

2.6.7.1 Toxicology: Overview

Test Article: BNT162b2

Type of Study	Species/ Strain	Method of Administration	Duration of Dosing	Dose (µg RNA/animal)	Total Volume (µL) ^a	GLP Compliance	Testing Facility	Study Number (Sponsor Reference Number)
Single-Dose Toxicity								
Not conducted								
Repeat-Dose Toxicity								
17-Day, 2- or 3-Dose (1 Dose/Week) Toxicity With a 3-Week Recovery Phase	Rat/ Wistar Han	IM Injection	17 Days (Dose days 1, 8, 15) or 10 Days (Dose days 1, 8) ^b	0 (Control Buffer ^c)	200 ^d	Yes	(b) (4)	38166 (NA)
				30 (BNT162a1)	60			
				10 (BNT162a1)	20			
				30 (BNT162b1)	60			
				100 (BNT162b1)	200 ^d			
				30 (BNT162c1)	70			
				100 (BNT162b2 [V8])	200 ^d			
17-Day, 3-Dose (1 Dose/Week) Toxicity With a 3-Week Recovery Phase	Rat/ Wistar Han	IM Injection	17 Days (Dose days 1, 8, 15)	0 (Saline) ^f	60	Yes	PWRD ^g	20GR142 (NA)
				30 (BNT162b2 [V9])	60			
				30 (BNT162b3)	60			
Genotoxicity								
Not conducted								
Carcinogenicity								
Not conducted								

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2.6.7.1 Toxicology: Overview

Test Article: BNT162b2 (continued)

Type of Study	Species/ Strain	Method of Administration	Duration of Dosing	Dose (µg RNA/animal)	Total Volume (µL) ^a	GLP Compliance	Testing Facility	Study Number (Sponsor Reference Number)
Reproductive and Developmental Toxicity								
Combined Fertility and Developmental (Including Teratogenicity and Postnatal Investigations)	Rat/ Wistar Han	IM Injection	21 and 14 days prior to mating, GD 9, GD 20	0 (Saline) ^f 30 (BNT162b1) 30 (BNT162b2 [V9]), 30 (BNT162b3)	60 60 60 60	Yes	Charles River Laboratories ^h	20256434 (RN9391 R58)
Local Tolerance								
Not conducted								
Other Toxicity Studies								
Not conducted								

GD = Gestation day; GLP = Good Laboratory Practice; IM = Intramuscular; (b) (4); NA = Not applicable;
PWRD = Pfizer Worldwide Research & Development; QW = Once weekly.

- a. Doses were administered as 1 application at 1 site unless otherwise indicated.
- b. QWx3 (Days 1, 8, 15) for BNT162a1, BNT162b1, and BNT162b2 (V8); QWx2 (Days 1, 8) for BNT162c1.
- c. Phosphate buffered saline, 300 mM sucrose.
- d. One application (100 µL) at 2 sites for a total dose volume of 200 µL.
(b) (4)
- f. Sterile saline (0.9% NaCl).
- g. Groton, CT, US.
- h. Saint-Germain-Nuelles, France.

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2.6.7.7A Repeat-Dose Toxicity

Report Title: Repeat-Dose Toxicity Study of Three LNP-Formulated RNA Platforms Encoding for Viral Proteins by Repeated Intramuscular Administration to Wistar Han Rats

Test Article: BNT162b2

Species/Strain: Rat/Wistar Han

Duration of Dosing: QWx3 (Days 1, 8, 15) for BNT162a1 (uRNA-LNP RBD), BNT162b1 (modRNA-LNP RBD), or BNT162b2 [V8] (modRNA-LNP SP2); QWx2 (Days 1, 8) for BNT162c1 (saRNA-LNP RBD)

Study Number: 38166^a

Lot Numbers: CoVVAC/090320 (BNT162a1), CoVVAC/100320 (BNT162b1), CoVVAC/130320 (BNT162c1), CoVVAC/160320 (BNT162b2 [V8])

Age at First Dose: ~8-9 Weeks

Duration of Postdose: 3 Weeks

GLP Compliance: Yes

Date of First Dose: 17 March 2020

Method of Administration: Intramuscular injection; 20 to 100 µL/administration site/dose^b

Vehicle/Formulation: Phosphate buffered saline, 300 mM sucrose/Solution

Special Features: Cytokine analysis (IFN-γ, TNF-α, IL-1β, IL-6, IL-10)

No Observed Adverse Effect Level: 30 µg (BNT162a1, BNT162c1), 100 µg (BNT162b1, BNT162b2)

Dose (µg RNA/animal)	Control (0)		BNT162a1 (30)		BNT162a1 (10)		BNT162b1 (30)		BNT162b1 (100)		BNT162c1 (30)		BNT162b2 (V8) (100)	
	QWx3		QWx3		QWx3		QWx3		QWx3		QWx2		QWx3	
Administration Sites/Dosing Day	2		1		1		1		2		1		2	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Number of Animals ^c	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Noteworthy Findings														
Died or Euthanized Moribund	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Body Weight (g) ^d														
Prior to Initiation of Dosing	257.6	213.8	1.0	1.0	1.0	0.89	1.0	1.0	1.0	0.90	1.0	0.91	1.0	0.90
Day 1	263.5	212.3	0.99	0.99	1.2†	1.0	1.0	1.0	1.2†	1.0	1.2†	1.0	1.2†	1.0
Day 2	268.9	215.1	0.93†	0.95	1.1†	0.98	0.95†	1.0	1.0	0.95	1.1†	0.98	1.0	0.96
Day 8	310.9	231.7	0.94†	0.99	1.1†	1.0	0.98	1.0	1.0	1.0	1.0	0.99	1.0	0.98
Day 9	319.8	237.0	0.87†	0.93*	1.0	0.95	0.93*	0.99	0.93†	0.94*	0.96	0.93†	0.92†	0.93*
Day 15	356.3	249.8	0.88†	0.97	1.0	0.98	0.95*	1.0	0.98	0.99	0.98 ^e	0.95 ^e	0.96	0.95

2.6.7.7A Repeat-Dose Toxicity

Study Number: 38166 (continued)

Dose (µg RNA/animal)	Control (0)		BNT162a1 (30)		BNT162a1 (10)		BNT162b1 (30)		BNT162b1 (100)		BNT162c1 (30)		BNT162b2 (V8) (100)	
Dosing Frequency	QWx3		QWx3		QWx3		QWx3		QWx3		QWx2		QWx3	
Administration Sites/Dosing Day	2		1		1		1		2		1		2	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Body Weight Gain (%) ^f														
Day 9	21.3	11.7	6.3	5.8	2.9	4.3	13.6	9.5	-3.5	3.6	-0.77	1.5	-4.1	1.2
Day 16	37.1	16.7	15.1	10.0	11.9	11.0	25.2	17.1	6.0	10.3	NA	NA	4.8	6.4
Food Consumption ^d – Relative (g/kg of body weight/day)														
Week 1	95.0	98.3	0.94*	0.97	0.83†	0.93*	0.96	0.98	0.77†	0.87†	0.81†	0.90†	0.78†	0.86†
Week 2	89.4	94.3	0.93†	0.96	0.90†	0.99	0.98	1.0	0.88†	0.98	0.86† ^e	0.98 ^c	0.89†	0.98
Clinical Observations	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Local Tolerance ^g														
Day 1 – Edema														
4 Hours Postdose	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24 Hours Postdose														
Edema, very slight	0	0	6	1	9	6	6	5	4	9	11	10	12	11
Edema, slight	0	0	2	0	0	0	2	6	0	0	0	0	0	0
48 Hours Postdose														
Edema, very slight	0	0	4	7	13	9	8	6	7	6	10	10	8	2
Edema, slight	0	0	3	5	0	0	2	6	0	0	3	1	0	0
96 Hours Postdose														
Edema, very slight	0	0	3	3	0	0	1	0	0	0	0	2	0	0
144 Hours Postdose	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Day 8 – Edema														
4 Hours Postdose														
Edema, very slight	0	0	0	0	0	1	0	0	0	0	0	0	0	0
24 Hours Postdose														
Edema, very slight	0	0	3	2	3	5	11	13	7	6	4	9	7	8
Edema, slight	0	0	7	9	0	1	3	1	0	0	0	0	0	0
Edema, moderate	0	0	4	3	0	0	0	0	0	0	0	0	0	0

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2.6.7.7A Repeat-Dose Toxicity

Study Number: 38166 (continued)

