REPRODUCTION TOXICITY STUDY REVIEW

STN number: 125300/0

DATS number/date/type of submission: DATS# 448295/8/29/2008/BLA

Relevant IND: -b(4)---

Sponsor: Novartis Vaccines, --b(4)----------, Italy

Manufacturer of vaccine product:
Novartis Vaccines, --b(4)----------, Italy

Reviewer name: Marion F. Gruber, PhD

Office/Division name/HFM#: Office of Vaccines Research and Review/HFM 408

Review completion date: January 9, 2009

Vaccine:
Trade name: Menveo
Nonproprietary name: Meningococcal (Groups A, C, W-135 and Y) Oligosaccharide CRM197 conjugate vaccine
The vaccine consists of two components, a lyophilized component containing the meningococcal A antigen conjugate and a liquid component containing the meningococcal C, W-135 and Y antigen conjugates. All conjugates are manufactured at the facility in Rosia, Italy. The meningococcal A antigen conjugate is filled and lyophilized at the facility in --b(4)---------- Rosia for final packing and release. The vaccine contains no adjuvant, no thimerosal and no preservative.

Intended clinical population/indication: Active immunization of individuals 11 through 55 years of age to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W-135 and Y.

Clinical formulation: The final formulation contains 10-5-5-5- ug per oligosaccharide of *N. meningitides* serogroups A, C, W and Y respectively, without adjuvant. The dose is 0.5 ml (after reconstitution).

Route of administration: IM

Clinical Studies: refer to section 5 of STN 125300

Studies reviewed within this submission:
Intramuscular dose-range developmental toxicity study of MenACWY conjugate vaccine in rabbits (UBA000-20)

Intramuscular reproductive and developmental toxicity study of MenACWY conjugate vaccine in rabbits, including a postnatal evaluation (UBA000-38)

Executive Summary:
The sponsor has performed 2 studies to evaluate the reproductive and developmental toxicity potential of MenACWY conjugate vaccine: a pilot dose-ranging developmental toxicity study vaccine in rabbits (UBA 000-20) to provide information for the selection of dosages to be used in the pivotal developmental toxicity study and a pivotal developmental toxicity study in rabbits (UBA000-38) .

UBA000-20: --b(4)---------- rabbits were dosed on study days (DS) -1, -15 and -29 prior to mating and on gestation days 7 and 20. Pre-mating dosing consisted of 1X (25 ug Men ACWY) or saline control only. Dosing on gestation days 7 and 20 consisted of 1x (25 ug Men ACWY) or 2X (50 ug Men ACWY), 0.5 ml and 1 ml, respectively, I.M. Animals (5/group) underwent Caesarean section on DG 29. Caesarean parameters were evaluated in this pilot study. No fetal skeletal and visceral evaluations were performed nor was a subgroup included to evaluate post-natal/preweaning development of the offspring. Treatment of animals with MenACWY vaccine did not induce vaccine related maternal death or abortion. Clinical signs during the pre-mating and gestation period, body weights and feed consumptions were comparable across treatment groups, except in group VII treated with 50/1.0 ug/ml test article. This group had a reduction in body weight (62% of the alum control) during the entire gestation period. However, this may be attributable to the small number of animals evaluated as no dose effect was observed, i.e, animals allocated to group III that also received 50 ug vaccine antigen did not have a reduction in body weight. There was a reduction in body weight and feed consumption in rabbits assigned to treatment groups subjected to blood draw for antibody analysis during the gestation period. This was likely due to the stress of the blood collection process since reduction in body weight and feed consumption was not observed in rabbits treated with the same dose of MenACWY vaccine but not subjected to antibody analysis. Caesarean- parameters were unaffected by treatment with MenACWY conjugate vaccine at both concentrations, i.e., 25 ug and 50 ug MenACWY vaccine -----b(4)----------. There appeared to be no treatment related effects on fetal viability, fetal body weight, sex, as well as gross fetal external examinations. The MenACWY vaccine was ----------b(4)----------. Immunization of maternal animals with either vaccine formulation resulted in the passage of the antibodies to the fetuses. Based on these study results, a dosage of 50/1.0 ug/ml -----b(4)---------- was deemed to be the highest dose for a planned developmental toxicity study in rabbits. Note that in the pivotal developmental toxicity study UBA0000-38, a dose of 25 ug of the MenACWY vaccine was used, corresponding to the clinical dose.

UBA000-38: ---b(4)---------- rabbits were dosed on study days (DS) -1, -15 and -29 prior to mating and on gestation days 7 and 20 either with MenCWY vaccine, 0.5 ml, I.M., 25 ug antigen or saline control. Animals were subdivided into subgroups of animals (27 rabbits/group), underwent Caesarean section on DG 29 or were allowed to rear their offspring. Treatment of animals with MenCWY vaccine did not induce vaccine related

maternal death or abortion. Clinical signs during the pre-mating, gestation and lactation period, body weights and feed consumptions were comparable across treatment groups. Mating and fertility indices as well as Caesaeran-sectioning, natural delivery and litter parameters were unaffected by treatment with MenACWY conjugate vaccine. There appeared to be no treatment related effects on fetal viability, fetal body weight, sex, gross external or soft tissue or skeletal examinations. F1 pup viability, body weight, sex, reflex and physical development were not affected by treatment with the vaccine. Thus, under the conditions of the study, the MenACWY vaccine does not appear to affect embryo-fetal pre-and postnatal development and does not appear to exert teratogenic effects. The sponsor is proposing language in section 8.1 of the product labeling that follows the format of the proposed rule entitled "Content and Format of Labeling for Human Prescription Drug and Biological products; Requirements for pregnancy and lactation labeling" (May 29, 2008). Even though it would be acceptable to include the subheadings as proposed in that rule in product labeling the proposed rule is not finalized and thus, the pregnancy labeling section 8.1 must include a pregnancy category and language as prescribed in current 21 CFR 201.57(9)(i)(A).
This will need to be addressed when negotiating the product labeling.

Recommendation: pregnancy category B

Pilot dose ranging developmental toxicology study UBA000-20

Study title:
Intramuscular dose-ranging developmental toxicity study of MenACWY conjugate vaccine in rabbits (UBA000-20)

Purpose of Study:
To provide information for the selection of dosages to be used in fertility and/or the developmental toxicity study of Men ACWY conjugate vaccine administered IM to --b(4)---------- female rabbits

Key study findings UBA000-20:
There were no signs of vaccine related maternal toxicities nor were there adverse effects on Caesarean parameters by treatment with MenACWY conjugate vaccine at both concentrations, i.e., 25 ug and 50 ug MenACWY vaccine -----b(4)----------. There appeared to be no treatment related effects on fetal viability, fetal body weight, sex, as well as gross external examinations. The MenACWY vaccine was ---b(4)----------b(4)----------. Immunization of maternal animals with either vaccine formulation resulted in the passage of the antibodies to the fetuses.

