STATISTICAL ANALYSIS PLAN (SAP)
BNT166-01

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Sponsor: BioNTech SE

Protocol number:	BNT166-01
Protocol title:	A randomized, partially observer-blind, dose-escalation, Phase I/II trial evaluating the safety and immunogenicity of investigational RNA-based mpox vaccine candidates
Protocol version:	6.0
Protocol date:	19DEC2024
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CRO name:	ICON plc, South County Business Park, Leopardstown, Dublin 18, D18 X5R3, Ireland
SAP author:	PPD

Prepared at ICON Clinical Research by:

Signed by:
PPD
Signer Name: PPD
Signing Reason: I approve this document
PPD
PPD

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Date

Reviewed at ICON Clinical Research by:

Signed by:
PPD
Signer Name: PPD
Signing Reason: I approve this document
PPD
PPD

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Date

Approved at BioNTech by:

Signed by:
PPD
Signer Name: PPD
PPD
PPD
PPD
Signer Name: PPD
Signing Reason: I approve this document
PPD
PPD

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Date

Signiert von:
PPD
Name des Unterzeichners: PPD
Signiergrund: Ich genehmige dieses Dokument
PPD
PPD

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SAP APPROVAL

This Statistical Analysis Plan (SAP) has been prepared, reviewed, and approved in accordance with the ICON standard operating procedure (SOP). Documentation of this process is filed in the trial master file (TMF).

1 VERSION HISTORY

Table 1: SAP Version history summary

SAP version	Version date	Change	Rationale
V1.0	02FEB2024	N/A	Original version
V2.0	08MAY2024	Changes throughout to reflect CTP 4.0 (except Substudy D) Addition of immunogenicity analysis section	Release of CTP 4.0
V3.0	10DEC2024	Changes throughout to include substudy D Update per CTP v5.0 Removal of 'solicited' terminology from IMP reactogenicity section(s). Addition of information on local and systemic section regarding reconstruction of reactogenicity data based on AE forms. Addition of clarification about immunogenicity analysis in analysis set section. More details added on analysis and grace period consideration in general section. Additional analysis of immunogenicity data added based on orthopoxvirus infection. Sensitivity analysis added in seroresponse section and corresponding definition.	Addition of Substudy D Release of CTP 5.0 Reconstructed reactogenicity events will be analyzed together with the events reported in the ediary as per FDA Guidance Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials Clarifications added based on learnings from first interim analysis. Additional analyses

V4.0	17APR2026	Changes throughout to reflect CTP v6.0 Replaced ‘subject’ with ‘participant’ throughout the document. Replaced ‘study’ with ‘trial’ throughout the document. In section 8.6.2 visits to be analyzed for each neutralizing antibody titers /antigen-specific antibody titers have been added in the table. Section 10.1 Appendix 1: Changes to protocol-planned analyses have been updated Clarification of safety analysis reporting and minor changes to section 8.5. Clarification of scope and timing of interim and final analysis in section 4.	Release of CTP v6.0 Updates to terminology Based on the decision from the sponsor Based on above changes Improvement of precision and alignment with other studies Clarification

2 INTRODUCTION

This is a randomized, partially observer-blind, dose-escalation, Phase I/II trial evaluating the safety and immunogenicity of investigational RNA-based mpox (monkeypox) vaccine candidates. This SAP describes the detailed procedures for the planned statistical analyses for protocol BNT166-01, version 6.0 dated 19th Dec 2024, to support the completion of the Clinical Study Report (CSR). This SAP includes the details of the presentation and analysis of data from the main trial and for analysis of data for the Internal Review Committee (IRC), and any applicable interim analyses. The tables, listings and figures shells for the trial will be presented in a separate Data Presentation Plan document(s).

The statistical analyses will be conducted by ICON clinical research using SAS® software Version 9.4 or higher.

2.1 Objectives and endpoints

The outcome measures and endpoints corresponding to the primary, secondary and exploratory objective for each Substudy are described in Table 2, Table 3 and Table 4.

Table 2: Objectives, outcome measures and endpoints – Substudy A

OBJECTIVES	OUTCOME MEASURES	ENDPOINTS
Primary objectives		
To describe the reactogenicity after one and two doses of each multivalent vaccine candidate.	For every group: • Proportion (%) of participants reporting solicited local reactions at the injection site from Dose 1 through Day 7 post-Dose 1 inclusive; and from Dose 2 through Day 7 post-Dose 2 inclusive. • Proportion (%) of participants reporting solicited systemic reactions from Dose 1 through Day 7 post-Dose 1 inclusive; and from Dose 2 through Day 7 post-Dose 2 inclusive.	• Solicited local reactions (pain, erythema / redness, induration / swelling) • Solicited systemic reactions (vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, and fever)
To describe the safety after one and two doses of each multivalent vaccine candidate.	For every group: • Proportion (%) of participants with at least one unsolicited AE occurring from Dose 1 through Day 28 post-Dose 1 inclusive. • Proportion (%) of participants with at least one unsolicited AE occurring from Dose 2 through Day 28 post-Dose 2 inclusive. • Proportion (%) of participants with at least one SAE occurring from Dose 1 through Day 201 post-Dose 1 inclusive. • Proportion (%) of participants with at least one AESI occurring from Dose 1 through Day 201 post-Dose 1 inclusive.	• Unsolicited AEs, SAEs and AESIs recorded by the investigator.
Exploratory objectives		
To describe the neutralizing antibody responses against vaccinia and mpox viruses elicited by each multivalent vaccine candidate.	For every group at 2 weeks after Dose 2: • Geometric mean titers. • Geometric means fold rise from baseline (pre-Dose 1). • Proportion (%) of participants with seroresponse[a].	• Vaccinia-specific neutralizing antibody levels. • MPXV-specific neutralizing antibody levels.
To describe the kinetics and specificities of humoral immune responses induced by vaccination with each multivalent vaccine candidate.	For every group, at all assessed timepoints: • Geometric mean titers.	• Vaccinia-specific and MPXV-specific neutralizing antibody levels. • Multivalent vaccine candidate antigen-specific binding antibody levels.

a. Seroresponse is defined as seropositivity after baseline for participants who were seronegative at baseline or two-fold or more increase of the antibody titer compared to the baseline titer for participants with a pre-existing antibody titer (Pittman et al.2019).