Dose (µg RNA/animal)	Control (0)		BNT162a1 (30)		BNT162a1 (10)		BNT162b1 (30)		BNT162b1 (100)		BNT162c1 (30)		BNT162b2 (V8) (100)	
Dosing Frequency	QWx3		QWx3		QWx3		QWx3		QWx3		QWx2		QWx3	
Administration Sites/Dosing Day	2		1		1		1		2		1		2	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
48 Hours Postdose														
Edema, very slight	0	0	3	0	0	0	8	9	1	0	0	0	0	3
Edema, slight	0	0	7	7	6	8	2	0	8	5	0	1	6	6
Edema, moderate	1	1	4	7	9	7	2	1	6	10	3	4	9	6
Edema, severe	0	0	0	0	0	0	0	0	0	0	2	0	0	0
96 Hours Postdose														
Edema, very slight	0	0	8	9	4	1	4	0	0	0	0	3	0	0
Edema, slight	0	0	1	2	1	0	0	0	0	0	0	0	0	0
144 Hours Postdose														
Edema, very slight	0	0	0	0	2	0	0	0	0	0	0	0	0	0
192 Hours Postdose														
Edema, slight	0	0	0	0	0	0	0	0	0	0	1	0	0	0
240 Hours Postdose	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-	-	NA	NA
Day 15 – Edema														
4 Hours Postdose	-	-	-	-	-	-	-	-	-	-	NA	NA	-	-
24 Hours Postdose														
Edema, very slight	0	0	3	6	10	8	10	7	0	0	NA	NA	0	0
Edema, slight	0	0	12	9	3	7	5	8	9	12	NA	NA	1	2
Edema, moderate	0	0	0	0	0	0	0	0	6	3	NA	NA	12	12
Edema, severe	0	0	0	0	0	0	0	0	0	0	NA	NA	2	1
48 Hours Postdose														
Edema, very slight	0	0	1	1	1	1	2	3	0	0	NA	NA	0	1
Edema, slight	0	0	3	4	2	4	3	2	1	4	NA	NA	1	3
Edema, moderate	0	0	0	0	0	0	0	0	4	1	NA	NA	4	1
96 Hours Postdose														
Edema, very slight	0	0	1	2	1	0	0	0	3	2	NA	NA	3	1
Edema, slight	0	0	2	3	1	0	0	0	0	0	NA	NA	2	3
144 Hours Postdose														
Edema, very slight	0	0	1	0	1	0	0	0	3	2	NA	NA	3	2

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2.6.7.7A Repeat-Dose Toxicity

Study Number: 38166 (continued)

Dose (µg RNA/animal)	Control (0)		BNT162a1 (30)		BNT162a1 (10)		BNT162b1 (30)		BNT162b1 (100)		BNT162c1 (30)		BNT162b2 (V8) (100)	
Dosing Frequency	QWx3		QWx3		QWx3		QWx3		QWx3		QWx2		QWx3	
Administration Sites/Dosing Day	2		1		1		1		2		1		2	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Edema, slight	0	0	0	0	1	0	0	0	0	0	NA	NA	2	2
192 Hours Postdose	-	-	-	-	-	-	-	-	-	-	-	-	-	-
240 Hours Postdose														
Edema, very slight	0	0	0	1	2	3	2	2	3	4	NA	NA	1	3
Edema, slight	0	0	0	0	0	0	0	0	1	1	NA	NA	4	2
288 Hours Postdose														
Edema, very slight	0	0	0	1	2	0	2	1	4	5	NA	NA	3	4
Edema, slight	0	0	0	0	0	0	0	0	0	0	NA	NA	2	1
336 Hours Postdose														
Edema, very slight	0	0	0	0	0	0	0	0	2	0	NA	NA	0	0
384 Hours Postdose														
Edema, very slight	0	0	0	0	0	0	0	0	2	0	NA	NA	0	0
432 Hours Postdose														
Edema, very slight	0	0	0	0	0	0	0	0	1	0	NA	NA	0	0
480 Hours Postdose														
Edema, very slight	0	0	0	0	0	0	0	0	1	0	NA	NA	0	0
528 Hours Postdose	-	-	-	-	-	-	-	-	-	-	NA	NA	-	-
Day 1 – Erythema														
4 Hours Postdose	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24 Hours Postdose	-	-	-	-	-	-	-	-	-	-	-	-	-	-
48 Hours Postdose														
Erythema, very slight	0	0	0	0	0	0	0	0	0	3	0	0	0	0
96 Hours Postdose														
Erythema, very slight	0	0	9	7	1	0	0	0	0	2	3	4	0	2
144 Hours Postdose	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Day 8 – Erythema														
4 Hours Postdose	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24 Hours Postdose														
Erythema, very slight	0	0	6	5	0	0	4	1	0	0	0	0	0	0

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2.6.7.7A Repeat-Dose Toxicity

Study Number: 38166 (continued)

Dose (µg RNA/animal)	Control (0)		BNT162a1 (30)		BNT162a1 (10)		BNT162b1 (30)		BNT162b1 (100)		BNT162c1 (30)		BNT162b2 (V8) (100)	
Dosing Frequency	QWx3		QWx3		QWx3		QWx3		QWx3		QWx2		QWx3	
Administration Sites/Dosing Day	2		1		1		1		2		1		2	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
48 Hours Postdose														
Erythema, very slight	0	0	7	9	0	0	1	1	0	0	0	0	0	0
Erythema, well defined	0	0	2	1	0	0	0	0	0	0	0	0	0	0
96 Hours Postdose														
Erythema, very slight	0	0	3	1	0	0	0	0	0	0	0	0	0	0
144 Hours Postdose														
Erythema, severe	0	0	0	0	5	4	0	0	0	3	4	2	3	5
192 Hours Postdose	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-	-	NA	NA
240 Hours Postdose														
Erythema, severe	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	0	NA	NA
288 Hours Postdose														
Erythema, severe	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	0	NA	NA
336 Hours Postdose														
Erythema, severe	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	0	NA	NA
384 Hours Postdose														
Erythema, severe	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	0	NA	NA
432 Hours Postdose														
Erythema, very slight	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	0	NA	NA
480 Hours Postdose														
Erythema, very slight	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	0	NA	NA
528 Hours Postdose														
Erythema, very slight	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1	0	NA	NA
Day 15 – Erythema														
4 Hours Postdose	-	-	-	-	-	-	-	-	-	-	NA	NA	-	-
24 Hours Postdose														
Erythema, very slight	0	0	1	2	1	1	1	2	0	1	NA	NA	0	0
48 Hours Postdose														
Erythema, very slight	0	0	2	1	3	1	1	0	0	0	NA	NA	1	2

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2.6.7.7A Repeat-Dose Toxicity

Study Number: 38166 (continued)

Dose (µg RNA/animal)	Control (0)		BNT162a1 (30)		BNT162a1 (10)		BNT162b1 (30)		BNT162b1 (100)		BNT162c1 (30)		BNT162b2 (V8) (100)	
Dosing Frequency	QWx3		QWx3		QWx3		QWx3		QWx3		QWx2		QWx3	
Administration Sites/Dosing Day	2		1		1		1		2		1		2	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
96 Hours Postdose														
Erythema, severe	0	0	5	5	0	0	0	0	0	0	NA	NA	0	0
144 Hours Postdose														
Erythema, very slight	0	0	3	1	0	0	0	0	0	0	NA	NA	0	0
Erythema, well-defined			0	3	0	0	0	0	0	0	NA	NA	0	0
192 Hours Postdose														
Erythema, very slight	0	0	0	1	0	0	0	0	0	0	NA	NA	0	0
Erythema, severe			2	2	0	0	0	0	0	0	NA	NA	0	0
240 Hours Postdose														
Erythema, severe	0	0	2	2	0	0	0	0	0	0	NA	NA	0	0
288 Hours Postdose														
Erythema, severe	0	0	2	2	0	0	0	0	0	0	NA	NA	0	0
336 Hours Postdose														
Erythema, very slight	0	0	2	0	0	0	0	0	0	0	NA	NA	0	0
Erythema, severe	0	0	0	2	0	0	0	0	0	0	NA	NA	0	0
384 Hours Postdose														
Erythema, very slight	0	0	2	0	0	0	0	0	0	0	NA	NA	0	0
Erythema, severe	0	0	0	2	0	0	0	0	0	0	NA	NA	0	0
432 Hours Postdose														
Erythema, very slight	0	0	2	0	0	0	0	0	0	0	NA	NA	0	0
Erythema, well-defined	0	0	0	2	0	0	0	0	0	0	NA	NA	0	0
480 Hours Postdose	-	-	-	-	-	-	-	-	-	-	NA	NA	-	-
Day 1 – I/H ^h	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Day 8 – I/H														
4 Hours Postdose	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24 Hours Postdose	-	-	-	-	-	-	-	-	-	-	-	-	-	-
48 Hours Postdose	-	-	-	-	-	-	-	-	-	-	-	-	-	-
96 Hours Postdose	-	-	-	-	-	-	-	-	-	-	-	-	-	-
144 Hours Postdose														

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2.6.7.7A Repeat-Dose Toxicity

Study Number: 38166 (continued)

