Toxicology Review of Nuvaxovid Vaccine

BLA 125817.0.2
Type and date of submission: Sequence 2, February 29, 2024

Applicant: Novavax Inc
Product: Novavax COVID-19 Vaccine, Adjuvanted (Nuvaxovid)
Related/referred products: IND 22430
Proposed indication for use: Active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) in individuals 12 years of age and older

Reviewer: (b) (6)

Précis
The sponsor submitted two toxicity study reports (57-day repeat intramuscular toxicity study with and without Matrix-M adjuvant in rabbits and developmental and reproductive toxicology study of intramuscular administration of SARS-C0V-2 rS nanoparticle vaccine with Matrix-M adjuvant or Matrix-M alone in rats), two pilot genotoxicity study reports (b) (4) and in vitro mammalian cell (b) (4) assay) of Matrix-M and their two respective confirmatory study reports. The two toxicity studies and the two confirmatory genotoxicity studies had been reviewed in IND 22430.

In the 57-day repeat intramuscular toxicity study, rabbits were administered intramuscularly 4 doses (3 weekly and one additional 21 days later) of 50 ug SARS-CoV-2 rS with 50 ug Matrix-M or 50 ug Matrix-M alone. Animals were well-tolerated. There were no biologically significant effects of the adjuvanted vaccine on clinical observations, mortality, body weights, food consumption, body temperature, ophthalmology, coagulation, organ weights and macroscopic examination. Transient elevations of CRP and fibrinogen and local inflammation reaction at the injection sites, indicative of acute reactions as expected.

In the developmental toxicity study of SARS-CoV-2 rS, female rats were administered intramuscularly 5 ug SARS-CoV-2 rS with 10 ug Matrix-M1 or 10 ug Matrix-M1 alone in 0.1 mL 27 days and 13 days prior to mating and on gestation days 7 and 15. There were no effects on mating performance, fertility, fetal weight, any naturally delivery or little parameters. It did not produce any fetal external, visceral, or skeletal malformations and variations and postnatal development.

Two genotoxicity studies were tested for Matrix-M1 adjuvant at (b) (4) mg/mL and (b) (4) mg/mL concentrations. At concentrations up to (b) (4) mg/mL (b) (4) µg per (b) (4)), it was negative in the (b) (4) test for all test strains except strain (b) (4) in the absence of (b) (4) activation, for which testing was limited to up to (b) (4) mg/mL due to contamination. It was also negative at

concentration up to (b) (4) mg/mL (b) (4) ug/mL per (b) (4)) for induction of (b) (4) test using (b) (4) .

Recommendation

There were no safety concerns or potential risks identified based on nonclinical safety data. Overall, the nonclinical safety assessment for Nuvaxovid was considered acceptable to support licensing from a toxicological standpoint.

The animal developmental toxicity study 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 rabbits administered a dose of Nuvaxovid (0.1 mL) on 4 occasions, two times prior to mating and two times during gestation. The study revealed no vaccine-related adverse effects on female fertility, fetal development, or postnatal development (see *Animal Data*).

Data

Animal Data

In a developmental toxicity study, female rabbits were administered a dose of Nuvaxovid (0.1 mL) by intramuscular injection on 4 occasions: 27 and 13 days prior to mating, and on gestation days 7 and 15. No vaccine-related adverse effects on female fertility, fetal development, or postnatal development were reported in the study.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Nuvaxovid has not been evaluated for the potential to cause carcinogenicity, genotoxicity, or impairment of male fertility.

Concurrence: (b) (6)