccine consisting of all three glycoconjugate serotypes in equal proportions. One dose (5 µg of each serotype Ia, Ib and III) will be studied. This is the lowest dose administered in previous studies in healthy non-pregnant women. An adjuvant will not be used and a second injection of the vaccine will not be administered in this study because previous studies have conclusively demonstrated no increase of immunogenicity when aluminum hydroxide was added to the vaccine formulation or when a second injection was administered to healthy adults.

A comprehensive review of the GBS candidate vaccine is contained in the Investigator's Brochure supplied by NVD; this document must be reviewed prior to initiating the study.

This trial will be conducted in compliance with the protocol, GCP and all applicable regulatory requirements.

2.0 OBJECTIVES

Immunogenicity Objectives

Primary

- To compare placental transfer of serotype-specific GBS maternal polysaccharide Ab among infants born to HIV⁺ and HIV⁻ mothers

Secondary

- To study the kinetics of the maternal vaccine-induced serotype specific GBS Ab geometric mean concentrations (GMCs) among HIV⁺ and HIV⁻ women.

Exploratory

- To study the transplacental serotype specific GBS Ab transfer in subjects who test positive for malaria.
- To investigate the relation between time from vaccination to delivery and antibody concentration in both mothers (at delivery) and infants (at birth)
- To investigate the decay of maternal serotype specific GBS Abs in infants

Safety Objectives

Pregnant Women:

- To assess safety and tolerability of a GBS trivalent vaccine in HIV⁺ and HIV⁻ women by incidence of local and systemic reactogenicity, adverse events, serious adverse events, and pregnancy outcome.
- To compare the paired (pre-vaccination, day of delivery), viral loads and CD4⁺ cell counts for the women in the HIV⁺ group.

Infants:

- To evaluate the health of newborns and infants of GBS vaccinated HIV⁺ and HIV⁻ mothers, by a clinical examination at birth and at 6 weeks of age.

3.0 STUDY DESIGN AND INVESTIGATIONAL PLAN

3.1 Overview of Study Design

A Phase II Open-Label, international Multi-Center Study of a Group B Streptococcus polysaccharide conjugate Vaccine administered intramuscularly to HIV Positive and HIV Negative Pregnant Women. Up to 270 pregnant women will be enrolled; Up to 180 HIV⁺ pregnant women stratified into 2 groups by CD4⁺ count [up to 90 subjects/group] and up to 90 HIV⁻ subjects. The sample size has been increased with the protocol amendment 2 from 180 to a maximum of 270 subjects to ensure a study population representative of both participating countries (Malawi and South Africa).

All subjects must first sign an informed consent form and be screened prior to being enrolled in the study.

3.2 Discussion of Overall Study Design

HIV⁺ with WHO stage I or II disease and CD4⁺ counts > 50 cells/μL, and HIV⁻ healthy pregnant women at 24-35 weeks gestation will be enrolled. HIV⁺ women will be stratified into 2 groups according to CD4⁺ count: (i) ≤ 350 cells/μL but > 50 cells/μL and (ii) > 350 cells/μL as obtained at screening. This stratification is based on the WHO threshold to initiate ART and excludes women with profoundly low CD4⁺ counts who may have impaired capacity to respond to vaccination in the first place. All study subjects will receive one injection of the GBS trivalent vaccine.

	Number of Subjects Per Group	
CD4 ⁺ Count	HIV ⁺	HIV ⁻
		up to 90
> 350 cells / μ L	up to 90	
\leq 350 cells / μ L and > 50 cells / μ L	up to 90	

Use of clinical measures such as fundal height (supplemented by recall of last menstrual period) may not be as reliable in HIV infected women. Since this study will in part evaluate the placental transfer of Ab (which can be affected by gestational age), a more accurate estimate will aid in interpreting placental Ab data. Accordingly, for this study gestational age will be determined by ultrasound assessment.

Local standard of care for HIV treatment of HIV positive pregnant women and infants will be carried out in parallel and will not be affected by the study participation. As part of local standard of care in both countries (Malawi and South Africa), the HIV status from infants born to HIV positive mothers will be evaluated at six weeks of age. The information on infant HIV status from infants born to HIV positive mothers will be collected as part of safety data information. Written informed consent must be obtained from the mother before obtaining information on the HIV status of their infants. Mothers who consent to provide this information will be contacted after the end of study visit by the study personnel. Data will be considered missing after three attempts to contact the mother.

Follow-up of subjects

Any local or systemic reactions occurring in vaccinated subjects within 7 days after injection will be recorded by the subject in a diary card. Subjects will specifically be asked to record systemic reactions such as any fever (*i.e.* oral temperature \geq 38°C or axillary \geq 37.5°C), chills, malaise, headache, myalgia, arthralgia, rash, nausea and/or fatigue. Subjects who require help in entering safety data in in the diary card will be helped by the site personnel who will visit them at home in the first week after injection. Support will be limited to data entry and is not intended influencing subject reported outcome. All adverse events will be collected until 30 days after the injection (Visit 5). From day 31 until the end of the trial all adverse events requiring a physician's visit will be collected. Serious adverse events will be collected throughout the study from mothers (see section 6). For infants all adverse events requiring a physician's visit and SAEs will be recorded. As part of the safety analysis the outcome of the pregnancy will be assessed. Moreover, health status of newborns will be assessed (incl. APGAR). Hospitalization due to normal delivery will not be treated as SAE in the context of this study.

Phone calls will be made at day 8 and 61 to monitor the subject's safety.

Blood will be collected for serology from pregnant women at day 1, 15 and 31, and from mothers and infants at delivery / birth (or within 72 hours). Optimally, umbilical cord newborn blood will be collected – if not available, blood may be collected from the newborn. From infants blood will be collected for serology also at the age of 6 weeks.

Mothers and infants will return at 6 weeks post partum for health status follow up. HIV⁺ mothers will be assessed for CD4 counts and HIV load. Blood collection for serology will be performed at this time point from the infant only.

3.3 Study Procedures and Flowchart

Written informed consent must be obtained before performing any trial specific tests or evaluations. A total of 6 study-related visits are planned for pregnant women / **mothers and 2 study visits** for newborns. The procedures performed at each visit for mothers and infants are provided in detail.

Visit 1: ♀ **Mother** Study Day -21 to 0 Screening Visit

1. Explain the study procedures and obtain signature of informed consent.
2. Check that eligibility criteria are met.
3. Assign a subject *screening* number.
4. Obtain medical history and record any concomitant medications that the subject is currently taking.
5. Perform screening for Hb by standardized automated method.
6. Perform diagnostic test for malaria (blood smear).
7. Perform a complete physical examination.
8. Assess gestational age of the fetus by ultrasonography (following international guidelines).
9. Unless HIV status is already known positive and documented, collect blood (approx.10 mL) for HIV testing. For HIV⁺ subjects, determine CD4⁺ count and viral load.
10. Assign date of appointment for the next visit.
11. Ensure subject information and data entry into EDC.