Study no.: UBA000-20

BLA section: *4.2.3.5.2.1* **page #**: 1 - 274

Conducting laboratory and location: --b(4)----------
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Study Director:
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Date of study initiation: May 6, 2005
Date of experimental study completion: September 20, 2005
Final report: August 18, 2006

GLP compliance:
US FDA Good Laboratory Practice Regulations (CFR Part 58)
Japanese Pharmaceutical Affairs Bureau, Ministry of Health, Labour and Welfare Good Laboratory Practice Standard for Safety Studies on Drugs, MHW Ordinance No. 21, March 1997
Revised OECD Principles of Good Laboratory Practice [C(97)186/Final]

QA reports: yes (X) no ( )

Test article, lot #:
MenCWY (15 ug) --b(4)---------- opaque with white suspension, lot number U79P32D1C
Men CWY (15 ug), clear colorless liquid, lot number U79P33D1D
MenA (10 ug) white lyophilized powder, lot number 002011
-----b(4)----------
0.9% sodium chloride injection, clear liquid, --b(4)------

Methods

Species/Strain/Supplier: ---b(4)----------] rabbits, --b(4)----------

Number/sex/group: 5/female rabbits/treatment group (male rabbits used for the purpose of breeding, not considered part of the test system)
Number of rabbits assigned to study: 45
Age: 5,5 months at arrival
Weight: 3.2– 4.3 kg at study assignment
Doses/rationale: The dose of 25 ug Men ACWY is the clinical dose. The 1X (25 ug MenACWY) and the 2X (50 ug Men ACWY) doses during gestation were selected to provide information on dose-response on potential maternal toxicity. The premating immunizations were performed to provide peak antibody titers at the time of organogenesis. The 2 doses during gestation on days 7 and 20 were selected to expose rabbits multiple times during organogenesis.
Route, formulation, volume: IM, 0.5 ml (or 1.0 ml) for each injection, (consecutive injections were alternated between hind legs starting with the right leg) this represents the proposed clinical route

Study design: Groups and treatment allocation

GROUP/ NUMBER	PREMATING		GESTATION	
	DOSE (UG)	Volume (ml)	DOSE (UG)	Volume (ml)
I [a](5)	0	0.5	0	0.5
II (5)	25	0.5	25	0.5
III (5)	25	0.5	50	1.0
IV (5)[b]	25	0.5	25	0.5
V[c] (5)	0	0.5	0	0.5
VI[c] (5)	25	0.5	25	0.5
VII[c] (5)	25	0.5	50	1.0
VIII[c] (5)[b]	25	0.5	25	0.5

a: saline control
b: rabbits selected only for sample collection for analysis of antibodies
c-----b(4)---------- vaccine

Mating procedures: After 35 days on study (first day of dosage administration considered DS1) virgin female rabbits were mated with male rabbits, one male rabbit per female rabbit, 20 USP units/kg of HCG was administered to female rabbits prior to mating, animals were observed continuously until mating confirmed to have occurred by observation, day of mating was designated DG 0. If females failed to mate they were placed with a second and then 3rd male, if mating was not confirmed following the third

pairing, the female was recorded as no confirmed date of mating and continued on the assigned dosing regimen and were Caesarean sectioned 29 days after the date of attempted mating.

Parameters and endpoints evaluated:
Clinical observation: Animals were inspected for viability 2x daily, injection sites were examined; rabbits were observed for abortions, premature deliveries and deaths before and after dosage administration, once daily on non dosage days and daily during postdosage period

Body weight: weekly during the predosage period, weekly during premating period, daily during gestation and daily during postdosage period.

Food consumption: daily

Gross necropsy of F0 generation:
All rabbits in groups I through III and V through VII were euthanized by I.V. administration of sodium pentobarbital on DG 29, Caesarean sectioned and a gross necropsy of the thoracic and abdominal and pelvic viscera was performed. Uteri of apparent nonpregnant does were examined to confirm absence of implantation sites, uteri and ovaries of apparently nonpregnant does were retained in neutral buffered 10% formalin. Uterus of each rabbit examined for pregnancy status, for each animal the number of corpora lutea in each ovary and the number and location of implantation sites, the number and distribution of resorption sites and live and dead fetuses and early and late resorptions were recorded for each uterine horn.

Fetuses, F1 generation: removed from uterus, each fetus was weighed and examined for gross lesions, live fetuses were euthanized by IP injection of sodium pentobarbital. All fetuses were examined internally to identify sex.

Rabbits in groups IV and VIII were euthanized after the last blood collection on GD 29, Caesarean-sectioned and a gross necropsy of the thoracic and abdominal and pelvic viscera was performed. Uteri of apparent nonpregnant does were examined to confirm absence of implantation sites, uteri and ovaries of apparently nonpregnant does were retained in neutral buffered 10% formalin. Blood samples were collected on premating days 3, 17 and 31, 48 hours postdosage. Blood samples were also collected on DG 7 and 29. Blood samples were collected from each fetal/placental unit in the litter using umbilical cord blood. Fetal cord blood were pooled by litter.

Results (*since this is a pilot study, results are summarized and data not shown in detail*)

Mortality, clinical and necropsy Observations (Table 1 and 2 of study report)
All does survived until scheduled sacrifice and no clinical observations were determined to be test article related. No gross lesions were identified during necropsy examinations.

Body weights and feed consumptions (Tables 3-6 and 7-10 of the submission)
Body weights and body weight gains during the premating period were comparable among the dosage groups. Body weights and body weight gains of the Men ACWY conjugate vaccine (---b(4)----) treated rabbits were comparable to the saline treated group during GD 0 - 29. There was some reduction in the body weight in the 50 ug dosage group of the MenACWY conjugate vaccine --b(4)----------. However, it is not clear whether this was treatment related because of lack of a dose effect and small number of animals evaluated. Feed consumption values were comparable during the premating and gestation period across groups. The 25/0.5 ug/ml treated rabbits in the antibody dosage groups IV and VII had slight reduction in feed consumption during the gestation period compared to the control group values, probably attributable to stress as a result of the blood collection process.

