

## Toxicology Review of VLA1553 Vaccine

BLA 125777.0.1

Type and date of submission: Sequence 1, September 21, 2022

Applicant: Valneva Austria GmbH

Product: VLA1553 (Chikungunya Vaccine, Live-attenuated)

Related/referred products: IND 17854

Proposed indication for use: Active immunization for the prevention of disease caused by Chikungunya virus in individuals 18 years and above

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

### Précis

The sponsor submitted study reports of a GLP repeated dose toxicity study in rabbits and a developmental toxicity study in rats in the first roll of BLA on August 17, 2022. The repeated dose toxicity study had been submitted and reviewed in the original IND 17854 in 2017. However, a draft instead of final study report of the developmental study was submitted. Thus, in response to our IR of September 8, 2022, the sponsor submitted in this sequence a final study report of the study.

In the developmental toxicity study of VLA1553, two groups of 44 female rats were administered intramuscularly control article (phosphate buffer) or  $1.9 \times 10^4$  TCID<sub>50</sub> in 0.5 mL of VLA1553 14 days prior to mating and on gestation day 6. The animals in each group were divided into littering and fetal embryo development (FED) phases. Additional 3 and 6 were assigned to control and treatment satellite groups, respectively, for milk immunogenicity analysis. 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. VLA1553 injection led to development of VLA1553-specific antibodies present in female rats, their offspring and in the milk of treated female rats. Based on the results, the vaccine was immunogenic in animals and there was evidence of placental and milk transfer.

### Toxicology Part Review

Title and study number: Pre and postnatal developmental study of VLA1553 by intramuscular injection in rats (Study#490901)

Performing laboratory: (b) (4)

Initiation date: January 15, 2021

Report date: December 24, 2021

Batch/lot number of test article: 2005040029

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: 196-295 g

Route and site of administration: Intramuscular in the right and left hind limbs

Volume of administration: 0.25 ml/hind limb

Frequency of administration and study duration: 14 days prior to mating and on gestation day 6; 8 weeks

Dose/animal:  $1.9 \times 10^4$  TCID<sub>50</sub> in 0.5 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 FED	No. Females Littering	No. Females Satellite (milk analysis)
1	Control article*	0	0.5	22	22	3
2	VLA1553	$1.9 \times 10^4$ TCID <sub>50</sub>	0.5	22	22	6

\*: PBS in sterile water

FED: embryo fetal development

Randomization procedure: No specific procedure was stated.

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 an overall one-way ANOVA F-test if Levene's test was not significant or the Kruskal-Wallis test if it was significant. If the overall F-test or Kruskal-Wallis test was found to be significant, then pairwise comparisons were conducted using Dunnett's or Dunn's test, respectively. Datasets with two groups were compared using a Dunnett's test or Dunn's test. For non-parametric data, the groups were compared using an overall Kruskal-Wallis test. If the overall Kruskal-Wallis test was found to be significant, then the above pairwise comparisons were conducted using Dunn's test. A Fisher's exact test was used to conduct pairwise group comparisons of interest.

The following parameters were evaluated

	Frequency or parameters of testing
F0 generation	
Mortality	Twice daily for viability
Cage observations	Daily for clinical observation
Postdose observations	Up to 4 hours postdose

Detailed clinical observations	Weekly in F0 and F1 animals
Body weights	Once during pretreatment then every 3 days from Day 1 up to GDs 0, 3, 6, 9, 12, 15, 18, 21 and lactation days 1, 4, 7, 10, 14, 17 and 21
Food consumption	Same as above
Estrous cycle monitoring	Day 15 until day of detection of a copulatory plug in situ
Mating	Daily for 7 days maximum
Duration of gestation	
F1 generation	
Littering phase	
Litter viability and deaths	Twice daily
Clinical observations	Daily
Pup body weights	PNDs 1, 4, 7, 10, 14, 17 and 21
Preweaning reflex developmental tests	
Negative geotaxis	PND 11
Auditory reflex	PND 16
Visual function	PND 18
Embryo fetal developmental phase	
Ovarian and uterine contents and macroscopic lesions	PND 21
Fetal body weight	PND 21
Fetal morphological examination	PND 21
Antibody analysis (both phases)	F0: Predose, before mating and GD21/PND21 thru jugular vein F1: GD21/PND 21 thru capillary action following decapitation or cardiac puncture

#### Results:

**Mortality:** There was no VLA-1553-related mortality. One female in control Satellite group died 10 days after dosing and one female in group 2 was euthanized because of abdominal hernia on day 15 after dosing. They were not considered to be test article related deaths.

**Clinical observation:** There were no test article-related clinical observations.

**Body weights and gravid uterine weights:** There were no test article-related effects on body weights. Slight (less than 10 %) increase in gravid uterine weights correlated with a higher mean number of fetuses in the dose group.

**Food consumption:** There were no test item related effects on food consumption.

Mating and pregnancy performance: There were no test article-related effects on the mating behavior. There were no differences in the pre-coital interval in either FE phase (2.9 days vs 2.4 days in the control) or the littering phase (2.4 days vs 2.5 days in the control). There were no differences in pregnancy rates (93% vs 92 % in the control) in the littering phase. In the FED phase, there was a low pregnancy rates (77%) in the control whereas all females were pregnant in the treatment group.

Examination of pregnancies/ovarian and uterine examination: Number of corpora lutea and implants were comparable to the control. There were no effects on pre- and post-implantation loss in the FED phase placental weights and fetal body weight were unaffected.

Delivery and reproductive parameters/littering data: There were no test item effects on gestation length, gestation index, live birth index, viability index, lactation index and sex ratio. A higher post implantation loss in the littering phase (9.1 % vs 2.8 % in the control) was within expected in the expected historical control of the testing facility and not observed in FED phase and therefore was not considered test item related.

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

Prewaning reflex development: There were no effects in all three reflex assessments.

Macroscopic examinations: There were no findings to the adult animals (F0).

Fetal examinations: The fused accessory lung lobe in a single fetus in the treatment group, a known occurrence at low background levels in the facility, was considered incidental and not test item related. There were no other external, visceral and skeletal malformation and variations.

Immunogenicity: All animals treated with VLA1553 developed VLA1553-specific antibodies. The antibodies were also detected in the offspring (fetuses and pups). VLA1553- specific antibodies were also detected in the milk of the VLA1553-treated female rats. In contrast, no VLA1553-specific antibodies were detected in the sera of animals treated with the control preparation (placebo), nor in their fetuses, pups or milk samples.

#### Assessment

Administration of VLA1553 once 14 days prior to mating and once on day 6 during the gestation phase 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 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 and the milk of the dams receiving the test article, indicating transfer of immunogenicity in utero and milk.

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 VLA1553 by intramuscular injection (delivered over two sites), once before mating and once in early organogenesis (Gestation Day 6) was well tolerated in rats at the intended human dose of  $1.9 \times 10^4$  TCID<sub>50</sub>/0.5 mL 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 the equivalent of a single human dose of IXCHIQ on 2 occasions, once prior to mating and once during gestation. These studies revealed no evidence of harm to the fetus due to the vaccine (see *Animal Data*).

##### *Data*

##### *Animal Data*

In a developmental toxicity study, the equivalent human dose of IXCHIQ was administered to female rats by the intramuscular route on 2 occasions: 14 days prior to mating, and on gestation day 6. 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

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

BLA125777.0

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