Visit 2: ♀ **Mother** Study Day 1 Injection

1. Check that all eligibility criteria are met.
2. Record any new or continuing concomitant medications.
3. Record any additional medical history.
4. Assess/record any AEs or SAEs since last visit.
5. Perform a brief complaint-focused physical exam and visual evaluation of the intended injection site.

6. Perform screening for malaria (blood smear).
7. Collect blood (approx. 10 mL) for GBS Ab assays.
Process blood and store serum as described in the Study Serology Manual
8. Obtain a subject number.
9. Administer injection.
10. Observe subject for 30 minutes post injection for any local or systemic reactions.
11. Provide diary card and explanation for use.
12. Assign date of appointment for the next visit.
13. Ensure subject information and data entry into EDC.

Visit 3 (Phone call): ♀ Mother Study Day 8 (-1/+1 day)

1. Record any new or continuing concomitant medications.
2. Record any additional medical history.
3. Assess/record any AEs or SAEs since last visit.
4. Assign date of appointment for the next visit.

Visit 4: ♀ Mother Study Day 15 (-2/+2 days)

1. Record any new or continuing concomitant medications.
2. Record any additional medical history.
3. Assess/record any AEs or SAEs since last visit.
4. Collect and perform review of diary card and provide subjects with the Memory Aid and explanation for use.
5. Collect blood (approximately 10 mL) for GBS Ab assays
Process blood and store serum as described in the Study Serology Manual
6. Assign date of appointment for the next visit.

Visit 5: ♀ Mother Study Day 31 (-4/+7 days)

1. Record any additional relevant medical history.
2. Record any new or continuing concomitant medications.
3. Assess/record any AEs or SAEs since the last visit.
4. Perform a brief complaint-focused physical exam.
5. Perform diagnostic test for malaria (blood smear).
6. Collect 5 mL blood from HIV⁺ subjects for CD4⁺ count and viral load.
7. Collect blood (approximately 10 mL) for GBS Ab assays
Process blood and store serum as described in the Study Serology Manual

8. Collect and perform review of subject Memory Aid and provide new memory aid and explanation for use.
9. Assign date of appointment for the next visit.
10. Ensure subject information and data entry into EDC.

Visit 6 (Phone call): ♀ Mother Study Day 61 (-4/+7 day)

1. Record any new or continuing concomitant medications.
2. Record any additional medical history.
3. Assess/record any AEs requiring a physician's visit or SAEs since last visit.
4. Assign date of appointment for the next visit.

Visit 7: ♀ Mother – Labor & Delivery

1. Collect blood (10 mL) for GBS Ab assays (blood may be collected up to 72 hrs after delivery).
Process blood and store serum as described in the Study Serology Manual
2. Collect 5 mL blood from HIV⁺ subjects for CD4⁺ count and viral load.
3. Record any new or continuing concomitant medications.
4. Assess/record any AEs requiring a physician's visit or SAEs since the last visit.
5. Record obstetrical outcomes such as gestational diabetes, failed induction, lacerations, cesarean deliveries, postpartum infection, eclampsia, chorioamnionitis
6. Collect and perform review of subject Memory Aid and provide new memory aid and explanation for use
7. Assign date of appointment for the next visit.
8. Ensure subject information and data entry into EDC.

Concurrent Visits

Visit 1: Birth ( WITHIN 72 HRS) Newborn

1. Conduct full physical exam.
2. Conduct newborn Apgar assessments.
3. Assess/record any AEs requiring a non-physician's visit or SAEs
4. Record any medication
5. Collect cord blood (10 mL) for GBS Ab assays. If cord blood not possible, collect 0.5 -1 mL blood.
6. Process blood and store serum as described in the Study Serology Manual
7. Ensure subject information and data entry into EDC.

Visit 8: ♀ Mother Follow up Visit 1

Concurrent Visits

1. Record any additional medical history.
2. Record any new or continuing concomitant medications.
3. Assess/record any AEs requiring a physician's visit or SAEs since the last visit.
4. Collect 5 mL blood from HIV⁺ subjects for CD4⁺ count and viral load.
5. Collect subject Memory Aid.
6. Perform a complete physical examination.
7. Ensure subject information and data entry into EDC.
8. Obtain from HIV positive mothers the signature of a separate informed consent to authorize the investigator to record the results of the HIV test performed on infants in the database

Visit 2:  Infant Study Day 42 (-7/+7 days)

1. Record medical history.
2. Assess/record any AEs requiring a physician's visit or SAEs since last visit
3. Record any new or continuing medications.
4. Conduct full physical exam.
5. Collect blood (0.5 -1 mL) for GBS Ab assays.
Process blood and store serum as described in the Study Serology Manual
6. Ensure subject information and data entry into EDC.

Times and Events Table

Study Periods	Screening ♀	Injection ♀	Post- Injection ♀	Post- Injection ♀	Post- Injection ♀	Post- Injection ♀	Post- Injection ♀ 	Follow -up ♀ 
Clinic Visit? (Yes/No) ^h	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Mother ♀ Clinic Visit Number	1	2	3	4	5	6 ⁱ	7	8
Study Day (Mother) ♀ (<i>Gestation in weeks</i>)	-21 to 0	1 (24-35)	8 (25-36)	15 (26-37)	31 (28-39)	61 ⁱ (32-43 ⁱ)	Delivery	n/a
Infant Clinic Visit Number							1	2
Study Day (<i>Infant age</i>)	n/a	n/a	n/a	n/a	n/a	n/a	1 (birth)	42 6 weeks
Study Visit Window (<i>Variance in days</i>)	n/a	n/a	-1/+1	-2/+2	-4/+7	-4/+7	(+72 hours)	±7
ICF	x							x ^k
Inclusion/Exclusion	x	x						
Medical history ^a	x	x	x	x	x	x		x ♀ x 
Physical exam	x ^b	x ^b			x ^b		x ^c 	x ♀ x 
Blood for HIV Tests ^e	x							
Blood for HIV load/CD4 ⁺ count (only for HIV ⁺)	x				x ^g		x ^g ♀	x ^g ♀

Malaria screening	x	x			x			
Hb testing	x							
Ultrasonography exam.	x							
Obstetric Outcomes ^d							x ♀	
GBS-Serology (blood)		x		x	x		x ♀ x 	x 
Vaccination		x						
Diary Card/Memory Aid Dispensed ^j		x		x	x		x ♀	
Diary Card/Memory Aid Reviewed/ Collected				x	x		x ♀	x ♀
Local/Systemic Reactions 30' post injection		x						
Assess AEs and SAEs ^f		x	x	x	x	x	x ♀ x	x ♀ x
Concomitant meds / meds for infants)	x	x	x	x	x	x	x ♀ x 	x ♀ x 
Study Termination								