Dose (µg RNA/animal)	Control (0)		BNT162a1 (30)		BNT162a1 (10)		BNT162b1 (30)		BNT162b1 (100)		BNT162c1 (30)		BNT162b2 (V8) (100)	
Dosing Frequency	QWx3		QWx3		QWx3		QWx3		QWx3		QWx2		QWx3	
Administration Sites/Dosing Day	2		1		1		1		2		1		2	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
I/H, slight	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Day 15 – I/H ^b	-	-	-	-	-	-	-	-	-	-	NA	NA	-	-
4 Hours Postdose	-	-	-	-	-	-	-	-	-	-	NA	NA	-	-
24 Hours Postdose	-	-	-	-	-	-	-	-	-	-	NA	NA	-	-
48 Hours Postdose	-	-	-	-	-	-	-	-	-	-	NA	NA	-	-
I/H, very slight	0	0	0	0	1	0	0	0	0	0	NA	NA	0	0
96 Hours Postdose	-	-	-	-	-	-	-	-	-	-	NA	NA	-	-
144 Hours Postdose	-	-	-	-	-	-	-	-	-	-	NA	NA	-	-
192 Hours Postdose	-	-	-	-	-	-	-	-	-	-	NA	NA	-	-
I/H, moderate	0	0	0	0	1	0	0	0	0	0	NA	NA	0	0
240 Hours Postdose	-	-	-	-	-	-	-	-	-	-	NA	NA	-	-
288 Hours Postdose	-	-	-	-	-	-	-	-	-	-	NA	NA	-	-
336 Hours Postdose	-	-	-	-	-	-	-	-	-	-	NA	NA	-	-
I/H, slight	0	0	0	0	0	0	1	0	0	0	NA	NA	0	0
384 Hours Postdose	-	-	-	-	-	-	-	-	-	-	NA	NA	-	-
I/H, very slight	0	0	0	0	0	0	1	0	0	0	NA	NA	0	0
432 Hours Postdose	-	-	-	-	-	-	-	-	-	-	NA	NA	-	-
I/H, very slight	0	0	0	0	0	0	1	0	0	0	NA	NA	0	0
480 Hours Postdose	-	-	-	-	-	-	-	-	-	-	NA	NA	-	-
Ophthalmology	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Auditory	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Body temperature (°C)														
Day 1														
4 Hours Postdose	37.4	37.4	37.9†	38.3†	37.7*	38.2†	37.6	37.7	38.7†	38.4†	38.3†	38.7†	38.5†	38.5†
24 Hours Postdose	37.5	38.3	38.5†	38.6	37.0	38.4	37.8	38.5	36.7†	38.3	36.6†	38.1	37.5	39.1†
Day 8														
4 Hours Postdose	37.3	37.6	37.9†	38.4†	37.6	38.0	37.5	38.2	38.0†	38.2*	38.0†	38.4†	38.1†	38.4†
24 Hours Postdose	37.3	38.4	39.0†	39.0	38.0	38.8	38.2†	38.7	39.0†	39.0	39.0†	39.0	38.9†	39.3†

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2.6.7.7A Repeat-Dose Toxicity

Study Number: 38166 (continued)

Dose (µg RNA/animal)	Control (0)		BNT162a1 (30)		BNT162a1 (10)		BNT162b1 (30)		BNT162b1 (100)		BNT162c1 (30)		BNT162b2 (V8) (100)	
Dosing Frequency	QWx3		QWx3		QWx3		QWx3		QWx3		QWx2		QWx3	
Administration Sites/Dosing Day	2		1		1		1		2		1		2	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Day 15														
4 Hours Postdose	38.3	38.9	38.2	38.7	37.6†	38.9	37.4†	37.6†	38.7*	39.2	38.6 ^c	38.7 ^c	38.6	39.1
24 Hours Postdose	38.0	39.0	38.9†	39.2	38.2	39.1	38.0	39.0	39.1†	39.4	NA	NA	39.1†	39.5*
Hematology/Coagulation ¹														
Red Blood Cell (10 ⁶ /µL)														
Day 4	7.270	7.654	7.218	7.295	7.754†	7.807	7.126	7.506	7.784†	7.589	7.796†	7.576	7.848†	7.578
Day 10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	7.708	7.419	NA	NA
Day 17	7.956	7.892	7.723	7.546	7.844	7.465*	7.751	7.248†	7.511	7.145†	NA	NA	7.670	7.115†
Hemoglobin (mmol/L)														
Day 4	8.60	8.87	8.43	8.57	8.99*	9.12	8.21*	8.70	8.93*	8.62	8.95*	8.78	9.11†	8.74
Day 10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	8.75	8.43	NA	NA
Day 17	9.14	9.08	8.67†	8.66	8.69†	8.38†	8.62†	8.13†	8.14†	7.85†	NA	NA	8.31†	7.93†
Hematocrit (%)														
Day 4	41.92	41.87	40.58	40.41	42.77	42.23	40.39*	41.39	42.53	40.49	42.66	40.31	42.88	40.15
Day 10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	41.46	38.86	NA	NA
Day 17	45.03	43.45	42.43†	41.74	41.10†	39.24†	42.66†	39.50†	38.79†	37.06†	NA	NA	39.65†	37.59†
Reticulocytes (10 ³ /µL)														
Day 4	307.0	195.7	74.9†	69.8†	116.3†	94.9†	171.1†	143.9*	112.5†	112.3†	77.1†	79.6†	85.5†	101.3†
Day 10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	192.7	184.4	NA	NA
Day 17	234.6	201.0	174.8†	199.8	190.4*	225.5	188.6*	209.9	223.3	226.7	NA	NA	172.9†	198.0
Platelets (10 ³ /µL)														
Day 10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	708.8	570.4	NA	NA
Day 17	1089.2	1068.1	804.7†	622.9†	805.1†	698.1†	930.6	876.8*	817.2†	702.2†	NA	NA	771.4†	704.4†
White blood cells (10 ³ /µL)														
Day 4	9.37	8.42	11.75	12.89†	10.57	8.72	10.00	8.31	10.91	9.05	12.89†	10.03	12.83†	10.40
Day 10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	20.12	15.27	NA	NA
Day 17	9.09	7.11	16.28†	14.50†	14.76†	11.02*	14.61†	12.74†	16.56†	14.41†	NA	NA	19.88†	15.00†
Neutrophils (10 ³ /µL)														
Day 4	1.50	1.11	3.43†	3.84†	1.41	1.11	1.46	1.13	1.32	1.73	2.52†	2.28†	2.00	2.52†

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2.6.7.7A Repeat-Dose Toxicity

Study Number: 38166 (continued)

Dose (µg RNA/animal)	Control (0)		BNT162a1 (30)		BNT162a1 (10)		BNT162b1 (30)		BNT162b1 (100)		BNT162c1 (30)		BNT162b2 (V8) (100)	
Dosing Frequency	QWx3		QWx3		QWx3		QWx3		QWx3		QWx2		QWx3	
Administration Sites/Dosing Day	2		1		1		1		2		1		2	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Day 10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	8.79	6.55	NA	NA
Day 17	1.46	0.95	7.74†	6.52†	5.35†	4.14†	5.89†	5.54†	7.98†	6.96†	NA	NA	10.29†	7.37†
Monocytes (10 ³ /µL)														
Day 4	0.29	0.19	0.41	0.44†	0.30	0.23	0.26	0.18	0.21	0.20	0.41	0.37†	0.27	0.22
Day 10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.63	0.39	NA	NA
Day 17	0.31	0.19	0.57*	0.37*	0.63†	0.44†	0.62†	0.44†	0.55*	0.40†	NA	NA	0.50	0.31
Eosinophils (10 ³ /µL)														
Day 4	0.121	0.134	0.121	0.175	0.119	0.104	0.124	0.158	0.119	0.107	0.097	0.137	0.110	0.162
Day 10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.094	0.092	NA	NA
Day 17	0.109	0.094	0.101	0.099	0.106	0.152*	0.231†	0.308†	0.360†	0.508†	NA	NA	0.566†	0.573†
Basophils (10 ³ /µL)														
Day 4	0.026	0.026	0.038	0.057†	0.047*	0.036	0.035	0.030	0.042	0.033	0.060†	0.047†	0.065†	0.043*
Day 10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.102	0.055	NA	NA
Day 17	0.030	0.019	0.063†	0.060†	0.069†	0.039*	0.060†	0.042†	0.063†	0.043†	NA	NA	0.074†	0.039*
Large unstained cells (10 ³ /µL)														
Day 4	0.09	0.09	0.66†	0.59†	0.22†	0.19†	0.15	0.11	0.22†	0.31†	0.41†	0.33†	0.35†	0.37†
Day 10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.38	0.87	NA	NA
Day 17	0.09	0.08	1.17†	0.86†	0.49†	0.48†	0.24†	0.43†	0.59†	0.63†	NA	NA	0.69†	0.54†
Fibrinogen (mg/dL)														
Day 10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	298.2	267.3	NA	NA
Day 17	106.1	114.4	309.1†	314.0†	271.0†	279.8*	271.4†	281.8†	310.0†	299.1†	NA	NA	323.9†	297.8†
Clinical Chemistry ⁱ														
Albumin (g/L)														
Day 4	29.48	31.61	26.70†	27.15†	27.48†	28.03†	28.27†	28.97†	27.41†	28.21†	27.22†	27.92†	26.79†	27.62†
Day 10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	27.32	27.35	NA	NA
Day 17	28.34	30.36	26.78†	27.68†	26.67†	27.69†	27.23†	27.38†	27.26†	27.17†	NA	NA	26.68†	27.03†
Globulin (g/L)														
Day 4	27.12	27.69	29.70†	28.95	27.62	25.67	31.43†	30.33*	29.59†	29.89	28.88*	27.28	29.11*	28.68