Caesarean and litter parameters (Tables 11 and 12 of the submission)
Pregnancy occurred in 2 - 4 does per dosage group (2 out of 5 rabbits were pregnant in the saline treated group). Caesarean and litter parameters were not affected by treatment with MenACWY vaccine -----b(4)---------- at 25 ug and 50 ug of the vaccine. The litter averages for corpora lutea, implantations, litter sizes, live fetuses, resorptions, live fetal body weights, % live male fetuses and percent resorbed conceptuses were comparable among the various dosage groups. There were no dead fetuses and no dam had a litter consisting of only resorbed conceptuses. There were no fetal gross external alterations (Table 13-17 of the submission)

Antibody analysis (Addendum 4 of the final report)
Serum bactericidal and geometric mean antibody titers (-b(4)------) were evaluated under non GLP conditions. Results showed that the Men ACWY vaccine was ----------b(4)----------. Maternal immunization with either vaccine formulation resulted in transfer of maternal antibody to the fetuses.

Discussion and Conclusions
UBA000-20: -b(4)---------- rabbits were dosed on study days (DS) -1, -15 and -29 prior to mating and on gestation days 7 and 20. Pre-mating dosing consisted of 1X (25 ug Men ACWY) or saline control only. Dosing on gestation days 7 and 20 consisted of 1x (25 ug Men ACWY) or 2X (50 ug Men ACWY), 0.5 ml and 1 ml, respectively, I.M. Animals (5/group) underwent Caesarean section on DG 29. Caesarean parameters were evaluated in this pilot study. Treatment of animals with MenACWY vaccine did not induce vaccine related maternal death or abortion. Clinical signs during the pre-mating and gestation period, body weights and feed consumptions were comparable across treatment groups, except in group VII treated with 50/1.0 ug/ml test article. This group had a reduction in body weight (62% of the alum control) during the entire gestation period. However, this may be attributable to the small number of animals evaluated as no dosage effect was observed, i.e., animals in group III did not show reduction in body weight. There was a reduction in body weight and feed consumption in rabbits assigned to treatment groups subjected to blood draw for antibody analysis during the gestation period. This was probably attributable to the stress of the blood collection process since

reduction in body weight and feed consumption was not observed in rabbits treated with the same dose of MenACWY vaccine but not subjected to antibody analysis. Caesarean-parameters were unaffected by treatment with MenACWY conjugate vaccine at both concentrations, i.e., 25 ug and 50 ug MenACWY vaccine -----b(4)----------. There appeared to be no treatment related effects on fetal viability, fetal body weight, sex, as well as gross external examinations. The MenACWY vaccine was ---------- ---------- --b(4)----------. Immunization of maternal animals with either vaccine formulation resulted in the passage of the antibodies to the fetuses. Based on these study results, a dosage of 50/1.0 ug/ml --b(4)---------- was deemed to be the highest dose for a developmental toxicity study in rabbits. Note that in the pivotal developmental toxicity study UBA0000-38, a dose of 25 ug of the MenACWY vaccine was used, corresponding to the clinical dose.

Reproductive and developmental toxicology study UBA000-38

Study title:
Intramuscular reproductive and developmental toxicity study of MenACWY conjugate vaccine in rabbits, including a postnatal evaluation (UBA000-38)

Purpose of Study:
To test for potential toxic effects resulting from MenACWY conjugate vaccine treatment in the test species before cohabitation, through mating, gestation and lactation

Key study findings UBA000-38:
There were no signs of vaccine related maternal toxicities nor were there adverse effects on mating and fertility parameters evaluated. Caesarean-sectioning, litter parameters and natural delivery parameters were also not affected by treatment of animals with 25 ug of meningococcal conjugate vaccine. There were no adverse findings on fetal viability, fetal body weight, sex, gross external, soft tissue or skeletal examinations in fetuses of dams assigned do the caesarean subgroup. Furthermore postnatal/preweaning pup development did not appear to be affected by treatment with vaccine, i.e., F1 pup viability, body weight, sex, reflex or physical development were unaffected by treatment with vaccines.

Study no.: UBA000-38

BLA section: *4.2.3.5.3.1* **page #**: 1 - 379

Conducting laboratory and location: ---b(4)----------
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Study Director:
----------b(4)----------

Date of study initiation: March 14, 2007
Date of experimental study completion: July 4, 2007
Final report: March 8, 2008

GLP compliance:
US FDA Good Laboratory Practice Regulations (CFR Part 58)
Japanese Pharmaceutical Affairs Bureau, Ministry of Health, Labour and Welfare Good Laboratory Practice Standard for Safety Studies on Drugs, MHW Ordinance No. 21, March 1997
Revised OECD Principles of Good Laboratory Practice [C(97)186/Final]
Note that the immunology assays were performed by ----------b(4)----------not in compliance with GLP

QA reports: yes (X) no ( )

Test article, lot #:
Men ACWY conjugate vaccine,
Appearance: clear, colorless liquid -----b(4)---------- and white to off-white cake or powder as in MenA vial, refrigerated

Lot number Z79P40I1 (-----b(4)-------)
Lot number Z010011 (MenA vial)

Information to document the identity, composition, strength, activity/purity and stability of the test article was provided by sponsor to testing facility, COA provided in appendix 3 of the final study report

The MenACWY conjugate vaccine was prepared by reconstituting the lyophilized contents of the MenA vial with the liquid contents of the MenCWY --b(4)--. MenACWY is comprised of oligosaccharides from meningococaal serogroups A, C, W-135 and Y that are each conjugated to the protein carrier CRM197. Serogroup A represents 10 ug and serogroups C, W-135 and Y represent 5 ug each of each 25 ug clinical dose. Each 25 ug dose of MenACWY was delivered in a dose volume of 0.5 ml formulated in --b(4)----------

Control article, lot#:
0.9% sodium chloride injection, USP, clear, colorless, liquid, room temperature
Lot number --b(4)-------

Animal diet:

Feed Type/Name: Certified Rabbit Chow #5322 (--------b(4)----------

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Availability: 150 g per rabbit per day until GD 6, after that 180 g/rabbit/day, for rabbits assigned to groups III and IV beginning LD1, 230 g/rabbit/day, beginning on DL1, approximately 500 g of certified feed offered each day
Analysis for contaminants: routinely performed by feed supplier, copies of results submitted to raw data, no contaminants detected

Water Source: Local water passed through reverse osmosis membrane (RO water)

Availability: *ad libitum* from individual water bottles
Analysis for contaminants: ---b(4)---- for chemical contamination and ---b(4)--- for bacteria