represents mother



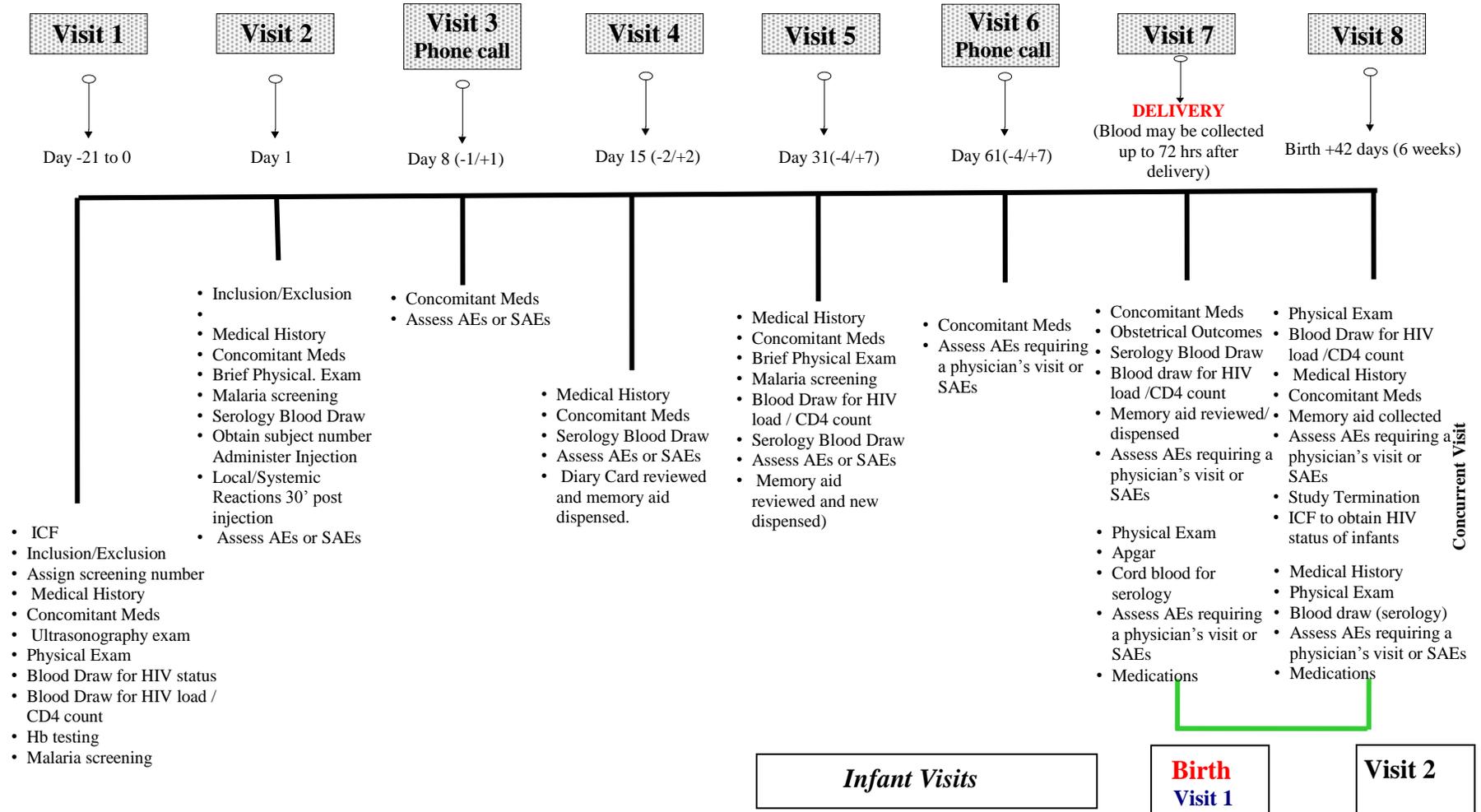
represents infants

- a. Full medical history required at screening for mother. Medical history of infant required for 6 week infant follow up. Medical history for mother, post screening visit refers to updates of medical history that are remembered and that occurred prior to start of study.
- b. PE must be performed by qualified health professional designated in Site Responsibility Delegation Log. Complete PE done for mother at screening visit 1 and visit 8. For brief physical exams of the mother (visits 2), the injection site (pre or post injection) and a complaint-focused physical examination should be conducted.
- c. Infant physical exam at birth to include Apgar score. Please refer to the EDC guidelines for the required components of the physical examination at birth.
- d. Outcomes such as *e.g.* gestational diabetes, failed induction, lacerations, cesarean deliveries, postpartum infection, eclampsia, chorioamnionitis.
- e. HIV testing will be performed using ELISA kits available at the study sites and may include HIVC, Determinante or Uni-Gold.
- f. AEs have to be recorded until day 31, AEs requiring a physician's visit and SAEs throughout the study for the mother. For infants, AEs requiring a physician's visit and all serious adverse events will be collected.
- g. HIV load and CD4 count have to be assessed only on the HIV positive women (blood HIV test positive at screening)
- h. Clinic visit "no" refers to telephone contact only with subject
- i. Phone call at day 61 should not be done if occurs on the same day of or after delivery
- j. Illiterate subjects will be supported in the diary card completion by the site personnel who will visit them at home in the first week after injection.
- k. Separate informed consent to authorize the investigator to record the results of the HIV test performed on the infants in the database

Early Termination Procedure

Any subject who terminates the study in the post-vaccination periods (post Day 1 – Birth) will be recommended to undergo Day 31 or day of birth (or within 72 hours thereof) study-related procedures to complete safety follow-up.

Visits for Pregnant Women and Infants



3.3.1 Subject Numbering

In compliance with GCPs, each subject will be unambiguously identified by a code, which allows the identification of all the data reported for each subject.

Proprietary numbering system
redacted

A screening number is assigned after signing the informed consent form. The screening number and the final subject number will be recorded in a screening log. Once assigned, a screening number or a subject number cannot be reused. In the event a subject does not meet eligibility and is considered a screen failure, the reason for screen failure must be documented. A subject who fails screening will not be assigned a subject number.

The investigator must keep track of the names of the subjects enrolled and their identifying number in a Subject Identification Code List.

Newborns will be identified by a number different from the one assigned to the mother.

Proprietary numbering system
redacted

3.3.2 Method of Assignment to Study Groups

Subjects will be assigned to study groups based on their HIV status (positive or negative). Those subjects who are HIV⁺ will be stratified into two groups;

- subjects with CD4⁺ counts of ≤ 350 cells/ μ L but > 50 cells/ μ L and
- subjects with > 350 cells/ μ L.

This stratification will be based on values obtained at the screening visit.

3.3.3 Blinding procedures

Not applicable. The study will be open label.

3.3.4 Vaccine Supply, Storage, Tracking and Labeling

The sponsor will supply the investigational vaccine to be used.

The investigator will acknowledge receipt of the investigational study vaccines. Study vaccines must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator or designee have

access. Upon receipt, investigator or designee will ensure study vaccines are received in good condition. The vaccines at the site must not be used before the appropriate shipping conditions have been checked and confirmed by sponsor to be authorized for use. Study vaccine will be labeled and will comply with the legal requirements of each country of trial conduct. All study vaccines must be stored according to the instructions specified on the labels.

Vaccines that have been stored differently from the manufacturer's indications **must not** be used unless the sponsor provides written authorization for use. In the event that the use cannot be authorized, vaccine supply will be replaced with fresh stock supplied by the sponsor.

Batches of investigational vaccines must be stored separately from normal hospital/practice stocks to prevent unintentional use of investigational products outside of the clinical trial setting.

