Appendix 1: Justification for the absence of studies in CTD Module 4 (part of 2.4)

CTD Section	Title	Reason not included in the dossier
4.2.1	**Pharmacology**	
4.2.1.1	Primary Pharmacodynamics	Study reports included.
4.2.1.2	Secondary Pharmacodynamics	No secondary pharmacodynamics studies were conducted with BNT162b2.
4.2.1.3	Safety Pharmacology	No safety pharmacology studies were conducted as they are not considered necessary according to the WHO guideline (WHO, 2005).
4.2.1.4	Pharmacodynamic Drug Interactions	Nonclinical studies evaluating pharmacodynamic drug interactions were not conducted as they are generally not considered necessary to support development and licensure of vaccine products for infectious diseases (WHO, 2005).
4.2.2	**Pharmacokinetics**	
4.2.2.1	Analytical Methods and Validation Reports (if separate reports are available)	No methods of analysis have been validated to support GLP TK studies of components of the BNT162b2; however, a qualified LCMS method was developed to support quantitation of the two novel LNP excipients for the non-GLP IV PK study (PF-07302048_06Jul20_072424).
4.2.2.2	Absorption	No specific absorption studies have been carried out with BNT162b2 or the novel lipid excipients as the vaccine is dosed IM. Study report included for PK of novel lipid excipients.
4.2.2.3	Distribution	Study report included.
4.2.2.4	Metabolism	Study reports included for metabolic stability and biotransformation of the novel lipid excipients.
4 2.2.5	Excretion	Study report included for excretion of novel lipid excipients.
4.2.2.6	Pharmacokinetic Drug Interactions (nonclinical)	No PK drug interaction studies have been conducted with BNT162b2.
4.2.2.7	Other Pharmacokinetic Studies	No other PK studies have been conducted with BNT162b2.
4.2.3	**Toxicology**	
4.2.3.1	Single-Dose Toxicity (in order by species, by route)	A separate single-dose toxicity study with BNT162b2 has not been conducted. Studies using N+1 dosing strategy was incorporated into the repeat dose studies (WHO, 2005).

CTD Section	Title	Reason not included in the dossier
4.2.3.2	Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)	Study report included for BNT162b2 (V8) (Study38166). Dosing phase summary and data report included for BNT162b2 (V9) (Study 20GR142).
4.2.3.3	Genotoxicity	No genotoxicity studies are planned for BNT162b2 as the components of the vaccine constructs are lipids and RNA that are not expected to have genotoxic potential (WHO, 2005).
4.2.3.3.1	In vitro	See above.
4.2.3.3.2	In vivo (including supportive toxicokinetics evaluations)	See above.
4.2.3.4	Carcinogenicity (including supportive toxicokinetics evaluations)	Carcinogenicity studies with BNT162b2 have not been conducted as the components of the vaccine constructs are lipids and RNA that are not expected to have carcinogenic or tumorigenic potential. Carcinogenicity testing is generally not considered necessary to support the development and licensure of vaccine products for infectious diseases (WHO, 2005).
4.2.3.4.1	Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)	See above.
4.2.3.4.2	Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)	See above.
4.2.3.4.3	Other studies	See above.

CTD Section	Title	Reason not included in the dossier
4.2.3.5	Reproductive and Developmental Toxicity (including range-finding studies and supportive TK evaluations)	Reproductive and developmental toxicity assessments are ongoing with BNT162b2 (V9) (Study 20256434). Macroscopic and microscopic evaluation of male and female reproductive tissues from the repeat-dose toxicity study with BNT162b2 (V8) showed no evidence of toxicity (Study 38166).
4.2.3.5.1	Fertility and early embryonic development	See above
4.2.3.5.2	Embryo-fetal development	See above
4.2.3.5.3	Prenatal and postnatal development, including maternal function	See above
4.2.3.5.4	Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.	Pre-weaning evaluations are included in the DART study (Study 20256434) indicated above.
4.2.3.6	Local Tolerance	Local tolerance of IM administration was evaluated in the repeat-dose toxicity studies (Study 38166 and Study 20GR142).
4.2.3.7	Other Toxicity Studies (if available)	See below
4.2.3.7.1	Antigenicity	Immunogenicity was evaluated as part of the primary pharmacology studies and the repeat-dose toxicity study (Study 38166).
4.2.3.7.2	Immunotoxicity	Stand-alone immunotoxicity studies BNT162b2 have not been conducted. However, immunotoxicological endpoints have been collected as part of the repeat-dose toxicity studies (Study 38166 and Study 20GR142).
4.2.3.7.3	Mechanistic studies (if not included elsewhere)	Mechanistic studies with BNT162b2 have not been conducted. Mechanistic studies are generally not required for vaccines (WHO, 2005).
4.2.3.7.4	Dependence	Dependence studies with BNT162b2 have not been conducted. Dependence studies are generally not required for vaccines (WHO, 2005).
4.2.3.7.5	Metabolites	Stand-alone studies with administration of metabolites of BNT162b2 have not been conducted and are generally not required for vaccines (WHO, 2005).
4.2.3.7.6	Impurities	Stand-alone studies with administration of impurities of BNT162b2 have not been conducted.

CTD Section	Title	Reason not included in the dossier
4.2.3.7.7	Other	No other studies with BNT162b2 evaluated in this submission have been conducted.

GLP = Good Laboratory Practice; IV = Intravenous; LCMS = Liquid chromatography mass spectrometry; PK = Pharmacokinetic; TK = Toxicokinetic; WHO = World Health Organization.

REFERENCES:

Study 38166. Engel L. Repeat-Dose Toxicity Study of Three LNP-Formulated RNA Platforms Encoding for Viral Proteins by Repeated Intramuscular Administration to Wistar Han Rats. 01 Jul 2020.

Study 20GR142. Giovanelli M. 17-Day Intramuscular Toxicity Study of BNT162B2 (V9) and BNT162B3C in Wistar Han Rats with a 3-Week Recovery. Study ongoing.

Study 20256434 (RN9391R58). Bouressam M. Combined Fertility and Developmental Study (Including Teratogenicity and Postnatal Investigations) of BNT162b1, BNT162b2 and BNT162b3 by the Intramuscular Route in the Wistar Rat GLP Study. Study ongoing.

PF-07302048_06Jul20_072424. Kraynov E. A Single Dose Pharmacokinetics Study of ALC-0315 and ALC-0159 Following Intravenous Bolus Injection of PF-07302048 Nanoparticle Formulation in Wistar Han Rats. TBD.

World Health Organization. WHO guidelines on nonclinical evaluation of vaccines. Annex 1. In: World Health Organization. WHO technical report series, no. 927. Geneva, Switzerland; World Health Organization; 2005:31-63.