

Toxicology Review - BEXSERO

- Toxicology Review of MenB (Bexsero[®])

STN: 125546.0

Type and date of submission: Original; July 24, 2014

Applicant: Novartis

Product: Bexsero[®] [Meningococcal group B vaccine (recombinant, adsorbed)]

Cross references: IND (b)(4)

Proposed indication: Active immunization against invasive disease caused by *Neisseria meningitidis* serogroup B strains of individuals from 10 years through 25 years of age.

Recommended clinical dose: 50 ug each of three M *Neisseria meningitidis* serogroup B protein antigens: NadA, NHBA and fHbp, 25 ug OMV-NZ and 0.5 mg Al (OH)₃

Reviewer: Ching-Long Joseph Sun, Ph. D., Division of Vaccines and Related Products Applications

The following three supportive studies with related MenB formulations were submitted:

CIQ 006- Multiple dose intramuscular safety and tolerability study of MenB287/OMV adjuvanted with Alum in -----(b)(4)----- rabbits

CIQ 007- Single dose intramuscular safety and tolerability study of MenB287/OMV adjuvanted with Alum in -----(b)(4)----- rabbits

UBA00002- Intramuscular developmental toxicity study of MenB NZ OMV vaccine in rabbits

MenB287+OMV NW vaccine, an earlier version, was tested in the single- and repeat-dose studies. MenZB (a MenB NZ OMV with no recombinant protein) was assessed in the developmental toxicity study. These three studies were not performed using the intended marketing formulation and considered not relevant to the product. Their reports are not reviewed.

The following three toxicological study reports, conducted using the intended marketing formulation, are considered relevant to the application:

1228-102- Single and multiple dose intramuscular toxicity study in -----(b)(4)----- rabbits

UBA-00041- Intramuscular dosage-range developmental toxicity study of *Meningococcal* B recombinant vaccine with or without OMV-NZ in rabbits

UBA-00044- Intramuscular fertility developmental and perinatal/postnatal reproduction toxicity study of *Meningococcal* B recombinant vaccine with OMV-NZ in female rabbits

The intramuscular single and multiple dose study has been reviewed in the original IND (b)(4) submission in 2004 (see IND review memo by Ann M. Pilaro, Ph. D. dated March 18, 2004). The intramuscular dose-range developmental study was to provide information for the selection of dosage to be used in the definitive fertility, developmental and perinatal/postnatal reproduction toxicity study. Thus, only the definitive reproductive and developmental study report is reviewed.

Review

Study title and number: Intramuscular fertility, developmental and perinatal/postnatal reproduction toxicity study of Meningococcal B recombinant vaccine with OMV-NZ in female rabbits, including a postnatal evaluation (Study # UBA00044)

Performing laboratory: -----(b)(4)-----

Initiation date: May 8, 2008
 Final report date: November 17, 2009
 Test article batch/lot #: X38D27N1
 Animal species and strain: -----(b)(4)----- rabbit
 Breeder/supplier: -----(b)(4)-----
 Number of female animals per group: 27
 Age: 6 months
 Body weight range: 2.8-4.0 kg
 Route and site of administration: Intramuscular at the hind limbs
 Volume of administration: 0.5 ml
 Frequency of administration and study duration: 5, 3 and 1 weeks prior to mating and days 7 and 20 of gestation period; 12 weeks
 Dose: 50 ug of each of the three rMenB antigens and 25 ug OMV-NZ antigen and 1.5 mg Al (OH)₃
 Stability: Information to document or certify the identity, composition, strength, activity/purity and stability of the test article was provided by the sponsor. A certificate of Analysis is provided in Appendix 3.
 Means of administration: 1 cc Syringe and 25 gauge needle
 Report status: Final
 Experimental design

Group*	Test article	rMenB** (ug)	OMV-NZ (ug)	Al (OH) ₃ (mg)	No. females/group
1	Control (saline)	0	0	0	27
2	rMenB/OMV-NZ	50	25	1.5	27
3	Control (saline)	0	0	0	27
4	rMenB/OMV-NZ	50	25	1.5	27

*: Groups 1 and 2 (cesarean sectioning); groups 3 and 4 (natural delivery)

** Each of the three antigens (287-953, 936-741 and 961c)

Randomization procedure: The animals were assigned based on body weight to dose groups by mean of computer-generated randomization procedures.

Statistical analysis plan: Clinical observations and other proportional data were analyzed using the Variance Test for Homogeneity of the Binomial Distribution.