The investigator will ensure that the investigational product(s) delivered to the site are used only in accordance with the approved protocol. Monitoring of drug accountability will be performed by the study monitor during site visits and at the completion of the trial.

The investigator will maintain an accurate record of products delivery to the site, the inventory at the site, the administration to the subjects, and the return to the sponsor of unused study vaccines. These records will include dates, quantities, batch number, expiration dates and the unique identifying number assigned to the investigational product and the subject.

A detachable label will be found either on the outer box or on the label of the primary container of the investigational product. The detachable label contains a unique identifier for each dose. The investigator must stick the detachable part of the label on the administration log upon dispensing of the vaccine to certify that the vaccine was effectively administered and for tracking purposes.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study vaccines, packaging and supplementary labels to NVD.

If the unused study vaccines are disposed at the site, the investigator must provide a copy of the site's procedure for destruction of hazardous material and documentation of the destruction. The following information must be included in the documentation of destruction:

- Lot number
 - Number of doses
 - Date of destruction

- Destruction code (if available)
- Method of destruction
- Destruction performed by:

3.3.5 Processing, Labeling and Storage of Serum Samples for Serology

For pregnant women, blood will be collected at study days 1, 15 and 31, and delivery (+72 hour collection window). Optimally, umbilical cord blood will be collected from newborn infants – if not available, newborn blood may be collected within 72 hours of birth. Infants will return at 6 weeks of age for blood collection (serology) and health status follow up.

Refer to the Serology Guideline for a detailed description of the processing, labeling, storage, and shipping of samples.

Samples will be retained in accordance with regulatory guidance for retention of essential study documents described in Section 10, provided that the integrity of the sample permits.

If the volume of serum samples permits, an aliquot of the sample will be kept locally for storage.

3.4 Duration of Subject's Expected Participation in the Entire Study

Expected subject trial participation interval: approximately 4 to 6 months for women (including a 6 week follow up with babies).

3.5 Stopping/Pausing Rules

There are no predetermined stopping rules other than those described in Section 4.3.

The sponsor or the investigator (following consultation with the sponsor) has the right to discontinue this study at any time. If the clinical study is prematurely terminated, the investigator is to promptly inform the study subjects and will assure appropriate therapy and follow-up for the subjects.

All procedures and requirements pertaining to archiving of the documents will be followed. All other study materials (study medication/vaccines etc) must be returned to the sponsor.

4.0 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

Inclusion Criteria
Pregnant women between 24-35 wks gestation at randomization as assessed by ultrasonography (biparietal diameter, femur length and abdominal circumferences) and between 18-40 years of age inclusive.
Individuals who have given written consent after the nature of the study has been explained according to local regulatory requirements.
Individuals who will be available for all scheduled visits (i.e. not planning to leave the area before the end of the study period).
Women who are HIV ⁻ or HIV ⁺ with WHO stage I or II disease and with CD4 ⁺ counts > 50 cells/ μ L

4.2 Exclusion Criteria

Exclusion Criteria
Individuals who are unwilling and/or unable to give written informed consent to participate in the study.
Individuals who will be unavailable for the duration of the study period.
Individuals who have had any vaccine within 15 days before enrollment through 15 days after the final study immunization. <i>Exception:</i> <ul style="list-style-type: none">Any vaccine that is recommended or allowed by local health authorities in pregnant women is permitted (includes tetanus toxoid vaccines).influenza vaccine adjuvanted with adjuvant different than alum may be administered up to 15 days prior to study vaccination and starting after delivery.
Individuals who receive any other investigational agent or investigational intervention during the course of the study.
CD4 ⁺ count \leq 50 cells/ μ L.
Women who are HIV ⁺ with WHO stage III or IV disease.
Severe anemia measured by Hb < 8 g/dL.
Individuals with a history of severe allergic reactions after previous vaccinations such as anaphylactic shock, asthma, urticaria, or other allergic reaction or hypersensitivity to any vaccine component.
Individuals with an acute infection (i.e. requiring treatment) within 7 days prior to enrollment.

Individuals with a fever (oral temperature $\geq 38^{\circ}\text{C}$ or axillary $\geq 37.5^{\circ}\text{C}$) on day of enrollment. They may be enrolled once the infection has resolved (as judged by investigator).
Receipt of immunosuppressive therapy within 30 days prior to enrollment (any systemic corticosteroid administered for more than 3 days, or in a daily dose > 15 mg/day prednisone or equivalent during any of 30 days prior to enrollment, or cancer chemotherapy) <u>Note:</u> topical corticosteroids are allowed (including inhalative or dermal application of corticosteroids)
Individuals with bleeding diathesis, or any condition that may be associated with a prolonged bleeding time.
Individuals who have received blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation in the past 12 weeks.
Individuals with behavioral or cognitive impairment or psychiatric disease that, in the opinion of the investigator, may interfere with the subject's ability to participate in the study (e.g. who are not able to comprehend or to follow all required study procedures for the whole period of the study).
Individuals with any progressive or severe neurologic disorder, seizure disorder, epilepsy or Guillain-Barré syndrome.
Individuals with history or any illness that, in the opinion of the investigator, might pose additional risk to subjects due to participation in the study.
Individuals who are part of study personnel or close family members conducting this study.

4.3 Withdrawal of Subjects from Therapy or Assessment

The subject can withdraw consent for participation in the study at any time without penalty or loss of benefit to which the subject is otherwise entitled. The investigator can withdraw a subject if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol.

A subject may not be eligible for subsequent vaccination /may be discontinued from the study following occurrence of hypersensitivity to any study vaccine or vaccine component.

If a subject withdraws from the study, the reason for withdrawal must be documented in the subject's medical record and reported in the "Study Termination" CRF. If the withdrawal of a subject resulted from an Adverse Event, the "Adverse Events" and/or "Prior and Concomitant Medications/Blood Products" CRFs, as applicable, will be completed. Breast feeding is allowed.

Withdrawn subjects will not be replaced.

5.0 TREATMENT OF SUBJECTS

All study-related vaccines are to be kept in a secure location in appropriate storage conditions, with temperature monitoring and separate from other vaccines.

5.1 Investigational Vaccine(s)

Investigational NVD GBS glycoconjugate vaccine will be supplied as individual vials of lyophilized product, with 24 µg of each antigen per 3 mL vial. Vaccine lots to be used in this study have been produced via Good Manufacturing Practices (cGMP).

Different lots of GBS glycoconjugate vaccine that may be used in this study are comparable based on product and process specifications.

At the time of injection, the formulation will be obtained by re-suspending the lyophilized vaccine vial contents with 2.4 mL of saline solution.

