Toxicology Review of MenQuad-TT Vaccine

BLA: 125701/0.0 and 0.19
Type and date of submission: Original submission; April 26, 2019; Amendment 19, December 9, 2019

Applicant: Sanofi Pasteur
Product: MenACYW polysaccharide tetanus toxoid protein conjugate vaccine
Cross references: IND 14171
Proposed use: Active primary and booster immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W and Y in individuals 2 years of age and older

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

Précis
Two pivotal toxicity study reports were submitted in support the licensure: (1) repeat-dose toxicity study in rats, and (2) prenatal and postnatal developmental toxicity in rabbits. The repeat dose toxicity study report was submitted and reviewed in the original IND 14171 submission.

The applicant provided the historical control data regarding implantation sites in the developmental toxicity studies in the response to an information request we sent by email on November 19, 2019.

In the developmental toxicity study, female rabbits (55/group) were administered intramuscularly of phosphor buffer or MenQuad-TT 30 days and 10 days prior to mating and on days 6, 12 and 27 of gestation at dose of 10 ug of each serogroup with (b) (4) ug of Tetanus toxoid protein carrier. There were no vaccine-related clinical or necropsy observations in the dams or in the pups. Data showed lower number of corpora lutea, implantation sites and litter sizes in the cesarean subgroup and lower implantation sites and delivered pups in the littering subgroup as compared with the concurrent controls. However, the number of corpora lutea, implantation sites and litter sizes in the cesarean subgroup and implantation sites in the littering subgroup are within the historical control ranges (9-12.1, 8-11.8, 7.7-11.5 and 8.4-10.5 respectively). The value for delivered pups (7.9) in the littering subgroups is marginally lower than the lower historical control data range (8.0). These differences were of no biological or toxicological relevance. It had no impact on mating and fertility parameters, ovarian and uterine examination, or natural delivery or litter observation parameters in the dams. There were no fetal external, soft tissue, or skeletal abnormalities attributed to vaccine administration. Postnatal development as measured by incisor eruption, fur growth and eye opening (physical development) and auditory, pupillary and righting reflexes (functional development) in the pups were unaffected.

Toxicology Study Review

Title and study number: MenQuad-TT- Developmental and reproductive toxicity study following repeated intramuscular administration in the rabbit (Study#AB21765)
Performing laboratory: (b) (4)
Initiation date: April 18, 2017
Final report date: September 6, 2018
Batch/lot number of test article: UD18371
Animal species and strain: (b) (4) rabbit
Breeder/supplier: (b) (4)
Number of females per group per phase: 30 (littering) and 25 (cesarean)
Age: 18-19 weeks
Body weight range: 3.3 to 5.1 kg
Route and site of administration: Intramuscular in the dorsal lumbar muscles
Volume of administration: 0.5 mL
Frequency of administration and study duration: 30 and 10 days prior to mating and days 6, 12 and 27 of gestation; 95 days
Dose/animal: 10 ug polysaccharide of each of four serogroups
Stability: The testing facility did not have formulation sampling for analysis since the test item was used as supplied.
Means of administration: Appropriate needle and syringe
Report status: Final

Experimental design

Group	Test Material	Dose (ug)	Dose volume (mL)	Dose frequency	No. Females (littering)	No. Females (cesarean)
1	Saline control	0	0.5	30 and 10 days prior to mating and GDs 6, 12 and 27	30	25
2	MenQuad	10*	0.5	Same as above	30	25

*: of each polysaccharide from serogroup A, C, W and Y with (b) (4) ug of Tetanus toxoid

Randomization procedure: Females were randomized assigned to groups. The randomizing stratification system was not specified.

