

Toxicology Review of V114 vaccine

BLA 125741

Type and date of submission: Original; October 21, 2020

Sponsor: Merck Sharp and Dohme Corp.,

Product: Pneumococcal 15-valent Conjugate Vaccine [CRM197 Protein], (b) (4)

Related/referred products: BBIND 014115, BBIND 014977, DMF (b) (4), BBMF (b) (4), DMF (b) (4), DMF (b) (4), DMF (b) (4), DMF (b) (4)

Proposed indication for use: Prevention of Pneumococcal Disease (Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F)

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

Précis

The applicant submitted toxicity study reports of the following:

- (1) 85-day intramuscular repeat-dose toxicity study in rats with a 28-day recovery period (study# TT 08-1077)
- (2) 85-day intramuscular toxicity study with a 4-week treatment-free period in rats (study# TT 16-1044)
- (3) 85-day (b) (4) toxicity study with a 4-week treatment-free period in rats (study TT 18-1028)
- (4) Intramuscular embryo-fetal developmental and preweaning toxicity study in rats (Study# TT 19-7090)
- (5) Intramuscular postnatal developmental toxicity study in rats (Study # TT19-7170)
- (6) Intramuscular embryo-fetal developmental toxicity study in rats (Study# TT19-7190)

The first two intramuscular toxicity studies, 08-1077 and 16-1044, had been reviewed in IND14115, IND 14977, respectively. The (b) (4) toxicity study (18-1028) did not use the intended marketing intramuscular route of administration and therefore is not relevant to the proposed marketing product.

The first embryo-fetal developmental and preweaning toxicity study in rats (19-7090) had been reviewed in IND 14977. The results of the second embryo-fetal developmental toxicity study (19-7190) were no longer needed based on results from a separate developmental toxicity study, and the study was terminated early. Thus, the the postnatal developmental toxicity (19-7170) is being reviewed.

In the postnatal developmental toxicity study, two groups of 60 female rats were administered intramuscularly control article (phosphate buffered saline) or 32 ug of V-114 in 0.5 mL 28 days and 7 days prior to mating and on gestation day 6 and lactation day 7. The animals in each group were divided into two cohorts to assess the F1 animals through PND 21 (cohort A) and through PND 56 (cohort B) as a potential recovery phase. However, it was deemed unnecessary to complete assessment of cohort B based on the results of cohort A, and the cohort B animals euthanized on PND 26-30. No effects on natural delivery or litter parameter or on pup external morphology, viability or body

weight were reported. No gross findings in the kidney, ureters or urinary bladder were observed in any of the F0 females or F1 pups. The results from the study may indicate that the observation of dilated renal pelvis occurred in pups in the previous embryo-fetal toxicity study (TT 19790) was not treatment-related. In the treatment groups, at least 10 of 15 serotypes were detected in 95 % of the F0 females and 98 % of the F1 pups, indicating sustained immunogenic responses over generation.

Toxicology Part Review

Title and study number: Intramuscular postnatal developmental toxicity study of V114 in rats (Study#TT-7170)

Performing laboratory: Merck (b) (4)

Initiation date: September 26, 2019

Report date: September 16, 2020

Batch/lot number of test article: L-002211889-006A004

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

Breeder/supplier: (b) (4)

Number of females per group per phase: 60

Age: 6 weeks

Body weight range: 106-161 g

Route and site of administration: Intramuscular in the right and left quadriceps

Volume of administration: 0.25 mL/quadricep or 0.5 mL/rat

Frequency of administration and study duration: 28 and 7 days prior to mating and on gestation day 6 and lactation day 7; 10-11 weeks

Dose/animal: 32 ug/ 0.5 mL (human dose)

Stability: The sponsor provided to the testing facility documentation of the identity, strength, purity, composition and stability for the test article. Stability of the test article over the course of the study has been demonstrated and is provided in the appendix.

Means of administration: Appropriate needle and syringe

Report status: Final

Experimental design

Group	Test Material	Dose (ug)	Dose volume (mL)	No. Females PND 21 Cohort A	No. Females PND 26-30** Cohort B
1	Control article*	0	0.5	30	30
2	V114	32 ug	0.5	30	30

*: PBS

** : Assigned originally to be necropsied on PND56 and deemed unnecessary and the study was terminated on PND 26-30

Randomization procedure: Females were randomized assigned to groups using a random allocation scheme based on body weight.