Table 5.1-1. *Composition of GBS trivalent vaccine reconstituted with saline solution (5 µg each antigen/ dose) for 0.5 mL of injectable suspension.*

NAME OF INGREDIENT	UNIT PER DOSE (1 DOSE=0.5ML)	FUNCTION
5 µg CPSIa-CRM, 5 µg CPSIb-CRM and 5 µg CPSIII-CRM		
ACTIVE SUBSTANCES		
GBS CPSIa-CRM	5 µg CPSIa-CRM	Active ingredient/antigen + carrier protein
GBS CPSIb-CRM	5µg CPSIb-CRM	
GBS CPSIII-CRM	5 µg CPSIII-CRM	
EXCIPIENTS		
<div style="border: 1px solid red; padding: 5px; display: inline-block;">Formulation Redacted</div>		
WFI	qs to 0.5 mL	Solvent

The vaccine must be stored between 2°C to 8°C, and protected from light. DO NOT FREEZE.

5.2 Control Vaccines/Placebo

Not applicable

5.3 Concomitant Vaccines or Treatment

Not applicable

5.4 Vaccines Preparation and Administration

GBS trivalent (5 µg each antigen/dose) vaccine for 0.5 mL of injectable suspension:

Final combined vaccine is generated by aseptically injecting 2.4 mL of saline solution (diluent) into the vial containing the lyophilized product. This reconstitutes the lyophilized GBS trivalent component with agitation. The final mixed vaccine is suitable for the administration of the 5/ 5/5 formulation (injection volume 0.5 mL). The product should be used immediately after reconstitution. Prior to administration, any air-bubbles should be removed (ejected) and the vaccine should be allowed to reach room temperature.

The principal investigator or designee will be responsible for the intramuscular administration of the vaccine to subjects enrolled into the study according to the procedures stipulated in this study protocol. This administration should preferentially be performed into the non-dominant arm.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:

The vaccination site should be disinfected with a skin disinfectant (e.g., 70% alcohol). Before vaccination, the skin must be dry. **DO NOT inject intravascularly or intradermally.**

Standard immunization practices should be observed and care should be taken to administer the injection intramuscularly (subjects should sit or lay while injected with the vaccine. As with all injectable vaccines, appropriate medical treatment and supervision will be readily available in case of anaphylactic reactions following administration of the study vaccine. In case of any anaphylactic or anaphylactoid reaction, emergency medication should be available at hand (e.g. Epinephrine 1:1000 and diphenhydramine or comparable). During 30 minutes of observation, the emergency medication should be placed near the subject.

Study vaccines should not be administered to individuals with known hypersensitivity to any component of the vaccines.

Vaccinations must not be administered to any subject with a clinically significant active infection (as assessed by the investigator) or a body temperature $\geq 38^{\circ}\text{C}$ when measured orally, on the intended date of vaccination.

If either of these is observed, vaccination should be postponed until the subject's temperature remains below 38.0°C when measured orally or below 37.5°C when measured axillary, or the investigator feels that the subject's illness has stabilized, as appropriate.

5.5 Other Concomitant Treatment or Vaccines

All medication taken by the subject within 21 days prior to the day of randomization is to be recorded on the "Prior and Concomitant Medications CRF. Prior medications include (at a minimum) all prescription medications taken regularly by a subject at the time of study enrollment. Medications administered to infants will be recorded in the CRF.

Concomitant medications include all prescription medications (including non-study vaccines) taken by/administered to the subject after enrollment into the study and must be documented on the "Concomitant " CRF.

5.6 Vaccination Compliance

The investigator is responsible for adequate and accurate accounting of vaccine usage. The investigator or designee will administer the study vaccines only to individuals included in this study following the procedures set out in this study protocol. The date, dosage, and time of the vaccinations must be recorded. The investigator must track vaccines received, used and wasted and will retain all unused or expired products as described in section 3.3.4.

6.0 IMMUNOGENICITY AND SAFETY ASSESSMENTS

6.1 Appropriateness of Measurements

The measures of immunogenicity used in this study (ELISA) employ methods that are widely used and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response).

The measures of safety used in this study are routine clinical procedures. They include a close vigilance for, and stringent reporting of, selected local and systemic reactions routinely monitored in vaccine clinical trials as indicators of reactogenicity.

6.1.1 Immunogenicity

Antibody responses will be determined by individual GBS serotype-specific ELISAs. All study subjects will have blood collected prior to immunization as a baseline. Maternal blood will also be collected at study day 15 (-2/+2) and study day 31 (-4/+6 days), as well as at day of delivery with a +72 hour collection window. Optimally, umbilical cord blood will be collected – if not available, newborn blood may be collected within 72 hours of birth. Infants will return at 6 weeks of age for blood collection (serology) and health status follow up.

6.1.2 Methods, Criteria and Timing for Assessing and Recording Immunogenicity Parameters

Topics such as sample shipment for samples which go abroad, location of analysis, and type of analysis of samples foreseen in this study are detailed in the Study Serology Manual. GBS Serology is done in a centralized laboratory in order to avoid the introduction of laboratory testing bias into the data.

Primary immunogenicity analysis will be based on serotype specific GBS Ab responses obtained on the day of delivery (72 hr collection window).

The primary study endpoint is placental transfer (%) of serotype-specific GBS Ab measured as [newborn blood Ab concentration/maternal Ab concentration x 100] among HIV⁺ (stratified by CD4 strata) versus HIV⁻ women-infant pairs. This will be assessed separately for each GBS serotype.

The secondary immunogenicity endpoint is the assessment of vaccine-induced maternal Ab level among HIV⁺ versus HIV⁻ women at randomization (study day 1), at study day 15 and 31 and at the time of delivery.

Gestational age and birth weight will be considered in the comparison analysis of placental transfer. Only infants born at ≥ 37 weeks gestation, or at least ≥ 2500 g birth weight, will be included in the primary immunogenicity analysis. Such infants are at highest probability of having placental transfer of Ab occur. Women who deliver prior to receiving the injection will not be included in the primary immunogenicity analysis.

6.2 Safety Parameters

Safety will be assessed in pregnant women / mothers by measuring the incidence of local and systemic reactogenicity up to 7 days post vaccination, adverse events until day 31, all adverse events requiring a physician's visit from day 31 until the end of the trial, and serious adverse events throughout the study in all groups. In addition, subjects will have an assessment of obstetrical outcomes. Infants will be monitored for AEs requiring a physician's visit, SAEs, and for general safety including newborn outcome (e.g. Apgar) through 6 weeks. As part of the safety data collection the HIV-status from infants born to HIV positive mothers, will be recorded, if available.

A full physical examination will be performed for each for each mother at visit 1 and visit 8 and a medical history will be obtained and a general health status determined. A complete physical examination for infants will be performed at infant visit 1 and 2.

CD4 counts and HIV load will be measured for the HIV⁺ pregnant women / mothers.

Local and systemic reactions and other adverse events will be collected throughout the study, as detailed in sections 6.2.1 to 6.2.5.

6.2.1 Local and Systemic Reactions¹

The occurrence of selected indicators of reactogenicity (listed below), which by definition, can only occur up to 7 days post vaccination, will be recorded on the “Local and Systemic Reactions” rather than the “Adverse Events” CRF.

Local Reactions:

Pain
Redness Ecchymosis
Swelling Induration

Systemic Reactions:

Chills Arthralgia Rash
Malaise Elevated temperature (fever)
Myalgia Nausea
Headache Fatigue

Other Indicators of Reactogenicity:

Stayed home due to reaction or reduction of daily activity
Use of analgesics/antipyretics

6.2.2 Adverse Events²

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

An unexpected adverse event is one that is not listed in the current Investigator’s Brochure or an event that is by nature more specific or more severe than a listed event.