Abbreviations: AE = adverse event; AESI = adverse event of special interest; MPXV = monkeypox virus; SAE = serious adverse event.

Table 3: Objectives, outcome measures and endpoints – Substudy B

OBJECTIVES	OUTCOME MEASURES	ENDPOINTS
Primary objectives		
To describe the reactogenicity after one and two doses of each multivalent vaccine candidate.	For every group: • Proportion (%) of participants reporting solicited local reactions at the injection site from Dose 1 through Day 7 post-Dose 1 inclusive; and from Dose 2 through Day 7 post-Dose 2 inclusive. • Proportion (%) of participants reporting solicited systemic reactions from Dose 1 through Day 7 post-Dose 1 inclusive; and from Dose 2 through Day 7 post-Dose 2 inclusive.	• Solicited local reactions (pain, erythema / redness, induration / swelling) • Solicited systemic reactions (vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, and fever)
To describe the safety after one and two doses of each multivalent vaccine candidate.	For every group: • Proportion (%) of participants with at least one unsolicited AE occurring from Dose 1 through Day 28post-Dose 1 inclusive. • Proportion (%) of participants with at least one unsolicited AE occurring from Dose 2 through Day 28 post-Dose 2 inclusive. • Proportion (%) of participants with at least one SAE occurring from Dose 1 through Day 201 post-Dose 1 inclusive. • Proportion (%) of participants with at least one AESI occurring from Dose 1 through Day 201 post-Dose 1 inclusive.	• Unsolicited AEs, SAEs and AESIs recorded by the investigator.

OBJECTIVES	OUTCOME MEASURES	ENDPOINTS
Exploratory objectives		
To describe the neutralizing antibody responses against vaccinia and mpox viruses elicited by each multivalent vaccine candidate.	<u>For every group at 2 weeks after Dose 2:</u> • Geometric mean titers. • Geometric means fold rise from baseline (pre-Dose 1). • Proportion (%) of participants with seroresponse[a].	• Vaccinia-specific neutralizing antibody levels. • MPXV-specific neutralizing antibody levels.
To describe the kinetics and specificities of humoral immune responses induced by vaccination with each multivalent vaccine candidate.	<u>For every group, at all assessed timepoints:</u> • Geometric mean titers.	• Vaccinia-specific and MPXV-specific neutralizing antibody levels. • Multivalent vaccine candidate antigen-specific binding antibody levels.

a. Seroresponse is defined as seropositivity after baseline for participants who were seronegative at baseline or twofold or more increase of the antibody titer compared to the baseline titer for participants with a pre-existing antibody titer (Pittman et al.2019).

Abbreviations: AE = adverse event; AESI = adverse event of special interest; MPXV = monkeypox virus; SAE = serious adverse event.

Table 4: Objectives, outcome measures and endpoints – Substudy D

OBJECTIVES	OUTCOME MEASURES	ENDPOINTS
Primary objectives		
To describe the reactogenicity after one and two doses of the multivalent vaccine candidate BNT166a.	• Proportion (%) of participants reporting solicited local reactions at the injection site from Dose 1 through Day 7 post-Dose 1 inclusive; and from Dose 2 through Day 7 post-Dose 2 inclusive. • Proportion (%) of participants reporting solicited systemic events from Dose 1 through Day 7 post-Dose 1 inclusive; and from Dose 2 through Day 7 post-Dose 2 inclusive.	• Solicited local reactions (pain, erythema / redness, induration / swelling) • Solicited systemic events (vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, and fever)
To describe the safety after one and two doses of the multivalent vaccine candidate BNT166a.	• Proportion (%) of participants with at least one unsolicited AE occurring from Dose 1 through Day 28 post-Dose 1 inclusive. • Proportion (%) of participants with at least one unsolicited AE occurring from Dose 2 through Day 28 post-Dose 2 inclusive. • Proportion (%) of participants with at least one SAE occurring from Dose 1 through Day 201 post-Dose 1 inclusive.	• Unsolicited AEs, SAEs and AESIs recorded by the investigator.

OBJECTIVES	OUTCOME MEASURES	ENDPOINTS
	• Proportion (%) of participants with at least one AESI occurring from Dose 1 through Day 201 post-Dose 1 inclusive.	
Exploratory objectives		
To describe the neutralizing antibody responses against vaccinia and mpox viruses elicited by the multivalent vaccine candidate BNT166a.	<u>At 2 weeks after Dose 2:</u> • Geometric mean titers. • Geometric means fold rise from baseline (pre-Dose 1). • Proportion (%) of participants with seroresponse [a].	• Vaccinia-specific neutralizing antibody levels. • MPXV-specific neutralizing antibody levels.
To describe the kinetics and specificities of humoral immune responses elicited by the multivalent vaccine candidate BNT166a.	<u>At all assessed timepoints:</u> • Geometric mean titers	• Vaccinia-specific neutralizing antibody levels. • MPXV-specific neutralizing antibody levels. • BNT166a antigen-specific binding antibody levels.

a. Seroresponse is defined as seropositivity after baseline for participants who were seronegative at baseline or two-fold or more increase of the antibody titer compared to the baseline titer for participants with a pre-existing antibody titer (Pittman et al.2019).

Abbreviations: AE = adverse event; AESI = adverse event of special interest; d = day; IMP = investigational medicinal product; mpox = monkeypox; MPXV = mpox virus; SAE = serious AE.

2.2 Trial design

The trial design is shown below in Table 5, Table 6 and Table 7 with graphical representation shown in section 2.3.

This study was originally planned as a randomized, partially observer-blind, dose-escalation, Phase I/II trial evaluating the safety, tolerability, reactogenicity and immunogenicity of investigational RNA-based multivalent vaccine candidates for active immunization against mpox. Since the groups to be dosed with BNT166c were never activated and Substudy C was removed from the trial, observer-blind and randomization elements of the trial have been removed so that this trial is an open-label trial.