Husbandry

Environmental conditions:
Temperature: RT 16^0C to 22^0C
Humidity: 30% to 70%
Air changes: positive airflow with minimum of –b(4)- changes per hour of 100% fresh air passed through ---b(4)--- HEPA filters
Photoperiod: 12 hour light: 12 hours dark fluorescent light cycle
Housing: Females were individually housed in stainless steel, wire bottom cages, except during mating period, rabbits assigned to natural delivery were supplied with a nesting box and nesting materials no later than DL 27

Methods
Species/Strain/Supplier: --b(4)----------] rabbits, --b(4)---------
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Number/sex/group: 27/female rabbits/treatment group (male rabbits used for the purpose of breeding, not considered part of the test system)
Number of rabbits acclaimed: 112
Number of rabbits assigned to study: 108
Age: 7 months at arrival
Weight: 2.9 – 4.5 kg at study assignment
Doses/rationale: 3 doses prior to gestation to ensure induction of high antibody titers (days -1, -15, and -29) plus 2 doses administered during gestation to expose fetuses to vaccine antigen and to maintain antibody titers (GD 7 and 20). Dose (25 ug/strain antigen) was selected as the highest anticipated dosage that could be used in the clinic
Route, formulation, volume: IM, 0.5 ml for each injection, (consecutive injections were alternated between hind legs starting with the right leg) these represent proposed clinical routes and volume

Mating procedures: After 35 days on study (first day of dosage administration considered DS1) virgin female rabbits were mated with male rabbits, one male rabbit per female rabbit, 20 USP units/kg of HCG was administered to female rabbits prior to mating, animals were observed continuously until mating confirmed to have occurred by observation, day of mating was designated DG 0. If females failed to mate they were placed with a second and then 3rd male, if mating was not confirmed following the third pairing, the female was recorded as no confirmed date of mating but considered to be at DG0. These rabbits continued on the assigned dosage regimen and were either Caesarean sectioned 29 days after the date of attempted mating or euthanized on day 34 when they did not naturally deliver a litter (group III and IV).

Culling procedures
Description: Litters were not culled during the lactation period to prevent selection bias in body weights and pup viability

Study design:
Randomization: Rabbits were assigned to dosage groups based on computer-generated (weight ordered) randomization procedures

Table I: Study design: Allocation of animals and treatment schedule

TREATMENT	GROUP* (NUMBERS/ GROUP)	DOSE TO ANIMALS (total mcg HA protein)	DAYS TREATMENT ADMINISTERED	DOSAGE VOLUME (ML)	RABBIT NUMBER
		F_1 FEMALES			F_1 FEMALES
SALINE	I (27)	-	DS-1, -15, -29 GD 7 and 20	0.5	1001-1027
MENACWY	II (27)	25 ug	DS-1, -15, -29 GD 7 and 20	0.5	1028-1054
SALINE	III (27)	-	DS-1, -15, -29 GD 7 and 20	0.5	1055-1081
MENACWY	IV (27)	25 ug	DS-1, -15, -29 GD 7 and 20	0.5	1082-1108

* Rabbits in groups I and II were Caesarean-sectioned, rabbits in groups III and IV were allowed to deliver naturally

Parameters and endpoints evaluated:
Clinical observation: Animals were inspected for viability 2x daily, injection sites were examined (onset, intensity and duration of signs recorded); rabbits were observed for abortions, premature deliveries and deaths before and approximately 60 minutes after dosage administration, once daily on non dosage days and daily during postdosage period

Body weight: weekly during the acclimation period, weekly during the dosage period (including DG 1, 15, and 29 and DG 0, 7, 10, 13, 16 and 20), on DG 23, 26, 29 and 34 (when necessary), For rabbits in groups III and IV, body weights were recorded on days 1, 5, 8, 11, 15, 18, 22, 25 and 29 postpartum

Food consumption: daily

Littering subgroup observations:
F0 generation: Day of parturition was considered day 0 of lactation; does were evaluated for adverse clinical signs during parturition, duration of gestation was evaluated, number of live and dead pups born in each litter was recorded after completion of parturition.

F1 generation pups (natural delivery subgroups III and IV)
Litters evaluated for viability at least 2x daily, pups in each litter counted daily, pups observed for clinical observations and appearance once daily beginning DL 5, pup weights were recorded on DL 5, 8, 15, 22 and 29.

Hair growth (from DL 5), eye opening (from DL 9), air righting reflex (from DL 10), acoustic startle (from DL 14) and pupil constriction was evaluated once (DL 22). The number of pups meeting the criterion was recorded on each day of testing, testing continued daily until the day the criterion was attained by all pups in the litter.

Gross necropsy of F0 generation:
After completing the 29 day lactation period, all surviving female rabbits were euthanized by IV administration of sodium pentobarbital and a gross necropsy of the thoracic and abdominal and pelvic viscera was performed, blood samples collected, number and distribution of implantation sites recorded, rabbits that did not deliver a litter were euthanized on DG 34 and examined for gross lesions, uteri of apparent nonpregnant does were examined to confirm absence of implantation sites, uteri and ovaries of apparently nonpregnant does were retained in neutral buffered 10% formalin.

Rabbits that died before scheduled termination were examined for cause of death, examined for gross lesions, hearts, lungs, liver, kidneys, stomach and spleen retained in 10% formalin for possible histological evaluation, pregnancy status and uterine contents were recorded, aborted fetuses were examined to the extent possible.

Necropsy of F1 pups: Pups that died before DL1 were evaluated for vital status at birth by removing the lungs and immersion of the lungs in water, pups with lungs that sank were designated stillborns, pups with lungs that float were designated life born. Pups that died on DL 2 to 29 were examined for cause of death, hearts, lungs, liver, kidneys, stomach and spleen retained in 10% formalin for possible histological evaluation, gross lesions retained in 10% formalin.

Caesarean subgroup observations:
F0 generation: Rabbits were euthanized by IV administration of sodium pentobarbital on DG 29, gross necropsy of thoracic, abdominal and pelvic viscera, blood samples collected, gravid uteri excised and weighed, uteri of apparently non-pregnant does examined by being pressed between glass plates to confirm absence of implantation sites, these uteri and ovaries retained in 10% formalin.

Uterus of each rabbit was examined for pregnancy status, for each animal the number of corpora lutea in each ovary and the number and location of implantation sites, the number and distribution of resorption sites and live and dead fetuses and early and late resorptions were recorded for each uterine horn.

Rabbits that died before scheduled termination were examined for cause of death and examined for gross lesions; heart, lungs, liver, kidneys, stomach and spleen were retained in 10% formalin, pregnancy status and uterine content were recorded, aborted fetuses were examined to the extent possible.