Continuous data (e.g., maternal body weights, body weight changes, food consumption values and litter averages for percent male fetuses, percent resorbed conceptuses, fetal body weights and fetal anomaly data) were analyzed using Bartlett's Test of

Homogeneity of Variances and the Analysis of Variance, when appropriate (i.e., Bartlett's Test was not significant). If the Analysis of Variance was significant, Dunnett's Test was used to identify the statistical significance of the individual groups. If the Analysis of Variance was not appropriate (i.e., Bartlett's Test was significant), the Kruskal-Wallis Test was used. In cases where the Kruskal-Wallis Test was statistically significant, Dunn's Method of Multiple Comparisons was used to identify the statistical significance of the individual groups. If there were greater than 75% ties, Fisher's Exact Test was used to analyze the data. Kit weights during the postpartum period were also analyzed by Analysis of Covariance (ANCOVA) using live litter size on lactation day (DL) 5 as the covariate.

The following parameters were evaluated

Parameters	Frequency of Testing
F0	
Viability checks	Twice daily
General appearance/clinical observations	Daily during the premating, gestation and postpartum periods and delivery day to lactation day 3 for groups 3 and 4 and 1 and 2 hours after each dosing
Injection site (modified Drize test)	One and two days after each doing
Maternal observations (groups 3 and 4)	DLs 4, 5, 8, 15, 22 and 28
Body weight	Weekly during pre-mating period and dosing period and DGs 0, 7, 10, 13, 16, 20, 23, 26, 29 and 34 (when necessary) and DLs 5, 8, 11, 15, 18, 22, 25, and 29 for groups 3 and 4
Food consumption	Daily
Maternal reproductive tract examinations (groups 1 and 2)	DG 29

Parameters	Frequency of Testing
Natural delivery F1 (groups 3 and 4)	
Viability checks	Daily on DLs 4-14
General appearance	Daily beginning on DL4 and afterward
Body weight	PNDs 5, 8, 15, 18, 22, and 29
Food consumption	Daily beginning on the PND 29 (the day of weaning)
Developmental landmarks	
Hair growth	PND 5
Eye Opening	PND 9
Air Righting Reflex	PND 10
Acoustic (Auditory) Startle	PND 14
Pupil Constriction	PND 22
Immunogenicity	
F0	Pre-dose, DSs 15 and 29 and DGs 7 and 20 and DG 29 (groups 1 and 2)/ DL29 (groups 3 and 4) thru the medial auricular artery or the inferior vena cava
F1	
Gross necropsy	Day 28 postpartum
Cesarean sectioning F1 (groups 1 and 2)	
Fetal visceral and skeletal examinations	DG 29

Results:

Mortality and abortion: No mortalities related to administration of the product occurred. Two does each were found dead. In the vaccine treated group, one doe was euthanized due to adverse clinical observation and one doe aborted was euthanized. The findings in the vaccine groups were not considered related to the product as the incidences were similar to that in the control group and necropsy observations did not indicate any relevant finding. The single abortion was within the provided historical control range. Clinical signs: Erythema and edema were reported in all groups with the number of does being slightly increased in the treatment groups compared to the control groups. All other clinical signs showed similar frequency in both control and vaccine treated groups.

Body weights: Maternal body weights were unaffected by administration of the rMenB with OMV-NZ during the premating, gestation, and lactation periods with slight lower body weight gain being observed from DGs 13 to 16 and DGs 0 to 29 in group 2 compared to group 1. However no difference was observed between group 3 and group 4.

Food consumption: Food consumption values were unaffected during the premating, gestation, and lactation periods except a mild transient decrease on DGs 7-10, 16-20 and 0-29 in group 2 and transient increase on DLs 11-15 in group 4.

Mating and fertility: Mating and fertility were unaffected. Mating occurred in 100% in the control groups and 96% the vaccine groups. Fertility rates were 96.3 %, 96.2 %, 100 % and 92 % in groups 1, 2, 3 and 4, respectively.

Gross pathology: Necropsy examination revealed no gross lesions related to the treatment.

Cesarean sectioning and litter examinations: No ovarian/uterine examinations and litter parameters were affected by the treatment. Corpora lutea, litter sizes, live fetuses, resorptions, implantation, percentage resorbed conceptuses, percentage of live fetuses, and fetal body weights were comparable between groups 1 and 2. All placentas appeared normal.

Fetal examinations: Fetal evaluations were based on 207 and 180 live fetuses in 26 and 25 litters in groups 1 and 2, respectively.

External alterations: One fetus in group 1 and three fetuses from one litter in group 2 had various flexions and rotations of the limbs. None of these alterations affected the bones of the limbs indicating that these were minor variation.

Soft tissue examinations: One fetus in group 1 presented with an interventricular septal defect and a persistent truncus arteriosus. No other malformations or variations occurred on study.