Statistical analysis plan: The best transformation for the data (none, log or rank) was determined depending upon the normality of the data distribution tested by the Shapiro-

Wilk's test and the homogeneity of the variances across groups tested by the Bartlett's test. Non- or log-transformed data were analyzed by parametric methods. Rank transformed data were analyzed using non-parametric methods. Data were then analyzed to test for a dose-related trend to detect the lowest dose at which there is a significant effect, based on the Williams test for parametric data or the Shirley's test for non-parametric data. Homogeneity of means was assessed by analysis of variances (ANOVA) for parametric data or Kruskal-Wallis test for non-parametric data. If no trend was found and means are not homogeneous, the data were analyzed by parametric or non-parametric Dunnett's test to look for significant differences from the control group. Selected incidence data were analyzed using a chi2 test for all groups followed by Fisher's two-tailed test with Bonferroni correction for each treated group versus the control if the chi^2 is significant. F0 pre-coital interval, F1 offspring physical development, and behavioral and functional tests were analyzed using a SAS software package. Levene's test was used to test the equality of variance across groups and Shapiro-Wilk's test was used to assess the normality of the data distribution in each group. Data with homogenous variances and normal distribution in all groups were analyzed using ANOVA followed by Dunnett's test. Data showing non-homogenous variances or a non-normal distribution in at least one group were analyzed using Kruskal-Wallis test followed by Wilcoxon's rank sum test.

The following parameters were evaluated.

	Frequency or parameters of testing
Clinical observations and survival	F0: Twice daily during treatment period and daily during other study days, weekly for physical examination F1: Daily post-partum and post-natal
Injection site observations	Pre-dose and daily after each dose and weekly on other days
Body weights	Twice weekly during pre-mating and meting periods, on days 0, 6, 9, 13,16,20, 24, 27, 29 and 34/35, and on days 4, 7, 11, 14, 17, 21, 28 and 35 of lactation
Food consumption	Daily
Mating	Daily
Cohabitation	Ten consecutive days
Littering group Pregnancy and parturition Date of parturition Gestation duration Nesting or nursing behavior Implantation sites	Day 35 post-partum
Cesarean group Pregnancy status Number of corpora lutea Gravid uterine weight Number of implantations	Day 29 post coitum

Number of live fetuses Number of embryonic/fetal death Fetal weight Fetal sex	
Litter data (littering group) External abnormalities of the pup Number of pups alive Weight of pups alive Verification of incisor eruption Onset and duration of fur growth Onset and duration of eye opening Surface righting reflex Pupillary reflex	 PND 0, 4, 7, 11, 14, 17, 21, 28 and 35 PND 4, 7, 11, 14, 17, 21, 28 and 35 PND 4 PND 4 PND 7 PND 11 PND 35
Immunogenicity evaluation	F0: Pretest, 3 days prior to mating, day 29 post-coitum F1: Day 29 post coitum/35 post-partum
Fetal examination (cesarean group) Visceral Skeletal	Day 29 post coitum

Results:

F0 generation

Mortality: There was no vaccine-related death. One treated female was found dead on gestation day 19. Dark lung lobes were observed, and this death was not considered vaccine-related. One control female and one treated female were euthanized following litter death. There were no necropsy findings for the control and the findings noted for the treated one were considered spontaneous in this species.

Clinical observation: There were no test article-related clinical observations during the study period.

Injection site observations: Hematoma and edema were observed in both control and treated groups with similar incidence and severity. There were no vaccine-related local reactions.

Clinical signs: All signs noted were observed in both groups and there were no vaccine-related clinical signs.

Body weight: There were no vaccine-related effects on body weight and weight gains.

Food consumption: There were no vaccine-related changes in food consumption.

Mating and fertility: There were no vaccine-related effects on fertility parameters (copulation index [98 vs 95%] and fertility index [100v s 96%]).

Maternal organ weight: There were no vaccine-related effects on ovaries weight.

Maternal macroscopic findings: There were no findings.

Gravid uterus weight: Slightly lower (9%) weight was seen in the treatment group but remained close to the historical control value.

Pre-implantation data: Number of corpora lutea (9.3 vs 10.4), implantation sites (8.8 vs 9.7) were lower as compared to the controls. However, they are within the historical control data ranges of 9-12.1 and 8.0-11.8, respectively. The percentage of pre-implantation loss was comparable (6.17 vs 6.31) in both groups.