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2.6.7.7A Repeat-Dose Toxicity

Study Number: 38166 (continued)

Dose (µg RNA/animal)	Control (0)		BNT162a1 (30)		BNT162a1 (10)		BNT162b1 (30)		BNT162b1 (100)		BNT162c1 (30)		BNT162b2 (V8) (100)	
Dosing Frequency	QWx3		QWx3		QWx3		QWx3		QWx3		QWx2		QWx3	
Administration Sites/Dosing Day	2		1		1		1		2		1		2	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Day 10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	28.08	26.15	NA	NA
Day 17	25.36	25.54	27.82†	29.02†	27.03	28.51	30.07†	30.12†	32.04†	29.23†	NA	NA	31.22†	30.07†
Albumin/Globulin Ratio														
Day 4	1.087	1.144	0.901†	0.938†	0.996†	1.095	0.902†	0.958†	0.929†	0.950†	0.944†	1.028†	0.923†	0.964†
Day 10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.975	1.049	NA	NA
Day 17	1.119	1.192	0.963†	0.962†	0.988†	1.076	0.908†	0.910†	0.853†	0.933†	NA	NA	0.856†	0.901†
Gamma glutamyl transferase (U/L)														
Day 4	0.95	0.88	4.21†	3.67†	2.93†	2.75†	2.52†	2.32	3.32†	3.72†	3.60†	3.77†	3.25†	4.01†
Day 10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	3.98	4.26	NA	NA
Day 17	1.62	1.21	4.43†	3.97†	3.04†	3.32†	3.59†	3.94†	4.18†	4.40†	NA	NA	4.83†	5.05†
Acute Phase Proteins														
α-1-Acid Glycoprotein (µg/mL)														
Day 4	64.7	79.8	465.0†	401.4†	304.7†	323.6†	381.9†	378.9†	454.9†	445.0†	431.1†	390.6†	446.8†	445.6†
Day 10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	416.3	409.7	NA	NA
Day 17	50.3	52.0	429.6†	467.7†	737.0†	649.4†	437.6†	463.0†	970.9†	980.9†	NA	NA	1043.6†	826.1†
α-2-Macroglobulin (µg/mL)														
Day 4	39.8	18.1	727.0†	126.2†	223.0†	57.1†	1434.6†	330.4†	2143.1†	1639.4†	685.5†	169.6†	2159.0	1362.6
Day 17	21.2	16.1	551.7†	269.3†	394.3†	102.5†	930.4†	724.0†	5927.3	2692.2	NA	NA	4604.5	1937.5
									†	†			†	†
Urinalysis (Day 17)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Immunogenicity	Neg	Neg	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos
Cytokines ^l	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Organ Weights ^d														
Spleen Absolute (g)	0.838	0.595	1.2	1.6†	1.3†	1.2	1.1	1.3*	1.2†	1.6†	1.2	1.3	1.3†	1.6†

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2.6.7.7A Repeat-Dose Toxicity

Study Number: 38166 (continued)

Dose (µg RNA/animal)	Control (0)		BNT162a1 (30)		BNT162a1 (10)		BNT162b1 (30)		BNT162b1 (100)		BNT162c1 (30)		BNT162b2 (V8) (100)	
Dosing Frequency	QWx3		QWx3		QWx3		QWx3		QWx3		QWx2		QWx3	
Administration Sites/Dosing Day	2		1		1		1		2		1		2	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Relative (g/1000 g body weight)	2.568	2.701	1.4†	1.7†	1.3†	1.3	1.2†	1.2	1.3†	1.5†	1.5	1.4	1.4†	1.6†
Gross Pathology														
Number Examined	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Injection site														
Indurated ^k	0	0	10	10	7	7	7	6	6	6	10	10	7	9
Incrusted	0	0	2	2	1	0	0	0	0	0	1	1	0	0
Lymph node, iliac														
Enlarged	0	0	1	1	4	3	6	4	7	8	1	2	5	6
Spleen														
Enlarged	0	0	2	4	5	2	1	1	5	7	5	1	2	7
Histopathology (Day 17 ^l)														
Number Examined	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Injection site ^b														
Fibrosis intramuscular/														
Interstitial														
Minimal	0	0	1	0	0	0	0	0	1	1	0	0	0	0
Mild	0	0	8	10	10	10	9	10	8	9	8	10	10	10
Moderate	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Fibrosis inter-/perimuscular														
Mild	0	0	10	10	10	10	9	10	10	10	8	10	10	10
Moderate	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Inflammation, mixed, subcutis (Injection site 1)														
Mild	0	0	0	0	0	0	1	0	2	0	0	0	0	0
Moderate	0	0	9	10	10	10	7	10	8	10	9	10	9	10
Marked	0	0	0	0	0	0	2	0	0	0	0	0	1	0

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2.6.7.7A Repeat-Dose Toxicity

Study Number: 38166 (continued)

Dose (µg RNA/animal)	Control (0)		BNT162a1 (30)		BNT162a1 (10)		BNT162b1 (30)		BNT162b1 (100)		BNT162c1 (30)		BNT162b2 (V8) (100)	
Dosing Frequency	QWx3		QWx3		QWx3		QWx3		QWx3		QWx2		QWx3	
Administration Sites/Dosing Day	2		1		1		1		2		1		2	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Inflammation, mixed, intramuscular/interstitial (Injection site 1)														
Minimal	0	0	1	0	0	0	0	0	1	0	0	0	0	0
Mild	0	0	4	8	8	4	1	4	3	8	4	3	4	9
Moderate	0	0	4	2	2	6	9	5	1	0	0	0	1	0
Inflammation, mixed, intramuscular/interstitial, multifocal (Injection site 1)														
Moderate	0	0	0	0	0	0	0	1	4	2	5	7	5	1
Inflammation, mixed, inter-/perimuscular (Injection site 1)														
Minimal	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Mild	0	0	3	0	0	0	1	0	0	0	0	0	0	0
Moderate	0	0	7	10	10	7	6	9	8	10	9	8	9	10
Marked	0	0	0	0	0	3	3	1	0	0	0	2	1	0
Inflammation, mixed, subcutis (Injection site 2)														
Mild	0	0	0 ^m	0 ^m	0	0	0	0	1	1	0	0	0	2
Moderate	0	0	3 ^m	0 ^m	0	0	0	0	9	9	0	0	10	8
Inflammation, mixed, intramuscular/interstitial (Injection site 2)														
Mild	0	0	2 ^m	0 ^m	0	0	0	0	5	6	0	0	4	9
Moderate	0	0	1 ^m	0 ^m	0	0	0	0	0	0	0	0	0	0

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2.6.7.7A Repeat-Dose Toxicity

Study Number: 38166 (continued)

Dose (µg RNA/animal)	Control (0)		BNT162a1 (30)		BNT162a1 (10)		BNT162b1 (30)		BNT162b1 (100)		BNT162c1 (30)		BNT162b2 (V8) (100)	
Dosing Frequency	QWx3		QWx3		QWx3		QWx3		QWx3		QWx2		QWx3	
Administration Sites/Dosing Day	2		1		1		1		2		1		2	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Inflammation, mixed, intramuscular/interstitial, multifocal (Injection site 2)														
Minimal	0	0	1 ^m	0 ^m	0	0	0	0	0	0	0	0	0	0
Moderate	0	0	0 ^m	0 ^m	0	0	0	0	5	4	0	0	6	1
Inflammation, mixed, inter-/perimuscular (Injection site 2)														
Minimal	0	0	1 ^m	0 ^m	0	0	0	0	0	0	0	0	0	0
Moderate	0	0	2 ^m	0 ^m	0	0	0	0	10	10	0	0	10	10
Myofiber degeneration														
Minimal	0	0	2	0	0	0	1	2	1	2	0	0	0	0
Mild	0	0	7	9	9	9	8	8	9	8	7	4	10	10
Moderate	0	0	0	0	0	0	0	0	0	0	1	5	0	0
Edema, subcutis														
Mild	0	0	1	0	1	1	4	4	1	2	0	0	1	2
Moderate	0	0	5	10	9	6	4	6	7	8	6	5	7	7
Marked	0	0	0	0	0	2	1	0	0	0	3	5	2	1
Oedema intramuscular/interstitial														
Minimal	0	0	1	8	6	1	2	2	1	1	1	1	0	0
Mild	0	0	1	2	1	7	6	7	7	9	8	9	10	10
Oedema inter-/perimuscular														
Minimal	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Mild	0	0	2	1	5	0	3	1	0	2	2	1	0	0
Moderate	0	0	4	9	5	8	6	8	8	6	6	8	6	6
Marked	0	0	1	0	0	1	1	1	0	2	2	1	4	5