This trial was originally planned to include four substudies. Since Substudy C was removed from the trial, this trial thus includes three substudies. Some substudies may be conducted in parallel, as required by the clinical plan, within the framework of the protocol..

Table 5: Trial Design – Substudy A

Substudy design	Substudy A is an open-label, dose-escalation, Phase I substudy to assess the reactogenicity, safety and immunogenicity of up to three dose levels of two multivalent vaccine candidates. This substudy will enroll ~64 healthy participants with no prior history of known or suspected smallpox vaccination (vaccinia-naïve participants). Vaccine candidate BNT166a will be evaluated at 10 (Group A1), 30 (Group A2), and 60 µg (Group A4) dose levels. Vaccine candidate BNT166c will be evaluated at 30 µg dose level (Group A3). Two doses will be given ~31 days (d) apart. The Groups A2 and A3 will be run simultaneously and, therefore, allocation to treatment for these two groups will be randomized. The sponsor may decide not to activate the group with BNT166c (Group A3), in this case there will be no randomization. Accordingly, the sponsor has decided not to activate Group A3. This substudy will inform Substudy D on the preferred dose level. Dosing in Substudy A will be initiated at dose level 10 µg in Group A1 with the dosing of the first four sentinel participants. These participants will be dosed at least 1 hour (h) apart. Provided that during 48 h after the fourth participant was dosed no group pausing rules (see Section 7.1 of protocol) are met and there are no safety findings judged by the sponsor or investigator to be of clinical concern, the next 12 participants will be dosed. Once all 16 participants of Group A1 have completed the 7 days (d) follow-up post-Dose 1, all available 7 d reactogenicity and safety data (including symptom-directed physical examination, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory data) will be reviewed by the trial IRC. If the trial IRC considers the reactogenicity and safety profile to be acceptable and no pausing rules are met, dosing will be opened for the next dose level (Groups A2 and A3).

	Dosing on the next dose level 30 µg will be initiated with four sentinel participants in Group A2 and four sentinel participants in Group A3. These participants will be dosed at least 1 h apart. Provided that during 48 h after the last participant was dosed no group pausing rules are met and there are no safety findings judged by the sponsor or investigator to be of clinical concern, the next 12 participants in Group A2 and 12 participants in Group A3 will be dosed. Once all 32 participants of Groups A2 and A3 have completed the 7 d follow-up post-Dose 1, all available 7 d reactogenicity and safety data (including symptom-directed physical examination, vital signs, 12-lead ECG, and clinical laboratory data) will be reviewed by the trial IRC. If the trial IRC considers the reactogenicity and safety profile to be acceptable and no pausing rules are met, dosing will be opened for the next dose level (Group A4). Dosing on the next dose level 60 µg will be initiated with four sentinel participants in Group A4. These participants will be dosed at least 1 h apart. Provided that during 48 h after the fourth participant was dosed no group pausing rules are met and there are no safety findings judged by the sponsor or investigator to be of clinical concern, the next 12 participants will be dosed. Provided no pausing rules are met, participants who received Dose 1 will proceed to receive Dose 2. If a pausing rule is met, administration of Dose 2 will be paused, pending trial IRC review of all available reactogenicity and safety data, and IRC endorsement of progression to Dose 2. Trial IRC review may be performed at any timepoint if there are any safety concerns. The IRC may decide to stop investigational medicinal product (IMP) administration to other participants in a particular group. The conduct of screening activities will be independent of the planned trial IRC reviews.
Substudy population	The trial population will be healthy participants with no prior history of known or suspected smallpox vaccination (vaccinia-naïve participants).
Geographic regions	Multiple sites in United Kingdom (UK) and the United States of America (US)
Investigational medicinal product	Dose: RNA-based mpox vaccines. Each multivalent vaccine candidate includes up to four monovalent RNA-LNP components (monovalent drug product [DP]). Each monovalent DP contains an LNP-encapsulated RNA encoding mpox virus protein (antigen). Each RNA is purified single-stranded, 5'capped N1-methylpseudouridine modified ("nucleoside-modified") RNA produced by *in vitro* transcription from a DNA template. Two candidates are listed below together with the mpox antigens targeted by each included monovalent DP: • BNT166a: antigens B6, A35, M1, and H3. • BNT166c: antigens B6, A35, and M1.

	Schedule: Two intramuscular (IM) doses of the multivalent vaccine candidate, one at Visit 1 (Day 1) and one at Visit 5 (Day 31). • BNT166a: 10 µg, 30 µg, and 60 µg • BNT166c: 30 µg Route of administration: IM; injections should be in the deltoid muscle, using the same non-dominant arm for all IMP doses.
Treatment and Substudy duration	The duration of trial participation will be ~14 months per participant. The substudies in this trial comprise of an ~4-week screening period and then an ~56 week assessment period with two visits with IMP administration and follow-up for up to 12 month after the last IMP dose.
Planned number of participants	In each group (A1, A2, A3, A4), 16 healthy participants.
Randomization and blinding	Randomization: Substudy A is an open-label, dose-escalation substudy. Trial participants will be assigned to receive trial treatment according to the assigned vaccine dose group. Blinding: Substudy A is an open-label substudy, site personnel will be aware of assigned treatment and dose.
Other features	An IRC will provide medical oversight of trial participant safety during the conduct of this trial, with a focus on guidance, management of emergent safety issues, and decision-making as outlined in the IRC charter. Since the BNT166 multivalent vaccine candidates will be evaluated for the first time in humans, this trial will be initiated with the dose-escalation Substudy A. Dosing in each substudy will start with an initial sentinel group, pausing rules will be followed, and there will be ongoing monitoring by a trial IRC that may pause, permanently discontinue administration of trial treatment, or even permanently terminate the trial at any point of time. A staggered participant dosing will be utilized in Substudies A, and B.

