

Toxicology Review of Pneumococcal 21 Valent Vaccine

BLA 125814.0

Type and date of submission: Sequence 1, October 19, 2023

Applicant: Merck Sharp & Dohme LLC

Product: Pneumococcal 21-valent conjugate vaccine (V116)

Related/referred products: IND 19316

Proposed indication for use: Prevention of invasive disease and pneumonia caused by *Streptococcus pneumonia* serotypes 3, 6A, 7F, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B in adults 18 years of age and older.

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

Précis

The sponsor submitted study reports of a 22-day intramuscular toxicity study in rats and a reproductive toxicity study in rats.

The intramuscular toxicity study had been submitted and reviewed in the original IND 19316 in 2019. The animals dosed with 42 ug (2 ug for each of the 21 serotypes) in 0.5 mL were well tolerated. The findings were typical local inflammatory reaction at the injection sites. All the findings at the injection site were reversible.

In the reproductive toxicity study of the vaccine, two groups of 44 female rats were administered intramuscularly control article (phosphate buffer) or 42 ug (2 ug for each of the 21 serotypes) in 0.25 mL of V116 28 and 7 days prior to mating and on gestation day 6 and lactation day 7. The animals in each group were divided into cohort 1 (cesarean-sectioning phase) and cohort 2 (natural delivery phase). Cohort 1 animals were euthanized on gestation day 21. Cohort 2 animals were allowed to deliver naturally and euthanized on lactation day 21. There were no effects on mating performance, or fetal weight, or any naturally delivery or litter parameters. It did not produce any fetal external, visceral or skeletal malformations. V116 injection led to development of V116 serotypes-specific antibodies present in female rats and their offspring. Based on the results, the vaccine was immunogenic in animals and there was evidence of placental transfer.

Toxicology Part Review

Title and study number: Reproductive toxicity study of V116 administered by intramuscular injection to (b) (4) rats (Study#22-9019)

Performing laboratory: (b) (4)

Initiation date: October 11, 2022

Report date: June 12, 2023

Batch/lot number of test article: 0001471935, 168 ug/mL l total polysaccharide

Animal species and strain: (b) (4) rat

Breeder/supplier: (b) (4)

Number of females per group per phase: 22

Age: 10 weeks

Body weight range: 183-220 g

Route and site of administration: Intramuscular into the right or left quadriceps on the hind limb (lateral proximal thigh muscle)

Volume of administration: 0.25 mL/left or right hind limb/animal

Frequency of administration and study duration: 28 and 7 days prior to mating and on gestation day 6 and lactation day 7; 10 weeks

Dose/animal: 42 ug (2 ug for each of the 21 serotypes) in 0.25 mL

Stability: The sponsor provided to the testing facility documentation of the identity, strength, purity, composition and stability for the test article. A certificate of analysis was provided to the testing facility and is presented in appendix 2.

Means of administration: Appropriate needle and syringe

Report status: Final

Experimental design

Group	Test Material	Dose (ug)	Dose volume (mL)	No. Females Cesarean	No. Females Delivery
1	Control article*	0	0.25	22	22
2	V116	42 ug**	0.25	22	22

*: PBS in sterile water

** : 2 ug/each of the 21 serotypes

Randomization procedure: The rats were assigned to dose groups based on computer-generated (weight-ordered) randomization procedures.

Statistical analysis plan: For parametric/non-parametric data, Levene's test was used to assess the homogeneity of group variances. The groups were compared using a Dunnett's test if Leven's test was not significant or Dunn's test if it was significant. For non-parametric data sets, the groups were compared using a Dunn's test.

The following parameters were evaluated.

	Frequency or parameters of testing
F0 generation	
Viability	Twice daily for viability
Clinical observations	Once during acclimation period and daily thereafter
Post-dose observations	Up to 3 hours following each dose
Dermal observation	Same as above

Detailed clinical observations.	Weekly in F0 and F1 animals
Body weights	Once during pretreatment then twice during pre mating period and every other day during the gestation and lactation
Food consumption	Twice weekly beginning on the first day of dose administration and GDs 0, 6, 9, 12, 15, 18, 20 and 25 and LDs 1, 4, 7, 10 and 14
Mating/cohabitation	Daily for 14 days until day of detection of a copulatory plug observed in situ or spermatozoa in smear of vaginal contents
Duration of gestation	
Natural delivery cohort	
Natural delivery observations	Twice daily beginning on GD 20
Litter viability and deaths	Twice daily
Clinical observations	Daily
Pup body weights	Days 1, 4, 7, 10, 14, 18 and 21 postpartum
Preweaning reflex and physical development	
Surface righting reflex	Day 1 postpartum
Air righting	Day 13 postpartum
Auditory startle reflex	Day 13 postpartum
Pupil constriction	Day 21 postpartum
Cesarean-section cohort	
Ovarian and uterine contents and macroscopic lesions	Gestation Day 21
Fetal body weight and sex	Same as above
Fetal morphological examination	Same as above
Antibody analysis (both phases)	F0: Predose, before mating and GD21/D21 postpartum thru jugular vein F1: GD21/D 21 postpartum thru following decapitation or inferior vena cava after euthanasia

Results:

Mortality: There was no V116-related mortality. One female in cohort 2 died during the LD 21 blood collection. This female was normal during the study. Upon completion of parturition, the litter consisted of 6 females and 4 males with normal maternal and litter observation. No visible lesions or observations were noted at necropsy. It was considered secondary to the blood collection process and not to be test article related deaths.