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2.6.7.7A Repeat-Dose Toxicity

Study Number: 38166 (continued)

Dose (µg RNA/animal)	Control (0)		BNT162a1 (30)		BNT162a1 (10)		BNT162b1 (30)		BNT162b1 (100)		BNT162c1 (30)		BNT162b2 (V8) (100)	
Dosing Frequency	QWx3		QWx3		QWx3		QWx3		QWx3		QWx2		QWx3	
Administration Sites/Dosing Day	2		1		1		1		2		1		2	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Hyperplasia, epidermis, widespread														
Mild	0	0	0	0	2	3	5	7	3	1	0	0	2	1
Moderate	0	0	4	9	7	4	4	1	7	9	9	10	7	9
Sciatic nerve, perineural Inflammation														
Minimal	0	0	0	0	0	1	0	1	3	1	0	0	1	1
Mild	0	0	0	0	0	0	0	3	2	2	0	0	2	3
Moderate	0	0	2	0	0	0	1	0	2	7	0	0	5	5
Marked	0	0	1	0	0	0	0	0	0	0	0	0	2	1
Bone femur Inflammation														
Minimal	0	0	0	1	0	1	0	0	1	2	0	0	0	0
Mild	0	0	0	0	0	0	0	0	2	3	0	0	2	7
Moderate	0	0	0	0	0	0	0	0	1	1	0	0	0	2
Mammary gland Inflammation, mixed; interstitium; focal														
Mild	0	0	0	0	0	2	0	0	1	0	2	1	0	0
Moderate	0	0	0	0	0	0	0	0	1	0	1	2	0	0
Lymph node iliac Plasmacytosis														
Minimal	0	0	2	2	1	1	0	0	1	0	4	1	0	0
Mild	0	0	3	1	6	6	2	1	4	4	1	6	9	2
Moderate	0	0	0	0	0	0	7	7	2	5	1	0	1	8
Marked	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Inflammation														
Minimal	0	0	4	1	0	1	0	0	0	2	1	2	1	1
Mild	0	0	1	5	0	2	0	0	3	3	1	3	7	5

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2.6.7.7A Repeat-Dose Toxicity

Study Number: 38166 (continued)

Dose (µg RNA/animal)	Control (0)		BNT162a1 (30)		BNT162a1 (10)		BNT162b1 (30)		BNT162b1 (100)		BNT162c1 (30)		BNT162b2 (V8) (100)	
Dosing Frequency	QWx3		QWx3		QWx3		QWx3		QWx3		QWx2		QWx3	
Administration Sites/Dosing Day	2		1		1		1		2		1		2	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Moderate Increased cellularity, germinal center	0	0	0	0	0	0	0	0	2	2	2	2	1	0
Minimal	4	3	3	1	0	1	1	2	1	0	0	0	0	0
Mild	4	0	5	6	6	7	9	4	7	6	8	10	8	6
Moderate	0	0	1	1	3	2	0	2	2	3	2	0	2	4
Skeletal muscle Infiltration, mixed (focal, multifocal)														
Minimal	0	0	0	1	0	0	0	0	1	2	0	0	5	0
Spleen Increased haematopoiesis														
Minimal	0	0	0	0	3	2	0	0	0	4	0	0	2	6
Mild	0	0	0	0	0	0	0	0	2	3	0	0	0	2
Liver Vacuolation, hepatocellular, periportal														
Minimal	0	0	1	4	1	5	0	2	5	1	1	6	5	2
Mild	0	0	0	6	0	1	0	8	3	9	0	4	4	8
Postdose Evaluation														
Number Evaluated	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Body Temperature (°C) Day 36	36.8	38.3	37.4	38.8	37.6	38.8	38.2*	38.7	37.5	39.1	NA	NA	37.0	39.2
Histopathology ⁿ Number Examined Injection site	5	5	5	5	5	5	5	5	5	5	5	5	5	5

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2.6.7.7A Repeat-Dose Toxicity

Study Number: 38166 (continued)

Dose (µg RNA/animal)	Control (0)		BNT162a1 (30)		BNT162a1 (10)		BNT162b1 (30)		BNT162b1 (100)		BNT162c1 (30)		BNT162b2 (V8) (100)	
Dosing Frequency	QWx3		QWx3		QWx3		QWx3		QWx3		QWx2		QWx3	
Administration Sites/Dosing Day	2		1		1		1		2		1		2	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Fibrosis intramuscular/interstitial														
Minimal	0	0	1	3	3	1	4	4	4	1	0	0	4	4
Fibrosis inter/perimuscular														
Minimal	0	0	1	1	1	4	0	1	2	5	1	4	1	0
Mild	0	0	4	4	4	1	5	4	3	0	0	0	4	4
Inflammation, inter-/perimuscular														
Minimal	0	0	3	2	4	3	1	1	3	2	1	3	1	0
Mild	0	0	2	2	0	0	4	4	2	2	0	0	4	4
Lymph node iliac														
Plasmacytosis														
Minimal	0	0	0	2	0	2	2	3	2	2	0	1	1	1
Mild	0	0	0	1	0	1	0	0	1	3	0	0	0	3
Increased cellularity, germinal center														
Minimal	1	2	3	2	1	1	3	1	1	0	4	3	1	0
Mild	4	2	1	3	4	3	1	4	4	3	1	1	4	3
Moderate	0	0	1	0	0	1	1	0	0	2	0	0	0	1
Skeletal muscle														
Infiltration, lymphocytic														
Minimal	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Liver														
Vacuolation, hepatocellular, periportal														
Minimal	1	0	0	0	0	0	0	0	0	0	0	1	0	0

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2.6.7.7A Repeat-Dose Toxicity**Study Number: 38166 (continued)**

* $p \leq 0.05$; † $p \leq 0.01$, significantly different from control based on appropriate trend or pairwise comparison. A full description of the statistical decision tree can be found in the final report for this study.

- = No noteworthy findings; F = Female; GLP = Good Laboratory Practice; IFN = Interferon; I/H = Induration/Hardening; IL = Interleukin; LNP = Lipid Nanoparticle; M = Male; modRNA = Nucleoside-modified mRNA; NA = Not applicable, Not available; Neg = Negative; Pos = Positive; QW = Once weekly; RBD = Receptor binding domain; saRNA = Self-amplifying mRNA; SP2 = Spike protein P2 mutant; TNF = Tumor necrosis factor; uRNA = Uridine mRNA.

a. Final, audited study report.

b. Groups 1, 5, and 7 each received 100 μL /administration site at 2 sites for a total dose volume of 200 μL . The remaining groups each received an administration at only 1 site for a total dose volume of 60 μL (Groups 2 and 4), 20 μL (Group 3), and 70 μL (Group 6).

c. Ten (10) animals/sex/group for the dosing phase (main study animals), and 5 animals/sex/group for the recovery phase. Additional satellite animals (3/sex/group) were used only for blood sampling for cytokine analysis.

d. Group means are shown for controls. Changes from controls, expressed as multiples, are shown for groups administered test article. Statistical significance is based on actual data and not on the multiples.

e. Values represent data obtained from recovery animals (5/sex).

f. Percent differences from Day 1 are shown.

g. For local tolerance, when animals received the test article over 2 injection sites (Groups 1, 5, and 7), only the highest severity score from either injection site was used to calculate incidence.

h. No noteworthy findings were observed at all time points on Day 1 (4, 24, 48, 96, and 144 hours postdose) and Day 15 (4 and 24 hours post dose).

i. Day 4 values represent data obtained from the first 5 main study animals/sex/group and all recovery animals (5/sex/group). Day 10 and 17 values represent data obtained at the end of the dosing phase from the main study animals only (10/sex/group).

j. Data obtained from all satellite animals (3/sex/group). Cytokine parameters evaluated were IFN- γ , TNF- α , IL-1- β , IL-6, and IL-10.

k. Observation of "indurated" includes observations of thickened injection site and/or muscle.

l. Day 10 for Group 6.

m. On Day 15, 6 animals (males 32, 34, 37, 39 and 42; female 60) were administered their third dose of BNT162a1 (Group 2) in the contralateral limb (Site II) due to local tolerance findings at the original injection site (Site I).

n. Day 31 for group 6; Day 38 for all other groups.