All AEs will be monitored until resolution or, if the AE becomes chronic, a cause identified. If an AE is unresolved at the conclusion of the study, a clinical assessment will be made by the investigator and medical monitor whether continued follow-up of the AE is warranted.

The severity of events reported on the “Adverse Events” CRF will be determined by the investigator as:

¹ Local and systemic reactogenicity is referred to as “solicited adverse events” to differentiate those events that were solicited on a checklist from other adverse events collected during the trial.

² Adverse Events collected in this study and that are not solicited on a checklist may also be referred to as “unsolicited Adverse Event” in the Clinical Study Report.

Mild: transient with no limitation in normal daily activity.
Moderate: some limitation in normal daily activity.
Severe: unable to perform normal daily activity.

Laboratory abnormalities will be graded according to the United States Food and Drug Administration (FDA), Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials.

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:

1. Not Related

The AE is not related if exposure to the investigational vaccine has not occurred, **or** the occurrence of the AE is not reasonably related in time, **or** the AE is considered unlikely to be related to use of the investigational vaccine, i.e. there are no facts (evidence) or arguments to suggest a causal relationship.

2. Related to the vaccine under study

Possibly Related

The administration of the investigational vaccine and AE are considered reasonably related in time **and** the AE could be explained by causes other than exposure to the investigational vaccine.

Probably Related

Exposure to the investigational vaccine and AE are reasonably related in time **and** the investigational vaccine is more likely than other causes to be responsible for the AE, **or** is the most likely cause of the AE.

The relationship of the study treatment to an AE will be determined by the investigator.

6.2.3 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires or prolongs subject's hospitalization

- Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect
- Is an important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Adverse events which do not fall into these categories are defined as **non-serious**.

It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the Medical History CRF. If the onset of an event occurred before the subject entered the trial (e.g., any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalization would not lead to an AE being classified as serious unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-existing condition.

Serious adverse events that are judged by the investigator to be possibly or probably related to the study vaccine should be reported to Novartis Vaccines and Diagnostics as related (i.e., suspected) events.

6.2.4 Pregnancies

Not applicable.

6.2.5 Methods and Timing for Assessing and Recording Safety Parameters

All study subjects will be observed for at least 30 minutes after a vaccination for evidence of immediate reactions in general and in particular for symptoms of allergic phenomena (such as rashes, itching, or other allergic manifestations). Each subject will be instructed to complete a diary card for 7 days following each administration, to describe local and systemic reactions. If a local and systemic reaction continues beyond 7 days after a vaccination, it will also be recorded on the "Adverse Events" CRF.

The period of observation for adverse events extends from the time the pregnant women sign the informed consent form until day 31. SAE and AEs requiring a physician's visit will be recorded for mothers and infants until the final study examination. This may include a period before and after an active treatment of an investigational product (study vaccine) or other medication.

Any medical event that occurs after the informed consent form is signed, but prior to receiving study vaccine/product and is related to a study procedure, will be documented as an adverse event and recorded on the Adverse Events CRF. Any medical event that occurs after the informed consent form is signed, but prior to receiving study vaccine/product and is not related to a study procedure, will be documented as a pre-existing condition and will be recorded on the Medical History CRF.

All adverse events, regardless of severity, will be monitored by the investigator until resolution or stabilization if it becomes chronic. All subjects experiencing adverse events - whether considered associated with the use of the study vaccine or not - must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible.

All findings must be reported on an "Adverse Events" CRF and on the "Vaccine Serious Adverse Event" form, if necessary, which is part of the investigator's study file.

All findings in subjects experiencing adverse events must be reported also in the subject's medical records.

All SAEs which occur during the course of the trial, whether considered to be associated with the study vaccination or not, must be reported **within 24 hours** or at the latest on the following working day by email (pdf), telephone or fax to NVD.

The "Vaccine Serious Adverse Event" form is to be completed for all SAEs and sent to the trial specific fax number provided to the investigator. The original is retained by the investigator. The event is also documented on the "Adverse Events" CRF. After receipt of the initial report, the Novartis clinical representative will review the information and contact the investigator if it is necessary to obtain further information for assessment of the event.

Any medication or other therapeutic measures used to treat the event will be recorded on the appropriate CRF(s) in addition to the outcome of the AE. Any serious adverse reaction (e.g. adverse event assessed as causally related to study vaccine by the investigator) must be reported to the EC in a timely manner. The sponsor will comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious and non-serious adverse vaccine reactions to the regulatory authority (ies) and the EC.

If required, a follow-up report including all new information obtained on the serious adverse event must be prepared and sent to the trial specific fax number provided to the investigator. The report should be marked "Follow-up report."

The investigator will submit, on request, copies of these reports to the EC and other relevant authorities. Adequate documentation will be provided to the sponsor showing that the EC has been properly notified.

Post-Study Events

Any AE occurring at any time outside the observation period or after the end of the study and considered to be caused by the study vaccine - and therefore a possible adverse reaction - must be reported.

6.4 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be available for reviewing safety signals in either vaccinated subjects or their infants.

7.0 STATISTICAL PLAN

Immunogenicity will be analyzed based on maternal and infants serotype specific GBS Ab responses obtained on the day of delivery (72 hr collection window). The primary analysis is based on the placental transfer (%) of the serotype specific GBS Ab. Placental Ab transfer is calculated as: $[\text{newborn blood Ab concentration}/\text{maternal Ab concentration} \times 100]$ for each woman-infant pair. Ab transfer will be assessed for each GBS serotype from mother-infant paired blood samples collected at the time of delivery.

Two secondary endpoints will be assessed:

1. Vaccine-induced maternal serotype specific GBS Ab levels at randomization, at study days 15 and 31 as well as at the time of delivery.
2. HIV load and CD4⁺ counts obtained pre-vaccination, at day 31, at delivery, and 6 week post delivery for each HIV⁺ subject.

Two exploratory endpoint will be assessed:

1. The results from a malaria test at screening, at the injection and at study day 31.
2. The decay of maternal serotype specific GBS Abs in infants at 6 weeks of age.

The placental transfer (%) of the serotype specific GBS Ab will be tabulated also by the malaria status of the enrolled women within each of the study groups: HIV⁻ women, HIV⁺ with CD4 count above 350 and HIV⁺ women with CD4 counts below 350 but above 50.

7.1 Statistical Hypothesis

Formally the null hypothesis for no difference between any two group means will be tested against the alternative hypothesis that the group means are different. Each test will be carried out at a significance level of $0.05/3=0.016$ to account for the multiplicity of testing of the three comparisons: each of the two HIV⁺ groups to the HIV⁻ group and between themselves.

The multiple endpoints (the three serotypes) do not require an additional multiplicity adjustment, since we require that the null hypothesis is rejected for all three serotypes at once and falls under the intersection – union type of multiplicity.