Table 6: Trial Design – Substudy B

Substudy design	Substudy B is a randomized, observer-blinded and sponsor-unblinded Phase I substudy to assess the reactogenicity, safety and immunogenicity of two multivalent vaccine candidates. This substudy will enroll ~32 healthy participants with prior history of smallpox vaccination (vaccinia-experienced). The smallpox vaccination status will be determined based on the medical record of vaccination before 1980 or the presence of the smallpox vaccination characteristic scar. Both multivalent vaccine candidates will be evaluated at 30 µg dose levels, two doses will be given ~31 d apart. Participants will be randomized 1:1. The sponsor may decide not to activate one of the groups, in that case this substudy will be a one group open-label substudy. Accordingly, the sponsor has decided not to activate Group B2, which was planned to be dosed with vaccine candidate BNT166c.

	Dosing in Substudy B will be initiated once the trial IRC deems the 7 d follow-up post-Dose 1 reactogenicity and safety data of the 10 µg Group of Substudy A participants are acceptable. The first four sentinel participants (two participants in each group) will be dosed at least 1 h apart. Provided that during 48 h after the last participant was dosed no group pausing rules (see Section 7.1 of protocol) are met and there are no safety findings judged by sponsor or investigator to be of clinical concern, the next four participants will be dosed. Once the first eight participants have completed the 7 d follow-up post-Dose 1, all available 7 d reactogenicity and safety data (including symptom-directed physical examination, vital signs, 12-lead ECG, and clinical laboratory data) will be reviewed by trial IRC. If the trial IRC considers the reactogenicity and safety profile to be acceptable and no pausing rules are met, dosing of the next 24 participants will start. Provided no pausing rules are met, participants who received Dose 1 will proceed to receive Dose 2. If a pausing rule is met, administration of Dose 2 will be paused, pending trial IRC review of all available reactogenicity and safety data, and trial IRC endorsement of progression to Dose 2. Trial IRC review may be performed at any timepoint if there are any safety concerns. The trial IRC may decide to unblind the treatment for affected participant(s), and/or to stop IMP administration to other participants in a particular group. The conduct of screening activities will be independent of the planned trial IRC reviews.
Substudy population	The inclusion of healthy participants with prior history of smallpox vaccination (vaccinia-experienced participants) in Substudy B.
Geographic regions	Multiple sites in United Kingdom (UK) and the United States of America (US)
Investigational medicinal product	Dose: RNA-based mpox vaccines. Each multivalent vaccine candidate includes up to four monovalent RNA-LNP components (monovalent DP). Each monovalent DP contains an LNP-encapsulated RNA encoding mpox virus protein (antigen). Each RNA is purified single-stranded, 5'capped N1-methylpseudouridine modified ("nucleoside-modified") RNA produced by *in vitro* transcription from a DNA template. The two candidates are listed below together with the mpox antigens targeted by each included monovalent DP: • BNT166a: antigens B6, A35, M1, and H3. • BNT166c: antigens B6, A35, and M1. Schedule: Two IM doses of the multivalent vaccine candidate, one at Visit 1 (Day 1) and one at Visit 5 (Day 31). • BNT166a: 30 µg • BNT166c: 30 µg

	Route of administration: IM; injections should be in the deltoid muscle, using the same non-dominant arm for all IMP doses.
Treatment and Substudy duration	The duration of trial participation will be ~14 months per participant. The substudies in this trial comprise of an ~4-week screening period and then an ~56 week assessment period with two visits with IMP administration and follow-up for up to 12 month after the last IMP dose.
Planned number of participants	In each group (B1 and B2), 16 healthy participants.
Randomization and blinding	Randomization: Substudy B is an observer blind, randomized trial. Trial participants will be assigned to receive trial treatment according to the assigned vaccine dose group. Blinding: Substudy B is an observer-blind, such that only site personnel receiving, storing, dispensing, preparing, and administering the trial treatment will be unblinded. All other site personnel, including the investigator(s), investigator staff, will be blinded to participants' assigned trial treatment. In particular, the individuals who perform participants' assessments and/or evaluate trial participant safety will be blinded. For Substudy B, the investigator(s) will assign the responsibility of the unblinded dispenser/administrators to site personnel who will not participate in the evaluation of any trial participant. To ensure adequate coverage, at least two unblinded dispenser/administrators will be assigned per site. Site personnel or pharmacy personnel should fulfill these roles. Contact between the unblinded dispenser/administrator and trial participants should be kept to a minimum. The investigator, trial coordinator, and any site personnel other than the unblinded dispensers/administrators must not be allowed to know the trial treatment assigned to any trial participant and must not be allowed to see the trial treatment and any containers. The sponsor may decide to not to activate one of the groups, in that case this substudy will be a one group open-label substudy. Accordingly, the sponsor has decided not to activate Group B2, which was planned to be dosed with vaccine candidate BNT166c.
Other features	As per Substudy A

Table 7: Trial Design – Substudy D

Substudy design	Substudy D is a one group, open-label, Phase IIa substudy to assess the safety, reactogenicity, and immunogenicity of one dose level of the multivalent vaccine candidate BNT166a. This substudy will enroll ~32 healthy participants with no prior history of known or suspected smallpox vaccination (vaccinia-naïve