Clinical observation: There were no test article-related clinical observations during the study except transient hindlimb swelling was observed in control (11/42) and V116-treated (18/41) females in both cohorts on GD6 following dose administration and/or the following day (GD7) in the hindlimb. Slightly higher incidence was likely treatment-related although being transient.

Dermal scoring: There were no V116-related dermal observations.

Body weights and gravid uterine weights: There were no test article-related effects on body weights or body weight gain during premating, gestation and lactation. In cohort 1, gravid uterine weights were not affected by V116.

Food consumption: Transient higher food consumption during premating was observed in 5/44 V116 treated females. All other females were similar within the group and comparable to control values. There were no V116-related effects on maternal food consumption during gestation and lactation periods.

Mating and fertility: There were no test article-related effects on the reproductive performance parameters. There were no differences in the pre-coital interval for both groups (2.6 days). Approximate of 95 and 93 % of the control and treated females were mated in the first 7 days of cohabitation. The mating index was comparable (95.5 % vs 93.2 %). Comparable for fertility index (85.7 % vs 80.5 %) and the pregnancy index (81.8 % vs 75 %) was reported.

Examination of pregnancies/ovarian and uterine examination (cohort 1): Pregnancy was confirmed in 18 and 17 females in the control and treated groups, respectively. Higher pre-implantation loss (21.58%) in the treatment group than the control group (16.04%) was reported. However, it was within the range of historical control values for the testing facility. Number of corpora lutea and post implants were comparable to the control. There were no effects on early and late resorptions, number of live and dead fetuses, fetal sex ratio and fetal weights.

Fetal examinations: All fetuses appeared normal in external examination. Upon visceral examination, a single fetus in the treatment groups had moderated dilation in lateral ventricles of the brain. However, this single finding was within the range of historical control incidences of the testing facility. There were no treatment-related fetal skeletal malformations. The skeletal variations observed were unrelated to 116 because they were within the historical range of the testing facility.

Delivery and reproductive parameters/littering data (cohort 2): Pregnancy was reported in 18 and 16 females in the control and treated groups, respectively. There were no test item effects on gestation, number of females with liveborn and stillborn pups, number of live born pups, post-implantation loss per litter and total implantation sites and gestation length. No abnormal maternal behavior nor pup clinical observations were reported.

Pup weights: There were no effects on the pup weights.

Preweaning reflex development: There were no effects in all four reflex assessments (surface righting, air righting, auditory startle and pupil constriction).

Macroscopic examinations: There were no findings to the adult animals (F0) and PND pups (F1).

Immunogenicity: In the treated females, the range of pre-dose samples that were negative (titer <500) for antibodies against V116 serotypes was 50% (22/44) to 100% (44/44). At least twelve serotypes were detected in 81% of F0 female samples (30/37) after administration of V116. Most of the serotypes in the F0 females showed a greater than 3-fold rise in titers after dosing. Responses from F1 fetus and pup samples were generally consistent with the responses observed in the corresponding F0 female samples. In the control F0 females, 84% of pre-dose samples were negative for antibodies against V116. Most control results at post-treatment timepoints were negative. Most of the post-treatment serotype-specific positives in controls had low titer results. The serotypes with the most positive responses within the control group were 20A, 33F, and 35B; however, the responses were present at pre- and post-dose timepoints. No serotypes showed greater than a 2-fold rise in response from pre-dose to post dose, except serotype 20A (2.6-fold rise).

Assessment

Administration of V1163 once 28 and 7 days prior to mating and on day 6 during the gestation phase and on day 7 during the lactation to F0 rats was tolerated well. It did not result in any test article-related effects on estrus cycling, mating and maternal systemic toxicity. There were test item related effects on fertility, pregnancy, gestation length, fetal weights, visceral and skeletal malformations and variation, pup weight and postnatal development.

Antibody titers were reported in most of all animals receiving the vaccine, indicating an active delivery of the test article to the animals. 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.

Conclusion: Administration of V116 by intramuscular injection twice before mating and once in early organogenesis (Gestation Day 6) and once during lactation (lactation day 7) was well tolerated in rats at dose of 42 ug (one-half the human dose).

It did not have any effects on female reproductive effects, fetal/embryonal development and postnatal developmental effects.

Recommendation

The BLA is approvable from a toxicological standpoint. The animal developmental data should be indicated in sections 8.1 and 13.1 of the PI as recommended below:

8.1 Pregnancy

Risk Summary

A developmental toxicity study has been performed in female rats administered one-half of the human dose of Trade name on 4 occasions, twice prior to mating and once during gestation and once during lactation. These studies revealed no evidence of harm to the fetus due to TRADENAME (see *Animal Data*).

Data

Animal Data

In a developmental toxicity study, one-half of the human dose of TRADENAME was administered to female rats by the intramuscular route on 4 occasions: 28 and 7 days prior to mating, on gestation day 6 and on lactation day 7. No TRADENAME-related adverse effects on fetal/embryo development or postnatal development were reported in the study.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

TRADENAME has not been evaluated for the potential to cause carcinogenicity, genotoxicity, or impairment of male fertility. In a developmental toxicity study in rats with TRADENAME there were no vaccine-related effects on female fertility [see Use in Specific Populations (8.1)].

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