The analysis of the secondary endpoints will be based on the differences between pre- and post-vaccination values and these obtained at the day of delivery and will test the null hypothesis that the mean equals 0 vs the alternative hypothesis that the mean is not equal to 0. These tests will be carried out for each of the two HIV⁺ groups at a significance level of 0.05 (no multiplicity adjustment).

7.2 Sample Size and Power Considerations

The dropout rate is expected to be approximately 15%, which provides for about 50 evaluable women per HIV status group out of the 60 enrolled per group. Assuming that about 80% of the women will deliver infants that are at ≥ 37 wks gestation or weight ≥ 2500 g at birth, this reduces the immunogenicity set to approximately 40 subjects. With a sample size of 40 we have about 95% power to detect 8% difference in the % of placental transfer between any two study groups, i.e. about $0.95^3=85\%$ for all three serotypes at once. The power calculation stipulates that the GBS serotype-specific Ab levels present in newborn blood relative to maternal antibody concentrations are uniformly distributed between 80% and 110% among HIV⁻ mothers³. The significance level alpha is set to $0.05/3 \sim 0.016$.

Gestational age and birth weight will be considered in the comparison analysis of placental transfer among the HIV⁺ and HIV⁻ groups. Infants who are at ≥ 37 wks gestation and/or weight ≥ 2500 g at birth have the highest probability of having significant placental transfer of Ab.

In addition, if the maximum number of subjects per group (i.e.90) is reached, holding true the same assumptions for the dropout rate and for the percentage of babies born at ≥ 37 wks gestation or weight ≥ 2500 g at birth, the number of evaluable subjects may increase up to 60 per group. With that sample size, the study will have about 95% power to detect 6.5% difference in the % of placental transfer between any two study groups, i.e. about $0.95^3=85\%$ power for all three serotypes at once.

Statistical Analysis Considerations

The primary immunogenicity analysis will be based on the Full Analysis Set (FAS). Multiplicity adjustment will be applied to the three primary comparisons among the three study groups: HIV⁺ with CD4 no less than 350, HIV⁺ with CD4 < 350 but above 50, and the HIV⁻ group. There will be no additional multiplicity adjustment for the multiple endpoints (the three serotypes) and for the significance tests related to the secondary immunogenicity objectives.

7.3 Population for Analysis

Definition of populations to be analyzed:

(a) All Enrolled Population

- all subjects who:
 - have signed an informed consent, undergone screening procedure(s) and pass all inclusion criteria and meet no exclusion criteria.

(b) Full Analysis Set (FAS)/Modified Intention-to-treat (MITT) population, Immunogenicity

- all subjects in the enrolled population who:
 - actually receive a study vaccination, and
 - provide at least one evaluable serum sample

(c) Per Protocol Set/ Per protocol (PP) population, Immunogenicity

- all subjects in the FAS/MITT Immunogenicity population who:
 - correctly receive the vaccine, and
 - provide evaluable serum samples at the relevant time points (for subjects in the immunogenicity subset), and
 - have no major protocol violation as defined prior to unblinding or analysis,

A major deviation is defined as a protocol deviation that is considered to have a significant impact on the immunogenicity result of the subject.

(d) Safety population

- All subjects in the enrolled population who:
 - receive a study vaccination
 - provide post vaccination safety data
 - provide post-baseline safety data

7.4 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height and weight at enrollment will be calculated overall and by HIV status group.

7.5 Immunogenicity Endpoints

7.5.1 Description of Response Variables

Primary: The primary analysis is based on the placental transfer (%) of serotype-specific GBS Ab defined as [newborn blood Ab concentration/maternal Ab concentration x 100] for each woman-infant pair, assessed for each GBS serotype at the time of delivery

Secondary: The secondary immunogenicity endpoints are the vaccine-induced maternal serotype-specific GBS Ab level at the time of delivery.

7.5.2 Statistical Methods for Immunogenicity Variables

A comparison analysis will be carried out based on the placental transfer (%) of serotype-specific GBS Ab by comparing the HIV⁻ group to each of the two HIV⁺ groups (CD4⁺ counts above or below 350), as well as between the two HIV⁺ groups. If necessary the pooled HIV⁺ subjects might be compared to the HIV⁻ group also. The comparisons will be done based on appropriately defined contrasts within the framework of ANCOVA model with HIV status as a single factor and gestational age and birth weight as covariates to alleviate the potential bias that the lack of randomization might introduce.

For the secondary immunogenicity endpoints the GMC's, means and their appropriated confidence intervals will be provided, by study group and time points. These will be tabulated for each serotype separately.

For the exploratory immunogenicity endpoint:

- GMC levels measured at delivery for mothers and at birth for infants, will be plotted against time elapsed between vaccination and delivery.
- GMCs and their appropriated confidence intervals will be provided, by study group for maternal serotype specific GBS Abs in infants as measured at 6 weeks of age. For each serotype separately.

7.6 Analysis of Safety (Endpoints) and Tolerability

All subjects who receive at least one immunization and provide some safety data will be considered evaluable for the safety analyses. The safety of the study vaccines will be assessed in terms of number of subjects exposed to study vaccines with reported local and systemic reactions, as well as the number of all subjects with reported SAEs and/or AEs per vaccine group. The safety analyses also will include data from the physical examination and any reactions or AEs observed by study personnel following vaccination. All SAEs and AEs (including onset of chronic illness) will be judged by the Investigator as either probably related, possibly related, or not related to vaccine and will be tabulated. All SAEs and AEs resulting in withdrawal from the study will be summarized.

Other safety analysis will be based on the HIV load and CD4⁺ counts obtained pre-vaccination, at day 31, on day of delivery, and 6 weeks post delivery for the HIV⁺ subjects.

7.6.1 Analysis of Extent of Exposure

Not applicable.

7.6.2 Analysis of Local and Systemic Reactions

Frequencies and percentages of subjects experiencing each reaction will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic reaction overall and at each time point will also be presented.

Post-vaccination reactions reported from day 1 to day 7 will be summarized by maximal severity and by vaccine group. The severity of local reactions, including injection-site ecchymosis, erythema, induration, and swelling will be categorized as none, 1 to ≤10 mm, 11 to ≤25 mm, 26 to ≤50 mm, 51 to ≤100 mm and >100 mm (severe local reactions).

The severity of pain and systemic reactions (i.e., change in eating habits, sleepiness, persistent crying, irritability, vomiting, diarrhea) occurring up to 7 days after each vaccination will be categorized as none, mild (transient with no limitation in normal daily activity), moderate (some limitation in normal daily activity), and severe (unable to perform normal daily activity).

7.6.3 Analysis of Other Adverse Events

All the adverse events occurring during the study judged either as related to vaccination or not by the investigator, will be recorded as specified in section 6.2.5. The original verbatim terms used by investigators to identify adverse events in the CRFs will be mapped to preferred terms using the MedDRA dictionary.

Adverse events will be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, as well as adverse events judged by the investigator as at least possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by vaccination group.

When an adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Additionally, three separate summaries will be produced: (i) serious adverse events, (ii) adverse events that are possibly or probably related to vaccine, and (iii) adverse events that are unrelated to vaccine. Data listings of all adverse events will be provided by subject.