	participants). Vaccine candidate BNT166a will be evaluated at a dose level of 60 µg. Two doses will be given ~31 d apart. Substudy D will be initiated after the interim analysis of Substudies A and B 1 month post-Dose 2 safety, reactogenicity, and immunogenicity data (from all participants who completed their Visit 9). This interim analysis will inform on the dose for Substudy D. If the safety, reactogenicity, and immunogenicity profile was assessed as acceptable and no pausing rules (see Section 7.1 of protocol) were met in Substudies A and B, Substudy D may be initiated. Trial IRC review will continue to be performed on a regular basis and may be performed at any timepoint if there are any safety concerns. The trial IRC may decide to stop IMP administration to other participants.
Substudy population	The trial population will be healthy participants with no prior history of known or suspected smallpox or mpox vaccination (vaccinia-naïve participants) or Orthopoxvirus infection.
Geographic regions	Multiple sites in United Kingdom (UK) and the United States of America (US)
Investigational medicinal product	Dose: RNA-based mpox vaccine. The multivalent vaccine candidate includes four RNA components formulated as LNPs. The multivalent DP contains LNP-encapsulated RNAs encoding mpox virus proteins (antigens). Each RNA is purified single-stranded, 5'-capped N1-methylpseudouridine modified ("nucleoside-modified") RNA produced by *in vitro* transcription from a DNA template. The mpox antigens targeted by the multivalent DP are B6, A35, M1, and H3 Schedule: Two intramuscular doses of the multivalent vaccine candidate, one at Visit 1 (Day 1) and one at Visit 6 (Day 31). Route of administration: Injections should be in the deltoid muscle, using the same non-dominant arm for all IMP doses.
Treatment and Substudy duration	The duration of trial participation will be ~1 months per participant. The Substudies in this trial comprise of an ~4-week screening period and then an ~56 week assessment period with two visits with IMP administration and follow-up for up to 12 month after the last IMP dose.
Planned number of participants	32 healthy participants will be enrolled
Randomization and blinding	Randomization: Substudy D is an open-label substudy. Blinding: Substudy D is an open-label substudy, site personnel will be aware of assigned treatment and dose.
Other features	As per Substudy A.

Per the protocol V4.0, the sponsor has decided not to activate BNT166c. Therefore, the remainder of the SAP focuses on BNT166a alone.

For an overview of the treatment groups and trial treatments, see Table 8.

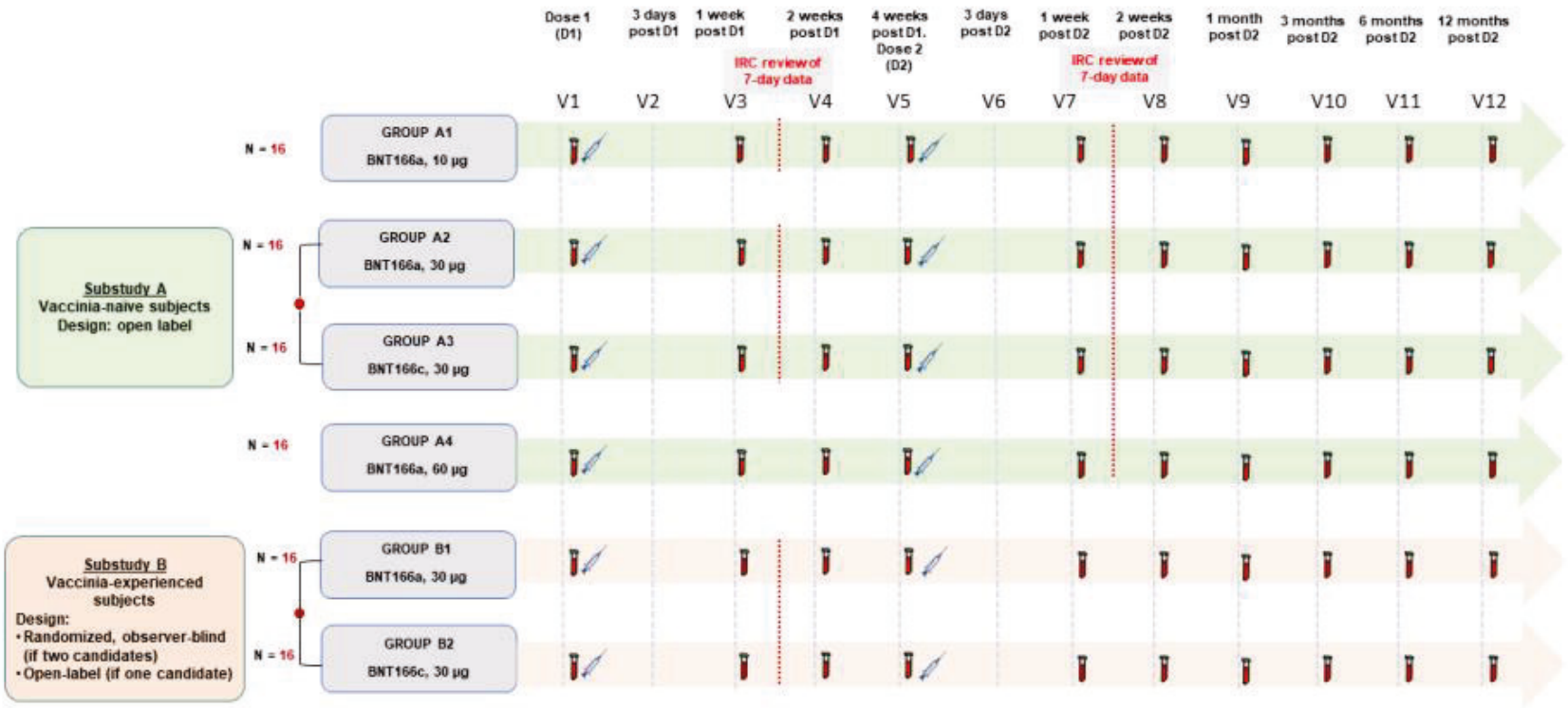
Table 8: Overview of treatment groups, populations, and trial treatments

Substudy	Group	Population[a]	IMP	Dose	Dosing route	No. of participants	Blinding
A	A1	Vaccinia-naïve	BNT166a	10 µg	IM	16	Open-label
	A2	Vaccinia-naïve	BNT166a	30 µg	IM	16	
	A4	Vaccinia-naïve	BNT166a	60 µg	IM	16	
B	B1	Vaccinia-experienced	BNT166a	30 µg	IM	16	Open-label
D	D1	Vaccinia-naïve	BNT166a	60 µg [b]	IM	32	Open-label

a) Vaccinia-naïve = no prior history of known or suspected smallpox vaccination. Vaccinia-experienced = medical record of vaccination before 1980 or the presence of the smallpox vaccination characteristic scar.
b) The dose was selected based on Substudy A and Substudy B data.
Abbreviations: IM = intramuscular; IMP = investigational medicinal product;