Fetuses, F1 generation: removed from uterus and euthanized by IP injection of sodium pentobarbital, blood samples collected from each fetus via vena cava and samples from each litter pooled, externally examined for gross external alterations, weights of fetuses were recorded, sex of each fetus was recorded, cavitated organs were evaluated in all fetuses by dissection, all fetuses were eviscerated, cleared stained with alizarin red S[(10)] and examined for skeletal alterations.

Laboratory investigations
Blood samples for hematology and clinical chemistry were collected from adult females pre-dose administration and on DS 15 and 29 as well as DG 7, 20 and 29. Samples of 1 to 2 ml each were collected from the medial auricular artery (in-life) and inferior vena cava (terminal blood collection).

Statistical methods
Clinical observations and other proportion data were analyzed using the variance test for homogeneity of the binominal distribution. Data from F0 generation rabbits were evaluated with the individual rabbit as a unit measured. Litter values were used in evaluation of pup data.

Results F0 Generation

Mortality/Clinical signs (summarized in Table 1, 16 and 29 of UBA000-38):
One doe in each of the control and vaccine groups were found dead, one doe in the vaccine group was euthanized due to an injury which presumably occurred during restraint for dosage administration, and another doe in the vaccine group delivered early on DG 29 (just before scheduled Caesarean-sectioning) and was sacrificed.

Does found dead (Groups I and II):
Group I (saline) doe (1022) was found dead on DG 29. Adverse clinical signs consisted of ungroomed coat (DG 17-24 and 26-29), and scant feces on DG 19-21 and 25-29. The animal lost weight on DG 10 through 29 (79 g). Feed consumption values were reduced after DG 12. All tissues appeared normal at necropsy except pale liver and red perioral substance. The litter consisted of 8 fetuses *in utero*, 2 of these had downward flexed forepaw, all other fetuses appeared normal.

Group II (vaccine) doe 1034 was found dead on GD 26. Adverse clinical signs were ungroomed coat (DG 14-19), scant feces (DG 14-16 and 23-25), soft feces (DG 15 and 16) and red substance in the cage pan (DGs 24 and 25). Weight loss occurred after DG 7 and feed consumption values were reduced after DG 13. All tissues appeared normal. The litter consisted of one early and eight late resorptions *in utero*.

Group II (vaccine) doe 1052 was euthanized on day 17 of study due to limited use and continuous extension of the left hind limb. There was tissue damaged in and around the hip joint presumably occurring during restraint for dosage administration on DS15. This rabbit received 2 dosage administration, one in each hind limb. The only AE observed during in-life was limited limb use on DS 15 and 17. The doe lost 25 g of body weight on DS 8-15 and feed consumptions were in general comparable. All tissues appeared normal at necropsy.

Group II (vaccine) doe 1037 delivered early and was sacrificed on GD 29. The only AE noted was scant feces on DGs 22 to 24 and 27 to 29. The doe began to lose weight on DGs 16-26. Feed consumption was reduced on DGs 16-28. The doe delivered 12 pups (9 live and 3 dead), 2 pups were partially cannibalized, all other pups appeared normal. All maternal tissues appeared normal at necropsy.

Table II: Clinical observations and skin reactions - F0 Premating

PARAMETERS	F0 FEMALES PREMATING (DS 1 - 35)			
	C-sectioning		Natural delivery	
	I	II	III	IV
Mortality	1	2	0	0
Found dead	1	1	0	0
Unscheduled euthanasia	0	1	0	0
Delivered and euthanized	0	1	0	0
Max. possible incidence*	945/27	927/27	945/27	945/27
Appearance:				
Erythema grade I	0/0	0/0	0/0	2/1
Ungroomed coat	4/1	7/1	5/1	2/1
Abnormal Stool	0/0	0/0	5/2	3/2
Scant feces	3/1	0/0	1/1	0/0

* Max. possible incidence: (days x rabbits)/no. rabbits exam/group

Table III: Clinical observations and skin reactions -F0 Presumed gestation

PARAMETERS	F0 FEMALES PRESUMED GESTATION (ANIMALS WITH CONFIRMED MATING DATE)			
	C-sectioning		Natural delivery	
	I	II	III	IV
Mortality	1	2	0	0
Found dead	1	1	0	0
Unscheduled euthanasia	0	1	0	0
Delivered and euthanized	0	1	0	1
Max. possible incidence*	810/27	717/24	846/26	844/26
Appearance:				
Erythema grade I	4/3	3/2	3/2	0/0
Ungroomed coat	12/1	13/3	28/3	28/2
Abnormal Stool	1/1	4/2	11/3	8/2
Scant feces	15/6	18/3	21/7	30/6
Red substance in cage	3/21	3/2	1/1	0/0

* Max. possible incidence: (days x rabbits)/no. rabbits exam/group

Table IV: Clinical observations and skin reactions -F0 Natural delivery group

PARAMETERS	F0 FEMALES ASSIGNED TO NATURAL DELIVERY	
	Natural delivery	
	III	IV
Mortality	0	0
Max. possible incidence	508/22	516/22
Appearance:		
Ungroomed coat	89/8	51/4
Sparse haircoat:	142/9	156/8
Abnormal Stool	5/2	5/3
Scant feces	11/6	12/5
No feces in cage pan	1/1	0/0

Comment: Clinical observations and skin reactions observed during the premating, gestation and lactation period did not significantly differ from control group values and were observed in only few rabbits in any group. These are not considered test article related.

Body weight: (summarized in Tables 2-7 and 30-32 of UBA000-38)
Observations during premating: Body weights and body weight gains during the premating period were not affected by administration of the test article (Table 2 and 3 of report UBA000-38).
Observations during gestation: Body weights and body weight gains during the gestation period were not affected by administration of the test article (Table 3 and 4 of report UBA000-38).
Observations during lactation: Body weight loss occurred in both the control and vaccine treated group during the lactation period reaching statistical significance on DG 11-15 in the vaccine treated group. Overall body weight gain on DLs 1–29 were significantly reduced in the vaccine treated group. However, average body weights during lactation were comparable between the treatment group IV and control group III (Tables 6 and 7 of report UBA000-38).

Table V: Maternal Body weights[1-] Gestation-Summary

EXAMINED F_0 PARENTS	GROUP	I	II	III	IV
RABBITS TESTED		27	26	27	27
PREGNANT		24	21	22	22
Body Weight GD 29		4.09±0.50	4.26 ±0.49	4.20±0.57	4.23 ±0.50
Body Weight Changes GD 0- 29		0.18±0.32	0.26±0.24	0.16±0.29	0.21±0.22
Feed Intake absolute GD 0-29 (g/day)		120.1±30.5	128.5±28.4	119.6±28.2	118.8±22.2

[1]: Recorded in grams, rounded to 3 significant digits and reported in Kilograms

Food consumption: summarized in Tables 8-13 and 33 - 35 of UBA 000-38)
Absolute (g/day) and relative (g/kg/day) feed consumption values during premating, gestation and lactation periods were comparable among treatment and control groups and did not significantly differ.

