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FINAL REPORT

Test Facility Study No. 20256434

Sponsor Reference No. RN9391R58

A Combined Fertility and Developmental Study (Including Teratogenicity and Postnatal Investigations) of BNT162b1, BNT162b2 and BNT162b3 by Intramuscular Administration in the Wistar Rat

GLP Study

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QUALITY ASSURANCE STATEMENT

This study has been audited by Quality Assurance in accordance with the applicable Good Laboratory Practice regulations. Reports were submitted in accordance with Standard Operating Procedures as follows:

QA INSPECTION DATES

Date(s) of Audit	Phase(s) Audited	Dates Findings Submitted to: Study Director	Study Director Management
29-Jun-2020 – 30-Jun-2020	Final Study Plan	30-Jun-2020	30-Jun-2020
23-Jul-2020	Study Plan Amendment 01	23-Jul-2020	23-Jul-2020
02-Oct-2020	Study Plan Amendment 02	02-Oct-2020	02-Oct-2020
14-Sep-2020	Physical development	14-Sep-2020	14-Sep-2020
23-Nov-2020 – 04-Dec-2020	Report Tables	04-Dec-2020	04-Dec-2020
23-Nov-2020 – 04-Dec-2020	Report – Materials and Methods	04-Dec-2020	04-Dec-2020
23-Nov-2020 – 04-Dec-2020	Data Review – Formulations	04-Dec-2020	04-Dec-2020
23-Nov-2020 – 04-Dec-2020	Data Review – Technical Operations	04-Dec-2020	04-Dec-2020
23-Nov-2020 – 04-Dec-2020	Data Review – Clinical Pathology	04-Dec-2020	04-Dec-2020
23-Nov-2020 – 04-Dec-2020	Data Review – Necropsy	04-Dec-2020	04-Dec-2020
23-Nov-2020 – 04-Dec-2020	Report	04-Dec-2020	04-Dec-2020
07-Dec-2020 - 10-Dec-2020	Report - Results	10-Dec-2020	10-Dec-2020

In addition to the above-mentioned audits, process-based and routine facility inspections were also conducted during the course of this study. Inspection findings, if any, specific to this study were reported by Quality Assurance to the Study Director and Management and listed as a Phase Audit on this Quality Assurance Statement.

The Final Report has been reviewed to assure that it accurately describes the materials and methods, and that the reported results accurately reflect the raw data.

DocuSigned by:
s 9(2)(a)
Signing Reason: I approve this document
Signing Time: 22-Dec-2020 | 02:41:07 EST
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s 9(2)(a)
Quality Assurance Auditor

GLP COMPLIANCE STATEMENT AND REPORT APPROVAL

The study was performed in accordance with OECD Principles of Good Laboratory Practice as required in Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004, Bonnes Pratiques de Laboratoire, Ministère de l'Emploi et de la Solidarité Française, No. 2000/5bis, arrêté du 14/03/2000.

OECD Principles of Good Laboratory Practice are accepted by Regulatory Authorities throughout the European Union, United States of America (FDA and EPA), and Japan (MHLW, MAFF, and METI) and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Exceptions from the above regulations are listed below.

- Antibody analysis (Appendix 26) was not conducted in compliance with GLP but in accordance with the Good Clinical Laboratory Practice (GCLP). This Test site was selected by the Sponsor because it has the most appropriate experience concerning the measurement of neutralizing antibody titres against the SARS-CoV-2 live virus by Microneutralization CPE-based method. The delegated phase for antibody analysis was fit for purpose, performed in adherence to the facilities SOPs and working instructions, by a research facility with proper expertise, and adequate history and by individuals specially trained in this technique (according to VisMederi management of personnel procedure). This exception did not adversely affect the outcome or interpretation of this study because the methods included appropriate controls to provide reliable data and analyses according to data integrity principles and local QA Report review will ensure compliance to internal procedures.

s 9(2)(a)

s 9(2)(a) PhD
Study Director

1. RESPONSIBLE PERSONNEL

Role/Phase	QAU	Name	Contact Information
Study Director	Charles River	s 9(2)(a), PhD	Address as cited for Test Facility
Test Facility Management	Charles River	s 9(2), General Director	Address as cited for Test Facility
Test Facility QAU	Charles River	s 9(2), MSc, Chemical Engineer	Address as cited for Test Facility
Principal Investigator (PI)			
Role/Phase	**GLP Compliance**	**Name**	**Contact Information**
Serum Antibody Analysis[a]	No (compliance with the GCLP)	s 9(2)	VisMederi Srl Strada del Petriccio e Belriguardo, 35 53100 Siena, Italy

[a]: Test Site selected by the Study Sponsor in agreement with the Study Director.

Summary of Results from "A Combined Fertility and Developmental Study (Including Teratogenicity and Postnatal Investigations) of BNT162b1, BNT162b2 and BNT162b3 by Intramuscular Administration in the Wistar Han Rat (20256434)"

BNT162b2 was administered by IM injection at the human clinical dose (30 µg RNA/dosing day) to 44 female Wistar Han rats (F0) 21 and 14 days prior to mating with untreated males and on Gestation Days (GD) 9 and 20, for a total of 4 dosing days. A separate control group of 44 F0 females received saline by the same route and regimen. This study also included assessment of two other LNP-formulated RNA vaccine candidates (BNT162b1 and BNT162b3) that did not proceed into Phase 2/3 clinical trials. Here, the study findings from BNT162b2 are summarized; findings from the BNT162b1 and BNT162b3 vaccine candidates also tested in this study were generally similar.

Following completion of a mating phase with untreated males, 22 rats/group underwent caesarean-section on GD 21 and were submitted to routine embryo-fetal development evaluations. The remaining 22 rats/group were allowed to litter and behaviour of the mothers and development of the offspring was observed until Postnatal Day (PND) 21.

There were no BNT162b2-related deaths during the study. IM administration of BNT162b2 before and during gestation to female Wistar rats resulted in non-adverse clinical signs and macroscopic findings localized to the injection site as well as transient, non-adverse body weight and food consumption effects after each dose administration. These maternal findings are all consistent with administration of a vaccine and an inflammatory/immune response and with those observed in the repeat-dose toxicity study with BNT162b2.

There were no BNT162b2-related effects on any mating or fertility parameters. There were no BNT162b2-related effects on any ovarian, uterine, or litter parameters, including embryo-fetal survival, growth, or external, visceral, or skeletal malformations, anomalies, or variations. There were no effects of BNT162b2 administration on postnatal offspring (F1) development, including postnatal growth, physical development (pinna unfolding and eye opening), neurodevelopment (pre-weaning auditory and visual function tests), macroscopic observations, and survival.

All of F0 females administered BNT162b2 developed a SARS-CoV-2 neutralizing antibody response and these responses were detectable in all fetuses and pups from the caesarean and littering groups, respectively. The animals in the saline control group did not exhibit an immune response to BNT162b2.

In conclusion, administration of BNT162b2 to female rats twice before the start of mating and twice during gestation at the human clinical dose was associated with non-adverse effects (body weight, food consumption and effects localized to the injection site) after each dose administration. However, there were no effects of BNT162b2 administration on mating performance, fertility, or any ovarian or uterine parameters in the F0 female rats nor on embryo-fetal or postnatal survival, growth, or development in the F1 offspring. An immune response was confirmed in F0 female rats following administration of each vaccine candidate and these responses were also detectable in the F1 offspring (fetuses and pups).