2.6.7.7B Repeat-Dose Toxicity

Report Title: 17-Day Intramuscular Toxicity Study of BNT162b2 (V9) and BNT162b3c in Wistar Han Rats With a 3-Week Recovery

Test Article: BNT162b2

Species/Strain: Rat/Wistar Han
Age at First Dose: 9 Weeks

Duration of Dosing: 17 Days (Dose days 1, 8, 15)
Duration of Postdose: 3 Weeks

Study Number: 20GR142
Lot Numbers: COVVAC/270320 (BNT162b2 [V9]), BCV/040620 (BNT162b3c)

Date of First Dose: 06 July 2020

Method of Administration: Intramuscular injection, QD, 60 µL/injection^a

GLP Compliance: Yes

Vehicle/Formulation: 0.9% sterile saline/Suspension

Special Features: None

No Observed Adverse Effect Level: NA

Dose (µg RNA)	Saline Control (0)		BNT162b2 (V9) (30)		BNT162b3c (30)	
	M	F	M	F	M	F
Sex						
Number of Animals ^b	15	15	15	15	15	15
Noteworthy Findings						
Died or Euthanized Moribund	0	0	0	0	0	0
Body Weight (g) ^c						
Prior to Initiation of Dosing (Day 6)	225.28	-	-	-	1.0	-
Day 11	295.83	-	-	-	0.93†	-
Day 15	311.47	-	-	-	0.94*	-
Body Weight Change (g)						
Days 1-4	-12.64	-11.61	-19.57†	-14.21	-20.92†	-15.75
Days 4-8	+28.44	+23.34	+36.01	+25.19	+33.75	+21.98
Days 8-11	+15.23	+3.71	+0.10†	+1.37	-1.71†	+3.92
Days 11-15	+15.64	+4.06	+18.82*	+10.14†	+18.71	+11.09†
Days 1-15	+46.67	+19.50	+35.35†	+22.49	+29.83†	+21.25
Food Consumption (g) ^c						
Days 1-4	50.88	37.79	0.84†	0.87†	0.76†	0.92†
Days 4-8	90.87	74.46	1.06	0.95	1.01	0.96
Days 8-11	64.77	48.27	0.83†	0.87†	0.78†	0.84†
Days 11-15	89.35	65.27	1.03	1.02	0.99	1.05
Days 1-15	295.87	225.80	0.97	0.94	0.91*	0.95

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2.6.7.7B Repeat-Dose Toxicity

Study Number: 20GR142 (continued)

Dose (µg RNA)	Saline Control (0)		BNT162b2 (V9) (30)		BNT162b3c (30)	
	M	F	M	F	M	F
Sex						
Clinical Observations	-	-	-	-	-	-
Local Tolerance ^d						
Day 1 – Edema						
Predose	-	-	-	-	-	-
4 Hours Postdose						
Edema, very slight	0	0	0	0	0	1
24 Hours Postdose						
Edema, very slight	0	0	5	5	7	8
Edema, slight	0	0	6	10	6	7
48 Hours Postdose						
Edema, very slight	NA	NA	1 (6)	0 (10)	0 (6)	0 (7)
Edema, slight	NA	NA	5 (6)	10 (10)	6 (6)	7 (7)
72 Hours Postdose						
Edema, very slight	NA	NA	5 (6)	0 (10)	2 (6)	0 (7)
Edema, slight	NA	NA	0 (6)	10 (10)	4 (6)	7 (7)
120 Hours Postdose						
Edema, slight	NA	NA	NA	10 (10)	4 (4)	7 (7)
144 Hours Postdose						
Edema, very slight	NA	NA	NA	0 (10)	4 (4)	0 (7)
Edema, slight	NA	NA	NA	10 (10)	0 (4)	7 (7)
Day 8 – Edema						
Predose	-	-	-	-	-	-
4 Hours Postdose	-	-	-	-	-	-
24 Hours Postdose						
Edema, slight	0	0	6	6	4	6
Edema, moderate	0	0	7	9	11	9
48 Hours Postdose						
Edema, slight	NA	NA	6 (13)	6	3	4
Edema, moderate	NA	NA	7 (13)	9	12	11
72 Hours Postdose						
Edema, very slight	NA	NA	2 (13)	1	2	0
Edema, slight	NA	NA	11 (13)	8	13	8

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2.6.7.7B Repeat-Dose Toxicity

Study Number: 20GR142 (continued)

Dose (µg RNA)	Saline Control (0)		BNT162b2 (V9) (30)		BNT162b3c (30)	
	M	F	M	F	M	F
Sex						
Edema, moderate 120 Hours Postdose	NA	NA	0 (13)	6	0	7
Edema, very slight Edema, slight 144 Hours Postdose	NA NA	NA NA	11 (11) 0 (11)	14 (14) 0 (14)	13 (13) 0 (13)	8 3
Edema, very slight Day 15 – Edema	NA	NA	1 (11)	0 (14)	0 (13)	1
Predose	-	-	-	-	-	-
4 Hours Postdose						
Edema, very slight	0	0	2	0	5	0
24 Hours Postdose						
Edema, very slight	0	0	1	0	1	0
Edema, slight	0	0	11	6	11	4
Edema, moderate	0	0	2	9	3	11
48 Hours Postdose						
Edema, very slight	NA	NA	0 (13)	1	0 (14)	0
Edema, slight	NA	NA	11 (13)	8	10 (14)	6
Edema, moderate	NA	NA	2 (13)	6	4 (14)	9
72 Hours Postdose						
Edema, very slight	NA	NA	2 (4)	0 (5)	1 (5)	0 (5)
Edema, slight	NA	NA	2 (4)	3 (5)	4 (5)	2 (5)
Edema, moderate	NA	NA	0 (4)	2 (5)	0 (5)	3 (5)
Day 1 – Erythema						
Predose	-	-	-	-	-	-
4 Hours Postdose	-	-	-	-	-	-
24 Hours Postdose						
Erythema, very slight	0	0	1	11	1	15
48 Hours Postdose						
Erythema, very slight	NA	NA	0 (6)	10 (10)	1 (6)	7 (7)
72 Hours Postdose						
Erythema, very slight	NA	NA	0 (6)	9 (10)	0 (6)	7 (7)
120 Hours Postdose						
Erythema, very slight	NA	NA	NA	9 (10)	0 (4)	7 (7)

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2.6.7.7B Repeat-Dose Toxicity

Study Number: 20GR142 (continued)

Dose (µg RNA)	Saline Control (0)		BNT162b2 (V9) (30)		BNT162b3c (30)	
	M	F	M	F	M	F
Sex						
144 Hours Postdose Erythema, very slight	NA	NA	NA	9 (10)	0 (4)	7 (7)
Day 8 – Erythema						
Predose	-	-	-	-	-	-
4 Hours Postdose	-	-	-	-	-	-
24 Hours Postdose Erythema, very slight	0	0	7	15	12	15
48 Hours Postdose Erythema, very slight	NA	NA	7 (13)	15	14	15
72 Hours Postdose Erythema, very slight	NA	NA	5 (13)	12	10	14
120 Hours Postdose Erythema, very slight	NA	NA	2 (11)	2 (14)	0 (13)	8
144 Hours Postdose	NA	NA	- (11)	- (14)	- (13)	-
Day 15 – Erythema						
Predose	-	-	-	-	-	-
4 Hours Postdose Erythema, very slight	0	0	0	0	1	0
24 Hours Postdose Erythema, very slight	0	0	0	12	0	15
48 Hours Postdose Erythema, very slight	NA	NA	0 (13)	3	3 (14)	12
72 Hours Postdose Erythema, very slight	NA	NA	0 (4)	2 (5)	0 (5)	4 (5)
Ophthalmology	-	-	-	-	-	-
Body temperature (°C) ^e						
Day 1	38.31	38.08	38.85†	38.50*	39.02†	38.58†
Day 8	37.07	37.81	38.05†	38.47†	38.33†	38.73†
Day 15	37.34	38.02	38.37†	38.15	38.43†	38.35
Hematology/Coagulation ^f						
Red Blood Cells (10 ⁶ /µL)						
Day 4	8.117	7.903	7.774*	7.381*	7.596†	7.470*
Day 17	7.584	7.423	7.169	6.872†	7.113	6.836†

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2.6.7.7B Repeat-Dose Toxicity

Study Number: 20GR142 (continued)