Mating and fertility: (summarized in Table 14 and 36 of UBA000-38)

Fertility parameters (mating/fertility index, corpora lutea, preimplantation loss, etc.):
Mating and fertility indices appeared to be unaffected by treatment with the MenACWY vaccine. Of 27 rabbits evaluated in each of groups I through IV, 27, 24, 26 and 26 does mated, respectively. Pregnancy occurred in 24/27 (88.9%), 21/26 (80.8%), 22/27 (81.4%) and 22 /27 (81.4%) does in the respective dosage groups. The fertility index was 88.9%, 87.5%, 84.6% and 84.6% in groups I – IV, respectively.

Table VIII: Reproductive parameters examined (in F_0 animals):

GENERATION		**F_0**			
DOSE (0.5 ml : DS 1, 15 , 29 ,GD 7 and 20)		**I CONTROL**	**II VACCINE**	**III CONTROL**	**IV VACCINE**
PREGNANCY					
Rabbits evaluated	N	27	26	27	27
Rabbits that mated	N %	27 100	24 92.3	26 96.3	26 96.3
Number of Females Achieving Pregnancy	N	24	21	22	22
Female Fertility Index (No. pregnant females.no./ no.females mated)	%	88.9	87.5	84.6	84.6

Necropsy of F0 generation (summarized in Tables 15 [16] and 37 of UBA000-38)
Necropsy observations included pale liver lobes, ulceration in fundic region of the stomach, small left ovary, uterine horns reduced to ligament, blind ended sac presented 8.0 cm from right ovary, fluid-filled cyst in left uterine horn and red area at injection site of right hindlimb. The stomach of one group II doe that delivered early contained pup tissue.

Comment: These observations are not considered vaccine related because they occurred in only one or two does in any dosage group (n=27 rabbits/group).

Caesarean data (summarized in Tables 17 - 18, and 38 - 40 in UBA000-38)

Table IX: Caesarean-sectioning observations F0 generation

GENERATION		F_0	
DAILY DOSE ((0.5 ml : DS 1, 15 , 29 ,GD 7 and 20)		GROUP I CONTROL	GROUP II VACCINE
PREGNANCY			
Rabbits tested	N	27	26
MATERNAL MORTALITY			
Number of Females Pregnant	N	24	21
Found dead	N	1	1
Delivered + euthanized	N	0	1
Rabbits pregnant + C-sectioned	N	23	19
GESTATION			
Gestation Length	MEAN S.D.	29*	29
CORPORA LUTEA			
Corpora Lutea/Dam	MEAN S.D.	8.3 1.9	8.6 2.0
IMPLANTATIONS			
Total # Implantations	N		
Implantations/Dam	MEAN S.D.	6.9 2.0	7.5 2.8
Preimplantation loss	MEAN S.D.	17.1 20.6	12.2 25.7
Postimplantation loss	MEAN S.D.	20.5 23.8	7.7 15.8
RESORPTIONS			
Does with any resorption	N	17	6
Does with all conceptuses dead or resorbed		1	0
Total # Early Resorptions		22	8
Early Resorptions	MEAN S.D.	1.0 1.1	0.4 1.0
Total # Late Resorptions	N	6	2
Late Resorptions	MEAN S.D.	0.3 0.5	0.1 0.3
Does with viable fetuses		22	19
BIRTHS – DAY 0			
Number Stillborns – Total Per Liter	N MEAN S.D.	0	1 0.0 0.2
Number Live-born – Total Per Liter	N MEAN S.D.	130 5.6 2.0	132 6.9 2.8
% Live male fetuses litter	MEAN S.D.	52.7 20.9	58.7 24.3
LIFE FETAL BODY WEIGTS/LITTER (G)	MEAN S.D.	45.91 5.50	46.7 8.84

* Caesarean group, thus all animals sacrificed on DG 29

Comment: Litter averages for corpora lutea, implantations, late resorptions, fetal body weights and percent live male fetuses were comparable between the saline (group I) and vaccine treated (Group II) groups. One doe in group I (control) had a litter consisting of

only resorbed conceptuses. There was one dead fetus in group II (vaccine). In group II (vaccine), litter averages for litter size and live fetuses were increased compared to the control group. Litter averages for postimplantation loss and early resorptions were increased in the control group compared to the vaccine group. In summary, Caesarean-sectioning and litter parameters were not adversely affected by MenACWY vaccine.

Results F1 generation

Caesarean-sectioning group-fetal necropsy (summarized in Table 19 - 23 and Tables 41 of UBA000-38)

Fetal alterations: defined as a) malformations (irreversible changes occurring at low incidences in the species and strain, not compatible with survival or normal life) and b) variations (common findings in the species and strain and reversible delays or accelerations in development). Evaluations were based on 130 and 132 live DG 29 Caesarean-delivered fetuses in 22 and 19 litters in groups I and II, respectively.

Table X: Fetal Alterations- F1 generation-Summary

GENERATION		**Rabbits assigned to C-sectioning**	
DOSAGE Group (ug/0.5 ml)		**I** 0	**II** 25
LITTER EVALUATED	N	22	19
FETUSES EVALUATED	N	130	133
LIVE	N	130	132
Litters with fetuses with any alteration observed	N (%)	9 (40.9)	10 (52.6)
Fetuses with any alteration observed	N (%)	10 (7.7)	13 (9.8)
% fetuses with any alteration/litter	MEAN S.D.	9.4 14.1	14.4 23.6
GROSS EXTERNAL ALTERATIONS			
Body: umbilical hernia			
Litter incidence	N(%)	0	1 (4.3)
Fetal incidence	N(%)	0	1 (0.6)
Fore and/or hindlimbs rotated			
Litter incidence	N(%)	1 (4.5)	0 (0.0)
Fetal incidence	N(%)	1 (0.8)	0 (0.0)
Tail: bent			
Litter incidence	N(%)	0 (0.0)	1 (5.3)
Fetal incidence	N(%)	0 (0.0)	1 (0.8)
Tail: short			
Litter incidence	N(%)	0 (0.0)	1 (5.3)
Fetal incidence	N(%)	0 (0.0)	1 (0.8)
SOFT TISSUE ALTERATIONS			
Protuding small intestine through umbilicus			
Litter incidence	N(%)	1 (4.5)	0 (0.0)
Fetal incidence	N(%)	1 (0.8)	0 (0.0)
FETAL SKELETAL ALTERATIONS			
Skull : Irregular ossification –summary of all irregular ossifications of the scull			
Litter incidence	N(%)	2 (9.1)	2 (10.5)
Fetal incidence	N(%)	2 (1.5)	3 (2.0)
Skull-other alterations:			
Hoid: ALA, Angulated			