Statistical analysis plan: None specified.

The following parameters were evaluated.

	Frequency or parameters of testing
F0 generation	
Mortality	Daily
Clinical observations	Daily for clinical observation 1-3 hours following dosing
Body weights	Weekly four weeks prior to mating, GD 0, 6, 8, 10, 12,14,16,18, 20, 21, 22, 24 and LD 0, 3, 7, 10, 14, 17 and 21
Food consumption	3-day intervals ending in PND 4, 11, 18 and 25 and 2-day intervals ending on GD 8, 14 and 20
Mating	Daily
Parturition and gestation	Four times daily from GD 21 until LD 0
Necropsy	LD21 with examination and collection of kidney, ureter and urinary bladder
Antibody analysis	LD 21
F1 generation	
Litter viability and deaths	Daily
Clinical observations	Daily
Body weights	PND 0, 7, 10, 14 and 21
External examinations	For malformation and variation on PND 0 and for gender on PND 0, 3, 7, 14 and 21
Developmental observations Hair growth Eye opening Acoustic startle Air righting Pupil constriction	Not determined/performed
Antibody analysis	PND21
Necropsy	PND 21 for cohort A with examination and collection of kidney, ureter and urinary bladder PND 26-30 for cohort B

Results:

F0 generation

Mortality: All animals survived until scheduled termination.

Clinical observation: There were no V114-related clinical signs.

BLA125741

Body weight: There were no V-114-related effects on body weight.

Food consumption: There were no V-114-related effects on food consumption.

Reproductive performance: There were no effects on the length of gestation and the numbers with live pups.

Postmortem findings: There were no test article-related gross findings in kidney, ureter or urinary bladder.

F1 Generation

Unscheduled deaths: There were no effects on pup survival. One female pup in the control group was euthanized on PND 21 due to clinical signs related to interruption to water access.

External examination and sex ration at birth: There were no external malformations or variations in treatment group and no alteration in sex rations at birth in F1 pups.

Clinical observations: There were no V-114-related clinical signs observed.

Body weight: There were no V-114-related effects on pup body weights.

Gross findings: There were no findings in kidney, ureter or urinary bladder.

Immunogenicity: Overall, majority of F0 females and F1 pups in control group showed negative results. The majority (95%) of F0 in dose group exhibited an immunogenic response. The F1 pups (98%) in dose group exhibited similar sustained immunogenic response to their corresponding F0, indicating sustained immunogenic response over generations.

Assessment

V114 was administered to female rats twice during the premating period (28 and 7 days prior to mating) and once during gestation (day 6) and once during lactation (day 7). It did not result in any effects on estrus cycling, mating and maternal systemic toxicity and fertility index. There was no effect on fetal weight, visceral and skeletal malformations or variations. There was no effect on pup weights during lactation. However, no postnatal neurodevelopment was assessed in the studies.

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 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

It can be concluded from the developmental studies in female rats that V-114 given prior to mating, during pre-mating and gestation periods did not have any effects on female reproductive effects and fetal/embryonal development. It did not reveal any effect on the pup weight during lactation. However, postnatal normal neuro-developmental effects were not assessed in the studies.

Recommendation on the PI regarding the animal data

(1) Revise section 8.1 as shown below.

8.1 Pregnancy

Risk Summary

Developmental toxicity studies have been performed in female rats administered TRADEMARK on four occasions; twice prior to mating, once during gestation and once during lactation. Each dose was equivalent to the adult human dose. These studies revealed no evidence of harm to the fetus due to TRADEMARK [*see Animal Data below*].

Data

Animal Data

Developmental toxicity studies have been performed in female rats at a dose equivalent to the adult human dose. In these studies, female rats received TRADEMARK (32 mcg/rat/dose) by intramuscular injection 28 days and 7 days prior to mating, on gestation day 6 and on lactation day 7. There was no evidence of embryofetal lethality or fetal malformations and variations and no adverse effect on pup weight was observed.

(2) Delete section 13.2. Animal Toxicology and/or Pharmacology.

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