Dose (µg RNA)	Saline Control (0)		BNT162b2 (V9) (30)		BNT162b3c (30)	
	M	F	M	F	M	F
Sex						
Hemoglobin (g/dL)						
Day 4	15.01	14.53	14.16*	13.56*	14.01†	13.56*
Day 17	13.82	13.83	12.53†	12.38†	12.81†	12.24†
Hematocrit (%)						
Day 4	48.04	44.91	43.37†	41.79*	43.79†	41.81*
Day 17	42.61	41.67	38.40†	38.09†	39.29*	37.21†
Mean Cell Hemoglobin (pg)						
Day 4	18.51	18.37	18.20	18.39	18.50	18.16
Day 17	18.27	18.62	17.48†	17.99†	18.01	17.89†
Mean Cell Hemoglobin Concentration (g/dL)						
Day 4	31.24	32.34	32.64†	32.49	32.04†	32.41
Day 17	32.46	33.18	32.65	32.50†	32.61	32.84
Red Cell Distribution Width (%)						
Day 4	12.27	11.11	12.83	11.39	12.44	11.97†
Day 17	11.63	11.33	14.12†	13.34†	13.73†	13.38†
Reticulocytes (10 ³ /µL)						
Day 4	392.1	301.7	107.4†	129.7†	104.6†	133.6†
Day 17	178.8	168.9	185.4	222.1*	194.0	203.3
White Blood Cells (10 ³ /µL)						
Day 4	7.60	6.01	10.70*	7.84	9.70	8.57*
Day 17	3.84	2.16	8.83†	5.70†	8.60†	6.37†
Neutrophils (10 ³ /µL)						
Day 4	1.083	0.920	2.470†	2.306	2.161*	2.879†
Day 17	0.674	0.409	4.449†	2.469†	4.351†	2.879†
Monocytes (10 ³ /µL)						
Day 4	0.109	0.093	0.199*	0.176	0.214†	0.234†
Day 17	0.071	0.056	0.234†	0.154†	0.254†	0.176†
Eosinophils (10 ³ /µL)						
Day 4	0.081	0.057	0.086	0.087*	0.091	0.123†
Day 17	0.056	0.029	0.141†	0.092†	0.122†	0.097†
Basophils (10 ³ /µL)						
Day 4	0.016	0.009	0.030*	0.017	0.037†	0.024†
Day 17	0.003	0.001	0.017†	0.008†	0.019†	0.010†

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2.6.7.7B Repeat-Dose Toxicity

Study Number: 20GR142 (continued)

Dose (µg RNA)	Saline Control (0)		BNT162b2 (V9) (30)		BNT162b3c (30)	
	M	F	M	F	M	F
Sex						
Large Unstained Cells (10 ³ /µL)						
Day 4	0.046	0.030	0.187†	0.126†	0.183†	0.133†
Day 17	0.026	0.010	0.209†	0.132†	0.323†	0.190†
Fibrinogen (mg/dL)						
Day 17	253.1	217.2	596.7†	541.9†	606.1†	563.1†
Clinical Chemistry ^g						
Albumin/Globulin Ratio						
Day 4	1.88	1.98	1.70†	1.71†	1.69†	1.69†
Day 17	1.85	1.96	1.65†	1.61†	1.65†	1.66†
Total Protein (g/dL)						
Day 4	6.10	6.26	5.90	5.65†	5.85	5.94
Day 17	5.39	5.44	5.51	4.98†	5.41	4.96†
Albumin (g/dL)						
Day 4	3.98	4.16	3.71†	3.56†	3.68†	3.73†
Day 17	3.50	3.60	3.43	3.07†	3.38	3.09†
Globulin (g/dL)						
Day 4	2.13	2.10	2.19	2.09	2.18	2.21
Day 17	1.89	1.84	2.08*	1.91	2.03	1.88
Acute Phase Proteins ^g						
α2-Macroglobulin (µg/mL)						
Day 4	113.4	212.1	2318.1†	703.8†	3911.6†	887.1†
Day 17	14.0	33.1	990.6†	521.0†	1794.2†	592.0†
α1-Acid Glycoprotein (µg/mL)						
Day 4	174.358	239.774	1642.265†	1906.314†	2351.791†	1677.103†
Day 17	47.672	95.959	1835.986†	1491.849†	2021.083†	1651.071†
Urinalysis (Day 17)	-	-	-	-	-	-
Immunogenicity	Neg	Neg	Pos	Pos	Pos	Pos
Organ Weights (Day 17) ^e						
Spleen						
Absolute (g)	0.5951	0.4382	1.29†	1.55†	1.34†	1.41†
Relative (g/100 g body weight)	0.2008	0.2202	1.42†	1.59†	1.52†	1.47†
Relative (g/g brain weight)	0.3120	0.2353	1.29†	1.62†	1.34†	1.43†

2.6.7.7B Repeat-Dose Toxicity

Study Number: 20GR142 (continued)

Dose (µg RNA)	Saline Control (0)		BNT162b2 (V9) (30)		BNT162b3c (30)	
	M	F	M	F	M	F
Sex						
Gross Pathology (Day 17)						
Number Examined	10	10	10	10	10	10
Injection site						
Abnormal color, pale/dark	0	1	2	3	1	0
Abnormal consistency, firm	0	0	2	4	2	7
Lymph node, draining						
Abnormal size, enlarged	0	0	1	1	0	4
Spleen						
Abnormal size, enlarged	0	0	0	0	0	1
Histopathology (Day 17)						
Number Examined ^h	10	10	10	10	10	10
Injection site						
Inflammation						
Minimal	4	5	0	0	0	0
Mild	0	0	7	7	5	9
Moderate	0	0	3	3	5	1
Edema						
Mild	0	0	8	9	8	9
Moderate	0	0	1	1	1	1
Lymph Node Iliac, Draining						
Increased cellularity, Plasma cell						
Minimal	0	0	1 (9)	1	4	1
Mild	0	0	4 (9)	1	3	5
Moderate	0	0	2 (9)	7	1	1
Increased cellularity, Germinal center						
Minimal	1	1	2 (9)	3	2	4
Mild	1	1	4 (9)	2	6	2
Lymph Node, Inguinal						
Increased cellularity, Plasma cell						
Minimal	0 (9)	0	1	2	1	4
Increased cellularity, Germinal center						
Minimal	0 (9)	1	1	3	1	6
Mild	1 (9)	0	4	3	5	3

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2.6.7.7B Repeat-Dose Toxicity

Study Number: 20GR142 (continued)

Dose (µg RNA)	Saline Control (0)		BNT162b2 (V9) (30)		BNT162b3c (30)	
	M	F	M	F	M	F
Sex						
Liver Vacuolation, Hepatocyte; Periportal Minimal	0	0	5	10	7	7
Spleen Increased cellularity, hematopoietic cell Minimal	0	0	10	9	10	10
Increased cellularity, Germinal center Minimal	0	0	5	6	5	5
Bone marrow, Sternum Increased cellularity, hematopoietic cell Minimal	0	0	10	10	10	10
Postdose Evaluation Number of Animals	5	5	5	5	5	5
Body Weight (g) ^c						
Day 11	330.74	-	1.05	-	1.00	-
Day 15	333.60	-	1.06	-	1.00	-
Day 18	341.42	-	1.05	-	1.01	-
Day 21	347.88	-	1.06	-	1.02	-
Food Consumption (g) ^c						
Days 1-21	383.66	-	1.15	-	1.08	-
Hematology/Coagulation Red Cell Distribution Width (%) Day 22	11.93	10.80	13.48†	13.04†	13.33*	13.32†
Clinical Chemistry Albumin/Globulin Ratio Day 22	1.76	1.90	1.72	1.72*	1.70	1.80
Globulin (g/dL) Day 22	2.10	2.26	2.26†	2.40	2.18	2.42
Local Tolerance Recovery Day 1 – Edema 72 Hours Postdose						
Edema, slight	NA	NA	2	3	4	2
Edema, moderate	NA	NA	0	2	0	3

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2.6.7.7B Repeat-Dose Toxicity

Study Number: 20GR142 (continued)

Dose (µg RNA)	Saline Control (0)		BNT162b2 (V9) (30)		BNT162b3c (30)	
	M	F	M	F	M	F
Sex						
Immunogenicity	Neg	Neg	Pos	Pos	Pos	Pos
Gross Pathology (Day 22)						
Number Examined	5	5	5	5	5	5
Lymph Node, Draining						
Abnormal size, enlarged	0	0	1	0	0	1
Lymph Node, Inguinal						
Abnormal size, enlarged	0	0	0	0	0	1
Histopathology (Day 22)						
Number Examined ¹	5	5	5	5	5	5
Injection site						
Inflammation						
Minimal	0	0	5	5	5	5
Lymph Node, Draining						
Increased cellularity, Plasma cell						
Minimal	0 (4)	0	4	4	5	3
Increased cellularity, Germinal center						
Minimal	0 (4)	1	3	2	2	4
Mild	0 (4)	0	1	1	2	1
Infiltration, Macrophage						
Minimal	0 (4)	0	2	1	2	1
Mild	0 (4)	0	1	2	2	3
Lymph Node, Inguinal						
Increased cellularity, Plasma cell						
Minimal	0	0	0	0	0	1
Increased cellularity, Germinal center						
Minimal	2	2	3	1	2	3
Infiltration, Macrophage						
Minimal	0	0	0	0	1	1
Spleen						
Increased cellularity, Germinal center						
Minimal	0	0	1	2	1	2

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2.6.7.7B Repeat-Dose Toxicity

Study Number: **20GR142 (continued)**

* $p \leq 0.05$; † $p \leq 0.01$, significantly different from control based on appropriate trend or pairwise comparison. A full description of the statistical decision tree can be found in the final report for this study.