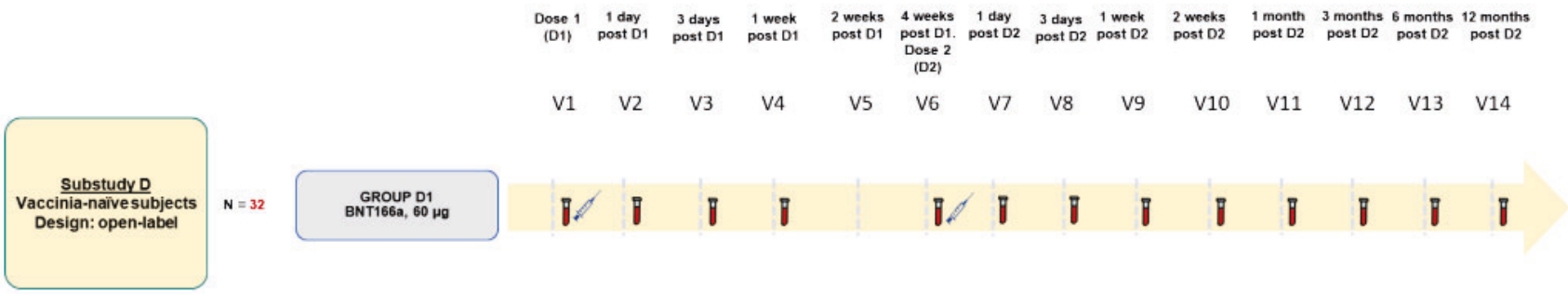
2.3 Schema (graphical representation of the trial)

Figure 1: Graphical representation of the trial – Substudies A and B



Notes: Syringes indicate vaccination. Blood vials indicate blood draws.
Per protocol V4.0, the sponsor has decided not to activate BNT166c. Therefore, cohorts A3 and B2 can be ignored.
Abbreviations: D = dose; IRC = Internal Review Committee; N = number of participants; V = visit.

Figure 2: Graphical representation of the trial – Substudy D

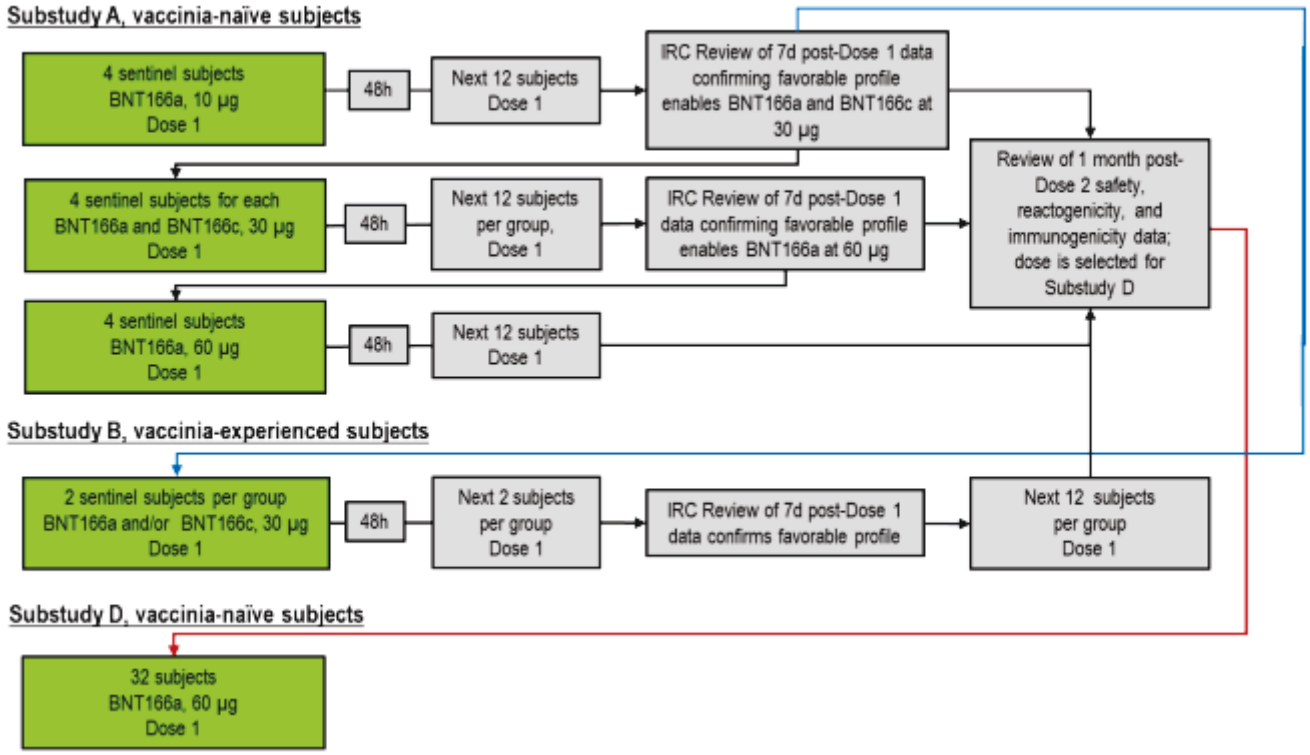


Notes: Syringes indicate vaccination. Blood vials indicate blood draws.

Abbreviations: D = dose; N = number of participants; V = visit.

Figure 3: The dosing scheme for Substudies A, B and D

This trial will use a staggered dosing process including dose-escalation for Substudy A and a staggered dosing process for Substudy B. For a graphical depiction of the dosing process for all substudies, see Figure 3 below.



Abbreviations: d = day(s); h = hour(s); IRC = Internal Review Committee

Note: The blue line indicates that the start of Substudy B .is dependent on IRC confirmation of a favorable safety profile in Substudy A. The red line indicates that the start of the Substudy D and the dose administered in this substudy is dependent on a review of data from Substudies A and B.