In addition, a listing of subjects withdrawn from the study because of an adverse event will be presented.

7.7 Interim Analysis

Interim Analysis

An interim immunogenicity analysis will be performed on data collected at the time of delivery to evaluate the proportion of maternal antibodies transferred to the newborns in either of the three study groups. The analysis will be carried out at the time when data up to delivery become available for at least 60 subjects per group, in each of the 3 groups (HIV⁻, HIV⁺ CD4^{>350}, HIV⁺ CD4^{≤350}) have delivered. The aim of the interim analysis is to give guidance on the population of interest for the phase III efficacy study.

8.0 STUDY MONITORING, AUDITING AND DOCUMENTATION

Study monitoring and auditing will be performed in accordance with the sponsor's standard operating procedures and applicable regulatory requirements (e.g., FDA, EMEA, ICH and GCP guidelines).

Investigators and/or their study staff will be trained on the study protocol and all applicable study procedures prior to subject enrollment. CRFs supplied by the sponsor must be completed for each enrolled subject. The data entries as well as study related documents will be checked by the sponsor and/or trained delegates of the sponsor.

8.1 Study Monitoring

Study progress will be monitored by NVD or its representative (e.g. a contract research organization) as frequently as necessary to ensure the rights and well-being of study subjects are protected, to verify adequate, accurate and complete data collection, protocol compliance and to determine that the study is being conducted in conformance with applicable regulatory requirements. Arrangements for monitoring visits will be made in advance in accordance with the monitoring plan, except in case of emergency.

8.2 Source Data Verification

Data recorded on the eCRF will be verified by checking the CRF entries against source documents (i.e., all original records, laboratory reports, medical records, subjects diaries) in order to ensure data completeness and accuracy as required by the study protocol. The investigator and/or site staff must make CRFs and source documents of subjects enrolled in this study available for inspection by NVD or its representative at the time of each monitoring visit.

At a minimum, source documentation must be available to substantiate subject identification, eligibility and participation, proper informed consent procedures, dates of visits, adherence

to protocol procedures, adequate reporting and follow-up of adverse events, administration of concomitant medication, study vaccine receipt/dispensing/return records, study vaccine administration information, and date of completion and reason. Specific items required as source documents will be reviewed with the investigator before the study

The source documents must also be available for inspection, verification and copying, as required by regulations, by officials of the regulatory health authorities (e.g. FDA, EMEA and others) and/or ECs. The investigator and study site staff must comply with applicable privacy, data protection and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

The subject or the subject's parents or legally acceptable representative(s) must also allow access to the subject's medical records. Each subject, or the subject's parent(s) or legally acceptable representative(s), should be informed of this prior to the start of the study.

9.0 DATA MANAGEMENT

An electronic data capture (EDC) system (e.g., Inform™) will be used to expedite the entry of data. The investigator will enter data into the web enabled EDC system preferably within 3 working days; the data will be stored in NVD's clinical database management system. eCRF data will be reviewed routinely by NVD BCDM Group and NVD clinical monitors.

All serology data analyzed by Clinical Serology, NVD, [redacted] will be entered into the Seroad database by Novartis Vaccines' Clinical Serology Laboratory, [redacted]. All results will be checked in the laboratory for validity and completeness.

For this protocol, antibody laboratory data will be transmitted via electronic data transmission (EDT).

9.1 Data Handling Procedures

Coding will be performed using the following dictionaries:

Adverse Events:	MedDRA
Concomitant illness:	ICD-9
Concomitant and intercurrent therapy:	WHO Drug Dictionary

9.2 Documentation of Study Findings

The investigator must review and electronically sign the eCRFs to verify their accuracy. Correction to data on eCRFs will be tracked via an audit trail within InForm™, web based electronic data capture system. Each correction will be identified by the person making the change and will include time, date, and reason for change. If corrections are made to a

previously and electronically signed CRF, the investigator, he or she must confirm and endorse the changes.

As part of the conduct of the trial, NVD may have questions about the Case Report Form data after the site has entered the data. These questions will be raised within InForm™. The Investigator will provide follow-up clarification and/or resolution of data issues raised by the monitor or the data manager.

An explanation must be provided and documented by the investigator for all missing data.

9.3 Data Protection

NVD respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

10.0 RECORD RETENTION

Investigators must retain all study records required by NVD and by the applicable regulations in a secure and safe facility. The investigator must consult a NVD representative before disposal of any study records, and must notify the sponsor of any change in the location, disposition, or custody of the study files.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. "Essential documents" are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents should be retained for a longer period however, if required by the applicable regulatory requirements or by an agreement with the sponsor *or* The Committee for Human Medicinal Products for Human Use (CHMP) requires retention for the maximum period of time permitted by the institution, but not less than 15 years. (ICH E6, 4.9.5)

It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (ICH E6, 5.5.12). These principles of record retention will also be applied to the storage of laboratory samples, provided that the integrity of the stored sample permits testing.

11.0 USE OF INFORMATION AND PUBLICATION

NVD assures that the key design elements of this protocol will be posted in a publicly accessible database such as ClinTrials.gov.

NVD also assures that key results of this clinical trial will be posted in a publicly accessible database within one year from the last subject's last study visit (LSLV).

12.0 ETHICS

12.1 Regulatory and Ethical Compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Informed Consent Procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), EC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the subject. In cases where consent is given by the subject's representative, the subject should be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol).

The process of obtaining informed consent will be documented in the subject source documents.

The HIV status of infants born to HIV positive mothers can only be obtained after these mothers have provided a separate written informed consent.

NVD will provide to investigators a separate document with a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by NVD before submission to the EC, and a copy of the approved version must be provided to the NVD monitor after EC approval.

In case of doubts on the ability of a subject to adhere to these requirements, that subject will not be allowed in the study.

12.3 Responsibilities of the Investigator and EC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Ethics Committee (EC) before study start. A signed and dated statement

that the protocol and informed consent have been approved by the EC must be given to NVD before study initiation.

Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to NVD monitors, auditors, NVD Clinical Quality Assurance representatives, designated agents of NVD, ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform NVD immediately that this request has been made.

12.4 Protocol Adherence

Investigators will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact NVD or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by NVD and approved by the EC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.5 Protocol Amendments

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects. An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on subject safety (e.g., change of telephone number(s), logistical changes).

Protocol amendments must be approved by NVD, Health Authorities where required, and EC.

In cases when an amendment is required in order to protect the subject safety, the amendment can be implemented prior to approval. Notwithstanding the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, NVD should be notified of this action and the EC at the study site should be informed within 10 working days.

13.0 REFERENCE LIST

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- ⁷ World Health Organization (WHO) Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a public health approach, 2006 revision
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- ¹⁰ Investigators Brochure Version 2. "GBS Trivalent Vaccine" Released 29 JUL 2010. Novartis Vaccine and Diagnostics.
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¹² Evaluation of Potential Reproductive Toxicity of the GBS Trivalent Vaccine in Rats and Rabbits, Released DEC 2010. Novartis Vaccine and Diagnostics.