GENERATION		Rabbits assigned to C-sectioning	
DOSAGE Group (ug/0.5 ml)		**I** 0	**II** 25
Litter incidence	N (%)	2 (9.1)	3 (15.8)
Fetal incidence	N (%)	2 (1.5)	3 (2.3)

Comment: There were no tissue or skeletal malformation that were attributable to vaccine treatments. Skeletal alterations, such as irregularities in skull ossification, irregularities in thoracic, lumbal and caudal vertebra, ribs, and fused sternal centra occurred with low frequency across treatment groups and thus, not considered attributable to vaccine treatment. There were no statistically significant differences across groups in the average numbers of ossifications sites per fetus for the hoid, vertebrae, ribs, sternum, forelimbs or hindlimbs (Table 23 of UBA 000-38). The average number of metacarpals per fetus/litter was significantly reduced ($p \leq 0.5$) (control: 5.00±0.00; vaccine 4.97± 0.06) but was within the historical control data of the testing facility.

Natural delivery observations (summarized in Tables 24 - 25, Tables 42-45 of UBA000-38)

Comment: Group III (control) and IV (vaccine) delivered 22 and 22 litters, respectively. Values for the number of does delivering litters, duration of gestation, averages implantations sites per delivered litter and live litter size, gestation index, number of does with stillborn pups and does with no liveborn pups, pup sex ratios, litter size and pup body weights were comparable among the two groups.

Table XI: Natural delivery observations (F0 Generation)

GENERATION		F0 GENERATION	
DOSE (0.5 ml : DS 1, 15 , 29 ,GD 7 and 20)		**III** SALINE	**IV** VACCINE
Rabbits assigned to natural delivery		**27**	**27**
PREGNANT	N	22	22
Delivered a litter	N (%)	22(100.0)	22(100.0)
Duration of gestation	N	32.3± 0.8	32.2± 0.7
Implantation sites Per delivered litter	N MEAN ± SD	123 6.5 ± 2.2	134 7.4 ± 2.9
Does with stillborn pups	N (%)	2 (9.1)	5 (22.7)
Does with no liveborn pups	%	0	0
Gestation Index*	%	100.0	100.0
Pups delivered total	N MEAN ± SD	140 6.4 ± 2.2	167 7.6 ± 2.6
Liveborn	N MEAN ± SD	136 6.2 ± 2.4	160 7.3± 2.9
Stillborn	N MEAN ± SD	4 0.2 ± 0.7	7 0.3± 0.6
Does with all pups dying days 1-5 postpartum	%	5 (22.7)	3 (13.6)
Does with all pups dying days 6-29 postpartum	N	0	2 (9.1)
Viability index**	%	70.6 96/136	71.2 114/160

GENERATION		F0 GENERATION	
DOSE (0.5 ml : DS 1, 15 , 29 ,GD 7 and 20)		**III** **SALINE**	**IV** **VACCINE**
Rabbits assigned to natural delivery		**27**	**27**
Lactation Index ***		92.7 89/96	88.6 101/114

* number of does with live offspring/number of pregnant does
** number of live pups on day 5 postpartum/number of liveborn pups on day 1 postpartum
*** number of live pups on LD 29 /number of live pups on day 5 postpartum

F_1 physical development:

Table XII: F1 – Generation-Physical development

GENERATION		F_1 LITTER	
		GROUP III **CONTROL**	**GROUP IV** **VACCINE**
LITTER SIZE			
Number Born – Total Per Litter	N MEAN S.D.	140 6.4 2.2	167 7.6 2.6
Liveborn		136	160
Stillborn		4	7
Total number found dead or euthanized due to clinical sign	N	47	59
Day 1 Days 2-5 Days 6-8 Days 9-15 Days 16-22 Days 23-29	N N N N N N	5/135 35/131 5/96 2/91 0/89 0/89	10/160 36/150 7/114 2/107 1/105 3/104
VIABILITY INDEX No. live pups LD 5/no. live pups LD1	%	70.6 96/136	71.2 114/160
SURVIVING PUPS			
Day 5 – Total Per Litter	 MEAN S.D.	 4.4 3.1	 5.2 3.4
Day 8 – Total Per Litter	N MEAN S.D.	 4.1 2.9	 4.9 3.4
Day 15 – Total Per Litter	N MEAN S.D.	 4.0 2.8	 4.8 3.4
Day 22 – Total Per Litter	N MEAN S.D.	 4.0 2.8	 4.7 3.4
Day 29 – Total Per Litter		 4.0 2.8	 4.6 3.2
LITTER WEIGHT (G)			
Day 0	 MEAN S.D.	Not recorded	Not recorded
Day 5	 MEAN S.D.	103.6 ± 29.6	94.0 ± 22.6

GENERATION		F_1 LITTER	
		GROUP III CONTROL	GROUP IV VACCINE
Day 8	MEAN S.D.	145.8 ± 44.5	133.0 ± 35.6
Day 15	MEAN S.D.	247.8 ± 64.6	238.9± 66.0
Day 21	MEAN S.D.	342.8 ± 86.8	333.3 ± 103.3
Day 29	MEAN S.D.	585.5 ± 138.0	570.4 ± 123.3

Clinical observations of F1 generation pups from birth to lactation day 29 were summarized in Tables 26 and 46 of UBA000-38 and included discoloration of hindlimbs, lumbar and sacral area, swollen and extended hindlimbs, splayed forelimbs, thin appearance. The only persistent clinical sign was head tilt in one group III pup. Findings occurred with low frequency across treatment groups and are not considered vaccine related.

F_1 evaluation/Developmental endpoints: (summarized in Table 27 and Table 47-51 of UBA000-38)
Reflex and physical development in F_1 pups was assessed in a minimum of 17 litters of group III and IV, respectively (because litters with no surviving pups were excluded from the analysis). An exception was an evaluation of 16 litters in group III for auditory startle reflex. There were no significant differences between groups III and IV in the average postpartum day that at least 50% of the pups in a litter met the criteria for hair growth, eye opening, air righting, auditory startle and pupil constriction in the surviving F1 generation pups with the exception of a transient but significant difference in the number of group IV pups that met the criterion for auditory startle on day 15 postpartum.

