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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

SPONSOR:
BioNtech SE
12 An der Goldgrube
Mainz, 55131
Germany

TEST FACILITY:

[redacted]

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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	Dates Findings Submitted to: 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.

[redacted]

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.

Study Director

1. RESPONSIBLE PERSONNEL

Role/Phase	[redacted]	Name	Contact Information
Study Director	[redacted]	[redacted] PhD	[redacted]
Test Facility Management	[redacted]	[redacted] General Director	[redacted]
Test Facility QAU	[redacted]	[redacted] MSc, Chemical Engineer	[redacted]

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2. ABSTRACT

The objective of this study was to assess the potential effects of BNT162b1, BNT162b2 and BNT162b3, vaccine development candidates to prevent Covid-19, and the concomitant immune response, on fertility and pre and postnatal development in the female Wistar (CRL:WI[Han]) rat.

BNT162b1, BNT162b2 and BNT162b3 were administered intramuscularly (IM) to F0 female Wistar rats 21 and 14 days before the start of mating (M-21 and M-14, respectively) and then on Gestation Day (GD) 9 and GD20, for a total of 4 dose days. A separate control group was administered saline by the same route and regimen. Each dose group consisted of 44 F0 females, 22 rats assigned to the caesarean subgroup, and 22 rats assigned to the littering subgroup. Each dose consisted of 30 µg mRNA /dosing day (0.06 mL/dose) IM injection in alternating quadriceps muscles.

Following completion of a mating phase with untreated males, 22 rats per group (nominally) underwent caesarean section on GD21 and were submitted to routine embryo-fetal development evaluations (caesarean subgroup). The remaining 22 rats per group (nominally) were allowed to litter and development of the offspring was observed up to weaning on Postnatal Day (PND) 21 (littering subgroup).

The following parameters and end points were evaluated in all F0 animals: Survival, clinical signs, body weights, body weight gains, food consumption, estrous cycles, mating performance, fertility and macroscopic observations. F0 females assigned to the caesarean subgroup were further examined for ovarian and uterine contents, gravid uterine weights and fetuses were evaluated for viability, sex, body weights, and external, visceral, and skeletal morphology. F0 females assigned to the littering subgroup were allowed to deliver naturally, and were further assessed for parturition, lactation, and maternal behavior, and were monitored to the day of euthanasia on Lactation Day (LD) 21. F1 offspring were assessed for survival, clinical signs, body weights, physical development (pinna unfolding and eye opening), preweaning auditory and visual function tests to screen for normal neurodevelopment, and macroscopic observations.

Blood samples were collected before administration of the first dose (baseline) and on the first day of cohabitation for each F0 female (both subgroups), on GD21 (caesarean subgroup), and on LD21 (littering subgroup females). Blood samples were also collected on GD21 from viable fetuses in each available litter (caesarean subgroup) and on PND21 from pups from each available litter (littering subgroup). Blood samples were evaluated for neutralizing antibody titres against SARS-CoV-2 live virus.

There were no deaths throughout the study related to any of the 3 vaccine candidates.

Intramuscular administration of BNT162b1, BNT162b2 and BNT162b3, 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.

There were no effects on estrous cycles, pre-coital interval, mating, fertility and pregnancy index, or on any ovarian, uterine, or litter parameters, including F1 pre and postnatal survival, growth, external, visceral, and skeletal morphology, or effects on pre-weaning physical and functional development of the F1 pups related to any of the 3 vaccine candidates.

Administration of 4 doses (2 prior to mating and 2 during gestation) of BNT162b1, BNT162b2, or BNT162b3 elicited SARS-CoV-2 neutralizing antibody responses in the majority of females just prior to mating (M0), at the end of gestation (GD21), and at the end of lactation (LD21). SARS-CoV-2 neutralizing titers were detected in most offspring (fetuses on GD21 and pups on PND21). SARS-CoV-2 neutralizing antibody titers were not observed in animals prior to vaccine administration or in saline-administered control animals.

In conclusion, intramuscular administration of BNT162b1, BNT162b2 and BNT162b3 before and during gestation to female Wistar (CRL:WI[Han]) rats was associated with non-adverse effects (body weight, food consumption and effects localized to the injection site) after each dose administration. There were no effects of any of the 3 vaccine candidates on mating performance or fertility in F0 female rats or on embryo-fetal or postnatal survival, growth, or development of 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).

3. INTRODUCTION

The objective of this study was to assess the potential effects of BNT162b1, BNT162b2 and BNT162b3, vaccine development candidates to prevent Covid-19, and the concomitant immune response, on fertility and pre and postnatal development in the female Wistar (CRL:WI[Han]) rat.

The design of this study was based on Guidelines from the International Conference on Harmonization, S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals; Department of Health and Human Services, Food and Drug Administration (FDA), 2006 Guidance on Developmental Toxicity Studies in Vaccines for Infectious Disease Indications; WHO guidelines on nonclinical evaluation of vaccines.

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FOI 2289

Pages 14-37 have been removed under section 47 of the FOI Act.

10. CONCLUSION

Intramuscular administration of BNT162b1, BNT162b2 and BNT162b3 before and during gestation to female Wistar (CRL:WI[Han]) rats was associated with non-adverse effects (body weight, food consumption and effects localized to the injection site) after each dose administration. There were no effects of any of the 3 vaccine candidates on mating performance or fertility in F0 female rats or on embryo-fetal or postnatal survival, growth, or development of 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).

FOI 2289

Pages 39-1,145 have been removed under section 47 of the FOI Act.