2.4 Schedule of activities

See section 10.4 Appendix 4 for the schedule of activities for each substudy.

3 STATISTICAL HYPOTHESES

There is no formal statistical hypothesis under test for any substudy.

4 INTERIM ANALYSES AND ANALYSIS SEQUENCE

Interim analyses of Substudies A and B will be performed at 1 month post-dose 2 for the safety, reactogenicity and immunogenicity data to inform further clinical development and to select the dose for Substudy D. An interim analysis of Substudy D 1 month post-Dose 2 safety, reactogenicity, and immunogenicity data will also be performed to inform further clinical development. Interim analyses may also be prepared at other timepoints e.g., after each substudy is concluded. Outputs, if any, to be provided will be agreed in separate documentation e.g. an agreed list of tables.

A final analysis combining of Substudy A, B and D will be performed once all participants have completed the last planned visit.

Analysis outputs to support the IRC will also be produced as required by the review schedule of the IRC. Further details can be found in the IRC charter for the trial.

5 SAMPLE SIZE DETERMINATION

No formal sample size calculations have been performed. The sample size for each group is mainly driven by typical first in human Phase I designs for the early detection of potential safety and reactogenicity events, and is considered adequate to support the trial objectives, while minimizing the number of trial participants exposed to an IMP. The probability of observing at least one AE for a given true event rate of 10% is 81.5% in 16 participants per group in Substudies A and B participants. For Substudy D, the probability of observing at least one AE for a given true event rate of 10% is 96.6% in 32 participants. The sample size of 32 participants in Substudy D has been chosen to provide supporting information regarding the immunogenicity of the IMP.

Permanently discontinued participants will not be replaced in the trial.

6 RANDOMIZATION AND BLINDING

6.1 Randomization

Since the sponsor has decided not to activate Group A3, Substudy A is an open-label, dose-escalation substudy. There are therefore now no further randomization requirements for this trial.

Since the sponsor has decided not to activate Group B2, Substudy B is a one group open-label substudy. There are therefore now no further randomization requirements for this trial.

Substudy D is a one group, open-label, Phase IIa substudy.

6.2 Blinding and unblinding

Substudy A is an open-label, dose-escalation substudy.

Since the sponsor has decided not to activate Group B2, Substudy B is a one group open-label substudy.

Substudy C is observer-blinded and sponsor-unblinded substudy in the study but was removed. There are therefore now no blinding/unblinding requirements for this trial.

Substudy D is a one group, open-label, Phase IIa substudy.

7 ANALYSIS SETS AND SUBGROUPS

Data for all participants will be assessed to determine if they meet the criteria for inclusion in each analysis set. All analysis sets will be assessed and documented prior to releasing the database. The below defined analysis sets are applicable for each Substudy A, B and D.

7.1 Analysis sets

Screened Set

All participants who provided informed consent.

Safety Analysis Set

All participants who received at least one dose of the IMP.

Analyses of all safety endpoints will be performed using the Safety Analysis Set and the IMP the participant received.

Immunogenicity Analysis Set 1

All participants who:

- received at least one dose of IMP,
- had a valid immune response assessment within an appropriate window (specified in Appendix 5),
- had no important protocol deviations that can confound immunogenicity data as determined by the sponsor.

Analysis of immunogenicity data based on the Immunogenicity Analysis Set 1 will be using the IMP the participant actually received.

Immunogenicity Analysis Set 2

All participants who:

- received the two doses of IMP,
- had a valid immune response assessment within an appropriate window (specified in Appendix 5),
- had no important protocol deviations that can confound immunogenicity data as determined by the sponsor.

Analysis of immunogenicity data based on the Immunogenicity Analysis Set 2 will be using the IMP the participant actually received.

Clarification: A participant will only be excluded from the Immunogenicity Analysis Set 1 and/or Immunogenicity Analysis Set 2 if the participant had an important protocol deviation that can confound **all** immunogenicity data as determined by the sponsor.

If a participant:

- has an important protocol deviation that can confound **subsequent** immunogenicity data as determined by the sponsor or;
- receives a non-trial Orthopoxvirus vaccination after enrollment,

then the participant will remain in the Immunogenicity Analysis Sets, and only samples before the event will be included in the analysis.

7.2 Protocol deviations

Protocol deviations (PDs) are failures to adhere to the inclusion/exclusion criteria and protocol requirements and will be classified into key (important) PDs and non-key (non-important) PDs for each substudy separately.

All PDs will be assessed and documented prior to releasing the database.

7.3 Subgroups

No subgroup summaries will be performed for any substudy.

8 STATISTICAL ANALYSES

8.1 General considerations

In general, all summaries will be presented by treatment group for each substudy. Where appropriate, data will also be summarized, by dose level and overall, across substudies per multivalent vaccine candidate.

No formal statistical comparisons between treatment group will be performed. Missing data, other than that described for partial or missing dates for AEs/Concomitant Medications/Vaccinations (as described below) will not be imputed.

Continuous variables will be summarized by treatment group using the following descriptive statistics: number of participants with non-missing data (n), mean or geometric mean depending on type of data, standard deviation (SD), median, minimum (min) and maximum (max), unless otherwise stated.

Categorical variables will be summarized by absolute (n) and relative frequencies (percentage [%]) of participants in each category and the number of participants with missing data ('missing' category will be presented if there is one or more missing value).

Analysis of antibody titers will be performed on natural log scale and the results will be exponentiated back to original scale.

For event-driven occurrence data (e.g., AE, concomitant medication, etc.) percentages will be based on the number of participants in the analysis set (N). For reported visit data (e.g., laboratory data etc.) percentages will be based on the number of participants with non-missing values.

The rates of binary endpoints might be provided along with the corresponding 2-sided 95% confidence intervals (CIs) using the exact method (Clopper-Pearson), as applicable.

All data collected during the trial will be listed based on Safety Analysis Set unless otherwise specified. For Substudy A, the data will be sorted by increasing vaccine dose level Within each of these categories (and for Substudy B and D), the data will be further sorted by site number, participant number, and date of assessment (if applicable).