F_1- generation Necropsy observations: (summarized in Table 28 and Table 52 of UBA000-38).
Necropsy observations were unremarkable and not considered attributable to MenACWY conjugate vaccine because the incidences were similar in the control and vaccine treated group and limited to only one or two pups per dosage group.

Serology results
Immune response to the MenACWY conjugate vaccine was evaluated in female rabbits receiving 5 IM injections of the vaccine and also in fetuses and 4 week old offspring. Animals were immunized by IM injections on days 1, 15, 29 pre-mating and again on gestation days 7 and 20. Blood was collected from does prior to the first injection, on days 1, on days 15 and 29 and on days 7 and 20 of gestation. Blood was also collected on day 29 of gestation (groups I and II) and on day 29 of lactation (groups III and IV). Blood samples were collected from each fetus and pooled by litter on day 29 of gestation (group

I and II). Blood was also collected from each pup after euthanasia on day 29 of lactation. Nine does per group with corresponding fetal pools or individual pups were selected on the basis of litter size (at least 6 fetuses or pups per doe) from groups II and IV and analyzed. Because immunogenicity responses were evaluated in a dose range developmental toxicity study (UBA00020) only samples from groups II and IV were analyzed. Nine females and their corresponding pooled fetal sera collected at day of gestation 29 from group II were analyzed for antibody functional activity.

For the 4 meningococcal antigens analyzed, a similar level of specific antibodies was observed in vaccine treated groups II and IV on gestation days 7 and 20. Titers decreased on gestation 29 and in particular lactation day 29. Titers for MenW and MenY antigens of does on lactation day 29 were similar to pre-study titers. Analysis of fetal sera showed that antibodies were transferred from maternal animals to fetus as fetal sera titers were higher than the maternal titers at the corresponding time points (day 29 gestation) or similar to maternal titers at day 20 of gestation. Pups sera results showed lower titers of MenA versus maternal titers on day of lactation 29. Pups showed similar titers for MenC, W and Y when compared to the corresponding maternal time point (day 29 lactation). Bactericidal responses in maternal sera were higher for MenA and MenC compared to MenW and MenY. Bactericidal titers of fetal sera pools were similar to corresponding maternal titers.

Discussion and Conclusions

UBA000-38: Animals were dosed on study days (DS) -1, -15 and -29 prior to mating and on gestation days 7 and 20 either with MenCWY vaccine, 0.5 ml, I.M., 25 ug antigen or saline control. Animals were subdivided into subgroups of animals (27 rabbits/group), underwent Caesarean section on DG 29 or were allowed to rear their offspring. Treatment of animals with MenCWY vaccine did not induce vaccine related maternal death or abortion. Clinical signs during the pre-mating, gestation and lactation period, body weights and feed consumptions were comparable across treatment groups. Mating and fertility indices as well as Caesaeran-sectioning, natural delivery and litter parameters were unaffected by treatment with MenACWY conjugate vaccine. There appeared to be no treatment related effects on fetal viability, fetal body weight, sex, gross external or soft tissue or skeletal examinations. F1 pup viability, body weight, sex, reflex and physical development were not affected by treatment with the vaccine. Thus, under the conditions of the study, the MenACWY vaccine does not appear to affect embryo-fetal pre-and postnatal development and does not appear to exert teratogenic effects.

The sponsor is proposing the following language for section 8.1 of the product labeling:

8.1 Pregnancy

Fetal risk summary

No data are available in humans to indicate that Menveo increases the overall risk of fetal anomalies. Based on animal data, Menveo is not predicted to increase the risk of developmental abnormalities.

Clinical considerations

There are no data indicating whether or not Menveo affects reproductive capacity or causes fetal harm when administered to a pregnant woman.

Inadvertent exposure

There are no data indicating whether Menveo affects labor or delivery. Considering the severity of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135, pregnancy should not preclude vaccination when the risk of disease clearly outweighs the risk of vaccination.

Data

Human data

To date no clinical trials have been specifically designed to evaluate the use of Menveo in pregnant or lactating women. Although the use of birth control measures, where appropriate, was an entry criterion for the clinical development studies, 34 women in studies V59P13 and V59P17 were found to be pregnant during the 6-month follow-up period. Of these 34 women, 28 were administered Menveo and six were administered Menactra.

After vaccination with Menveo, there have been four spontaneous abortions; three were assessed as unrelated and one assessed as possibly related based on temporal association with vaccination. There have been two live births, both of which resulted in normal infants. The remaining 22 subjects have ongoing pregnancies at the time of writing of this document.

Animal data

Female rabbits received three intramuscular doses of Menveo before mating and two doses during gestation. Each dose was approximately 15-fold higher than the human dose on a body weight basis. There were no effects on pregnancy or parturition. Menveo was not teratogenic and had no effects on fetal viability (mortality or resorptions) or fetal body weights. There were no post-natal developmental abnormalities in offspring through day 29 of lactation.

Comments to sponsor to be communicated at the time of labeling negotiations:

1. The suggested language follows the format of the proposed rule entitled "Content and Format of Labeling for Human Prescription Drug and Biological products; Requirements for pregnancy and lactation labeling" (May 29, 2008). However, as the proposed rule is not finalized, the pregnancy labeling section 8.1 must include a pregnancy category and language as prescribed in current 21 CFR 201.57(9)(i)(A). This will need to be addressed when negotiating the product labeling.

2. If the new pregnancy labeling subsection format is used, the suggested language under the *Fetal risk summary* and *Clinical considerations* section needs to be revised to make it clear that there are no sufficient human data to state absence of the vaccine on reproductive parameters. In this regard the sentence "No data are

available in humans to indicate that Menveo increases the overall risk of fetal anomalies" will need to be deleted. Similarly, the sentence "There are no data indicating whether or not Menveo affects reproductive capacity or causes fetal harm when administered to a pregnant woman" will need to be deleted. The clinical consideration section will need to be revised to include information on risk to the pregnant women and the fetus form the disease. Inadvertent exposure should indicate that there are no human data. Also, inadvertent exposure should be part of the clinical considerations section. Details will need to be discussed with the labeling team. The sentence "There are no data indicating whether Menveo affects labor or delivery" will need to be deleted. There should be further discussion whether inserting such statement is adequate for a vaccine labeling.

3. Further discussions with the review and labeling team are necessary to determine how to write section 8.1 of product labeling given that current regulations still require pregnancy category.

4. It is recommended that the sponsor establishes a pregnancy registry for this vaccine to obtain data on exposure during pregnancy.

Recommendation: Pregnancy Category B

Supervisor Concurrence: Yes ___ No ___