- = No noteworthy findings; F = Female; GLP = Good Laboratory Practice; M = Male; NA = Not applicable, results not yet available; Neg = Negative; Pos = Positive; QD = Once daily.

- a. Each animal received a single intramuscular injection on each dose day.
- b. Ten (10) animals/sex/group for the dosing phase (main study animals), and 5 animals/sex/group for the recovery phase.
- c. Group means are shown for controls. Changes from controls, expressed as multiples, are shown for groups administered test article. Statistical significance is based on actual data and not on the multiples.
- d. Fifteen (15) animals/sex/group examined unless otherwise indicated in ().
- e. Values represent the highest group mean postdose body temperature after each dose.
- f. Day 4 mean values for 7 animals/sex/group.; Day 17 mean values for 9 or 10 animals/sex/group.
- g. Day 4 mean values for 8 animals/sex/group.; Day 17 mean values for 9 to 10 animals/sex/group.
- h. Ten (10) animals/sex/group examined unless otherwise indicated in ().
- i. Five (5) animals/sex/group examined unless otherwise indicated in ().

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2.6.7.12 Reproductive and Developmental Toxicity – Fertility and Development

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

Test Article: BNT162b2

Design Similar to ICH 4.1.1, 4.1.2 and 4.1.3: Yes
Species/Strain: Rat/Wistar Han
Age at First Dose (F): 11 weeks
Date of First Dose: 27 July 2020

Duration of Dosing (F): 4 Days (21 and 14 days prior to mating, GD 9, GD 20)
Day of Mating (F): GD 0
Day of Cesarean Section: GD 21
Day of Dams and Pups Necropsy: PND 21

Study Number: 20256434
Sponsor Reference Number: RN9391R58
Lot Numbers: CoVVAC/100320 (BNT162b1), CoVVAC/270320 (BNT162b2), BCV/040620 (BNT162b3)
GLP Compliance: Yes

Special Features: None

Method of Administration: Intramuscular injection, 0.06 mL/injection
Vehicle/Formulation: 0.9% sterile saline/Suspension
Control Article: Sterile physiological saline (0.9 % NaCl)

No Observed Adverse Effect Level: Not reported

Dose (µg mRNA) ^a	Saline Control (0)	BNT162b1 (30)	BNT162b2 (30)	BNT162b3 (30)
Dams				
Number of Females				
Caesarean Subgroup	22	22	22	22
Littering Subgroup	22	22	22	22
Clinical Observations				
Injection site				
Premating swelling ^b	0	43	44	43
Gestation swelling ^b	0	5	10	20
Lactation swelling ^b	1	0	3	2
Premating Body Weight (g) ^c				
Prior to Initiation of Dosing (Day 1)	216.49	1.00	1.01	1.02
Prior to Initiation of Mating (Day 22)	240.13	0.99	1.00	1.01

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2.6.7.12 Reproductive and Developmental Toxicity – Fertility and Development

Study Number: 20256434 (continued)

Dose (µg mRNA) ^a	Saline Control (0)	BNT162b1 (30)	BNT162b2 (30)	BNT162b3 (30)
Premating Body Weight Change (g)				
Days 1-4	4.85	-0.55§	-0.64§	-0.17§
Days 1-22	23.64	20.00	20.39	20.94
Gestation Body Weight (g) ^c				
End of Gestation (GD 21)	365.98	0.98	0.96*	0.96*
Gestation Body Weight Change (g)				
GD 9-12	13.55	7.48§	5.70§	5.73§
GD 18-21	34.10	29.33§	24.82§	29.24§
Lactation Body Weight	-	-	-	-
Premating Food Consumption (g) ^c				
Days 1-8	18.49	0.90§	0.91§	0.91§
Days 1-22	18.43	0.97§	0.98	0.98
Gestation Food Consumption (g) ^c				
GD 9-12	22.95	0.87§	0.84§	0.83§
GD 18-21	23.41	0.98	0.97	0.99
Lactation Food Consumption	-	-	-	-
Number of Females Paired	44	44	44	44
Number of Females Failed to Mate	0	1	0	0
Number of Females Inseminated	44	43	44	44
Number of Pregnant Females	43	41	42	44
Number of Mistimed Pregnancy Females	0	0	0	1
Number of Not Pregnant Females	1	2	2	0
Number Euthanized Moribund Post-partum (Littering subgroup)	0	0	0	1 ^d
Number Total Litter Death Post-partum (Littering subgroup)	0	1	0	1
Necropsy Observations (Macroscopic)				
Injection site				
Firm area	0	7	9	14
Enlarged	0	7	8	14
Oedematous area	0	0	1	0
Pale	0	2	4	10

2.6.7.12 Reproductive and Developmental Toxicity – Fertility and Development

Study Number: **20256434** (continued)

Dose (µg mRNA) ^a	Saline Control (0)	BNT162b1 (30)	BNT162b2 (30)	BNT162b3 (30)
Cesarean Subgroup				
Cesarean Section Observations				
Number Evaluated	21	20	21	22
Mean Number Corpora Lutea	14.7	15.3	15.5	15.0
Mean Number Implantations	14.1	14.6	14.0	13.8
Mean % Preimplantation Loss	4.09	4.77	9.77*	7.96
Mean % Postimplantation Loss	6.10	3.36	5.85	8.64
Mean Number Early Resorptions	0.8	0.5	0.7	1.0
Mean Number Late Resorptions	0.1	0.0	0.2	0.2
Fetuses				
Number Fetuses /Litters Evaluated	277/21	282/20	276/21	275/22
Mean Number Live Fetuses	13.2	14.1	13.1	12.5
Mean Number Dead Fetuses	0	0	0	0
Mean Fetal Body Weight (both sex) (g)	4.89	4.86	4.90	4.84
Sex Ratios (% males)	46.96	48.09	50.66	49.84
Fetal Observations				
External Malformations	-	-	-	-
External Variations/Abnormalities	-	-	-	-
Number Fetuses/Litters Evaluated	277/21	282/20	276/21	275/22
Visceral Malformations	-	-	-	-
Visceral Variations/Abnormalities	-	-	-	-
Number Fetuses/Litters Evaluated	133/21	135/20	132/21	132/22
Skeletal Malformations	-	-	-	-
Skeletal Variations/Abnormalities	-	-	-	-
Number Fetuses/Litters Evaluated	144/21	147/20	144/21	143/22
Littering Subgroup				
Number with Mistimed Pregnancy	0	0	0	1
Number with Total Litter Death	0	1	0	1
No. of Natural Deliveries	22	21	21	20
Number Euthanized Moribund Post-Partum	0	0	0	1 ^d
No. of Litters with Stillborn Pups	3	4	2	2
No. of litters with All Stillborn Pups	0	0	0	1

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2.6.7.12 Reproductive and Developmental Toxicity – Fertility and Development

Study Number: 20256434 (continued)

Dose (µg mRNA) ^a	Saline Control (0)	BNT162b1 (30)	BNT162b2 (30)	BNT162b3 (30)
Mean No. Pups/Litter	13.3	11.9	13.1	11.4*
Mean No. Liveborn Pups	13.0	11.0	13.0	11.3*
No. of Total Litters Losses	0	1	0	1
Pre-Birth Loss (%)	6.80	12.22	8.22	13.76*
No. of viable litters at Weaning (PND 21)	22	20	21	19
Gestation Index (%)	100	100	100	95
Live Birth Index (%)	98.0	93.2	99.3	94.7
Postnatal Survival to Day 4 (%)	99.0	98.3	98.9	99.1
Postnatal Survival to Weaning (No. of pups)	175	154	163	152
Lactation Index (PND 4-PND 21) (%)	99.4	100.0	100.0	100.0
Sex ratio at Weaning (PND 21) (Males %)	49.7	50.6	47.6	49.3
Change in Pup Body Weight (g)	-	-	-	-
Pup Clinical Signs	-	-	-	-
Pup Necropsy Observations	-	-	-	-
Immunogenicity				
Dams	Neg	Pos	Pos	Pos
Fetuses	Neg	Pos	Pos	Pos
Pups	Neg	Pos	Pos	Pos

* p<0.05, § p<0.001; Dunnett Non-Parametric 2-Sided. A full description of the statistical decision tree can be found in the final report for this study.

- = No noteworthy findings; F = female; GD = gestation day; GLP = Good Laboratory Practice; ICH = International Conference on Harmonisation; mRNA = messenger RNA; Neg = negative; PND = postnatal day; Pos = positive.

- a. Each dose consisted of a 0.06 mL intramuscular injection in alternating quadriceps muscles.
- b. Complete recovery was noted between each of the dose administrations. Swelling (associated or not with limping and/or piloerection for 1 or 2 days after the second dose only) was noted at the injection site.
- c. Group means are shown for controls. Changes from controls, expressed as multiples, are shown for groups administered test article. Statistical significance is based on actual data and not on the multiples.
- d. Difficulties during parturition.

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