Post implantation data: Post-implantation loss (2.36 vs 3.42 %) was comparable in both group and below the historical control value (6.3 %). Lower live litter size than the controls (8.5 vs 9.4) was observed but within the historical control data range of 7.7-11.5.

Parturition and gestation length: All females (28) in each group completed delivery and duration gestation (31 days) was comparable in both groups.

F1 generation

Cesarean group

Fetal weight and sex: Fetal weight was comparable with controls. The percentage of male fetuses was similar in both groups.

Fetal external, visceral and skeletal examinations: There were no vaccine-related fetal external, visceral or skeletal malformations.

Littering group

Clinical observations: There were no test article-related clinical signs in the pups.

Pup weight, viability and litter sizes: There was no effect on viability and weight. Slightly lower implantation sites (8.5 vs 9.4) are within the historical control data range of 8.4-10.5. Lower delivered pups/litter (7.9 vs 9.3) were observed in the vaccine-treated group but only marginally lower than the lower historical control value of 8.0. Thus, these small differences when compared with historical control values may not considered biologically significant.

Functional development: There were no test article-related effects on the physical or functional development when compared with controls.

Immunogenicity evaluation: The presence of anti-MenQuad-TT antibodies was observed in all females after the 5^{th} administration on gestation day 29 or lactation day 35. The

levels were slightly lower than those measured before mating. Its presence was demonstrated in in all fetuses which were higher than those in their mothers and in 63 out of 66 pups. The antibodies were not detectable in control females, fetuses and pups nor in treated females before immunization.

Administration of MenQuad TT twice during the premating period (30 and 10 days prior to mating) and three times during gestation (GDs 6,12 and 27) to female rabbits was well tolerated. It did not result in any test article-related effects on mating and maternal systemic toxicity. There was no test article related effect on female fertility index, fetal weight, fetal visceral and skeletal malformations and variations and postnatal development.

Antibody titers were reported in all animals receiving the vaccine, indication an active delivery of the test article to the animas. The titers also reported in the fetuses and pups from the dams receiving the test article, indicating transfer of immunogenicity in utero.

GLP study deviations or amendments: Minor protocol amendments were recorded in the draft report. None of them influenced the quality, integrity or interpretation of the results.

Investigation Brochure: Not applicable.

Assessment
There were no MenQuad-TT-related clinical or necropsy observations in the F0 generation dams or in the F1 generation pups. Administration of MenQuad TT vaccine had no impact on fertility parameters, ovarian and uterine examination and litter parameters or natural delivery parameters. There were no fetal external, soft tissue or skeletal abnormalities attributed to administration of the vaccine. Postnatal development in the F1 generation pups were unaffected by the vaccine administration.

Recommendation
The BLA has adequate nonclinical toxicology data in support licensure of the vaccine. It is approvable from a toxicological perspective.

Animal developmental study results should be indicated in the appropriate sections of package insert according to the new content and format requirements of the Pregnancy, Lactation and Females and Males of Reproductive Potential subsections of labeling for human prescription drug and biological products. The recommended revisions for them are recommended below:

8.1 Pregnancy
Risk Summary
A developmental toxicity study has been performed in female rats administered a full human dose (0.5 mL) of TRADMARK on two occasions prior to mating and three occasions during gestation period. TRADMARK prior to mating, during gestation and

lactation. The study revealed no evidence of harm to the fetus due to TRADMARK (see Animal Data).

Animal Data

In a developmental toxicity study female rabbits received a human dose of TRADMARK by intramuscular injection on five occasions: 30 days and 10 days prior to mating and gestation days 6, 12 and 27. No adverse effects on pe-weaning development up to post-natal day 35 were observed. There were no vaccine-related fetal malformations or variations observed.

8.3 Females and Males of Reproductive Potential
(Animal Data are irrelevant and should be deleted.)

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
TRADMARK has not been evaluated for carcinogenesis or mutagenic potential or for impairment of male fertility in animals. TRADMARK had no effects on female fertility in rabbits. (see 8.1. Animal data).

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