Skeletal examinations: A hemivertebra at the 9th thoracic vertebrae with an associate rib was observed in one fetus in group 1. No other skeletal malformations occurred. In group 2, some variations in the skull (irregular ossification and hole in the parietal) were observed in 3 and 7 fetuses, respectively. In group 2, four fetuses had mis-aligned caudal vertebrae, one fetus had a short rib, four fetuses had fused sternal centra and five fetuses had incompletely ossified pubic bones. These findings were not considered significant as the malformation was a common variation in this strain of rabbit and the variations were within the historical control data for the testing facility.

Natural delivery observations

Clinical observations, reflex and physical development and functional observation battery: They were not affected by maternal treatment with the vaccine except higher percentage of pups in group 4 exhibited the air righting reflex on postnatal days 11 and 12.

Pup necropsy observations: Total of 68 groups 3 pups and 38 group 4 pups were found dead, stillborn or were euthanized due to adverse clinical signs. Of these pups, 20 control and 11 vaccine group pups had no milk present in stomach.

Immunochemistry: Specific bacterial antibodies (SBA) against the four vaccine strains were observed in all treated animal. Fetal antibody titers on DG29 were similar to maternal titers on DG20 and were higher than maternal titers on DG29. Pup titers on DL29 were lower or similar to maternal titers. The results confirmed the active delivery of the vaccine and that antibodies were passed to fetuses and persisted in pups through day 29 of lactation.

Assessment

Dose selection was based on the result from a dosage-range study where MenB doses of 50/25 ug for each of the three antigens and 100/50 ug of OMV were intramuscularly administered to female ----(b)(4)--- rabbits. Gravid uterine weights, food consumption, mating and fertility indices and cesarean-sectioning and litter parameters were unaffected by treatment with rMenB +/- OMV-NZ. Given that the antibody exposure was not higher in the 100/50 ug dosage group than the 50/25 ug dosage group, the latter was chosen to be an appropriate dosage level to evaluate the developmental toxicity study in rabbits.

There were no biologically significant treatment-related effects on mating or fertility or reproduction in the F0 generation does. In addition, there were no effects on any ovarian, uterine, or litter parameter. Maternal treatment with the vaccine did not cause any reflex and physical development parameters in the F1 generation kits and there were no apparent adverse effects on postnatal growth or development in the F1 generation offspring.

MenB/OMV-NZ administration elicited very high serum antibody titers in F0 generation, indicating active delivery of the test article. Maternal antibody transfer was demonstrated in the F1 generation fetuses during the period of major organogenesis, as well as in the F1 generation kits during the postpartum period.

There were no vaccine-related external, soft tissues and skeleton abnormalities (malformation and variations) during fetal examinations.

Based on overall findings in the reproductive and developmental toxicity study, it can be concluded that female rabbits received intramuscular administrations three times during pre-mating and two times during gestation periods at dose of 50 ug/ each antigen of the three rMenB protein antigens and 25 ug of OMV-NZ antigen with 1.5 mg Al (OH)3 adjuvant were well tolerated.

GLP study deviations or amendments: No protocol amendments were recorded in the draft report that influenced the quality, integrity or interpretation of the results.

Conclusions

In the single and multiple dose intramuscular toxicity study, rabbits were intramuscularly administered once or five times intramuscular administration during eight weeks. The vaccine (antigens with OMV-NZ) at dose equivalent to the absolute human dose or 15 times the human dose on a body weight basis (4 kg in rabbits and 60 kg in humans)

was well tolerated with minimal effects. It produced higher fibrinogen, leukocyte counts and globulin values that are indicative of inflammation. Together with higher creatinine kinase value suggested skeletal muscle involvement which is likely involved at the injection sites. All these changes, although treatment-related, were mild and transient. In the reproductive and developmental toxicity study, five intramuscular administrations of the vaccine at equivalent of the absolute human dose or 15 times the human dose on a body weight basis during pre-mating and gestation periods revealed no significant reproductive and developmental effects in rabbits. Thus, a pregnancy category B as the applicant proposed is appropriate in section 8.1 of the package insert.

Package Insert

Sections 8 and 13 of the package insert should be revised as recommended below:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B:

Reproduction studies have been performed in female rabbits at doses up to 15 times the human dose on a body weight basis and have revealed no evidence of impaired female fertility or harm to the fetus due to BEXSERO. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, BEXSERO should be used during pregnancy only if clearly needed.

Insufficient clinical data on exposed pregnancies are available. The potential risk for pregnant women is unknown. Nevertheless, vaccination should not be withheld when there is a clear risk of exposure to meningococcal infection.

8.3 Nursing Mothers

It is not known whether BEXSERO is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BEXSERO is administered to a nursing woman.

13 NONCLINICAL TOXICOLOGY

BEXSERO has not been evaluated for carcinogenic, mutagenic potential or male fertility.

Concurrence: Martin D. Green, Ph. D., Division of Vaccines and Related Products Applications