All trial data will be presented at the visit assigned in the Case Report Form (CRF)/visit assigned in external data, as applicable. Any data collected at unscheduled visits (unless used for deriving baseline or immunogenicity data) will be listed only and will not be included in any summaries/analysis.

For all immunogenicity analyses, grace periods are defined to allow extended visit windows, please see Appendix 5.

For the first interim analysis of Substudy A and B, samples will be assigned to the grace period in which the samples were collected. However, no samples will be assigned from a pre-dose visit to a post-dose grace period or vice versa. Data collected outside expanded windows specified in Appendix 5 will be excluded from analyses.

For all subsequent analyses of BNT166-01 immunogenicity data, samples will only be assigned to the grace period of their respective visit. Unscheduled visits will be assigned to the grace period in which the sample was collected. Data collected outside expanded windows specified in Appendix 5 will be excluded from analyses of the affected timepoint.

If two samples are assigned to one grace period, the following approach will be taken:

- the non-missing assessment closest to the target visit day will be used.
- If two non-missing post-baseline assessments are equidistant from the target visit day the later sample will be used.

8.1.1 General definitions

The below definitions are applicable for all substudies.

Baseline is defined as last available value prior to first dose of trial IMP. This baseline definition will also be used for the calculation of geometric mean fold rise (GMFR) and Seroresponse.

Change from baseline: Unless otherwise specified, this will be calculated as follows:

Change from baseline = post-baseline assessment value – baseline assessment value.

If either the baseline or post-baseline assessment value is missing, the change from baseline is set to missing as well.

Body mass index (BMI) will be calculated as follows:

$$\text{BMI}\left(\frac{\text{kg}}{\text{m}^2}\right) = \frac{\text{Weight (kg)}}{\text{Height(m)}^2}$$

Temperatures collected in °F will be converted to °C as follows:

$$°C = (°\text{F} - 32) * 5/9$$

Measurements collected in inches will be converted to centimeters (cm) as follows:

$$cm = inches * 2.54$$

Duration will be calculated as follows:

Duration = last observation date – first observation date + 1.

For local/systemic reactions, if an event persists beyond Day 7, the duration of the event will be derived using the start and the end date of the AE (as recorded on the AE electronic CRF page).

For conversion of days to months or years the following rules will be applied:

- 1 month = 30.4375 days
- 1 year = 365.25 days

Trial Day will be calculated as follows:

- If assessment/onset date < date of first trial IMP dose, then trial day = assessment date – date of first trial IMP dose
- If assessment/onset date >= date of first trial IMP dose, then trial day = assessment/onset date – date of first trial IMP dose + 1

That is, trial day 1 indicates the date of first trial IMP dose.

The day relative to dose 2 will be calculated as follows:

- If assessment/onset >= date of second trial IMP dose, then day relative to dose 2 = assessment/onset date – date of second trial IMP dose + 1

8.1.2 Analysis visit

The analysis visits will be defined separately for all Substudies A, B, and D.

For summaries of safety data, laboratory data, vital signs, ECG, and physical exam, the analysis visits post vaccination will be based on the visits reported and validated in the electronic data collection (EDC) database.

For baseline the last available records prior to the date and time of the first dose of IMP will be selected.

8.1.3 Handling missing data

Missing data, other than that described for AEs and concomitant medications will not be imputed.

For the purposes of assigning duration for unsolicited AEs, partial or missing AE dates will be handled as follows:

Onset Date:

- If the day of the month is missing, the onset day will be set to the first day of the month (01MMMYYYY) unless it is the same month and year as the first dose of trial IMP. In this case, the onset date will be assumed to be the date of the first dose of trial IMP.
- If the onset day and month are both missing, the day and month will be assumed to be January 1 of the same year (01JANYYYY) in which the AE was reported, unless the event occurred in the same year as the first dose of trial IMP. In this case the event onset will be assumed to be the day and month of the first dose of trial IMP.
- A completely missing onset date will be assumed to be the date of the first dose of trial IMP.

End Date:

- If the day of the month is missing, the end day will be set to the last day of the month (e.g. 31MMMYYYY).
- If the end day and month are both missing, the day and month will be assumed to be December 31 (e.g. 31DECYYYY).
- A completely missing end date will be assumed to be the minimum of date of trial discontinuation and date of data extract.
- If the imputed end date is less than the onset date, use the onset date as the imputed end date.

For the purposes of assigning prior or concomitant flag for medications/vaccinations, partial or missing medication/vaccination dates will be handled as follows:

- If end day is missing and month/year are non-missing, then day is set to the last day of the month (e.g. 31MMMYYYY).
- If end day/month are missing and year is non-missing, then day is set to the end of the year (e.g.31DECYYYY).
- If imputed end date is less than the start date, use the start date as the imputed end date.
- If the start date year is missing, the start date is set to one day prior to IMP start date.
- If the start date year is less than the trial IMP first dose date, then:
  - If the month is missing, the start date is assumed to be mid-year point (e.g. 01JULYYYY).
  - Else if the month is not missing, the start date is assumed to be mid-month point (e.g. 15MONYYYY).
- If the start date year value is greater than the year of the trial IMP first dose date, then:
  - If the month is missing, the start date is assumed to be the year start point (e.g. 01JANYYYY).
  - Else if the month is not missing, the start date is assumed to be the month start point (e.g. 01MONYYYY).
- If the start date year value is equal to the year of the trial IMP first dose date:
  - If the month is missing or the month is equal to the month of the trial IMP first dose date, then the start date is assumed to be same day as the IMP first dose date.
  - Else if the month is less than the month of the trial IMP first dose date, the start date is assumed to the mid-month point (e.g.15MONYYYY).
  - Else if the month is greater than the month of the trial IMP first dose date, the start date is assumed to be the month start point (e.g.01MONYYYY).

If complete end date is available and the start date assumed from the steps above is greater than the end date, then the assumed start date should be set to the end date.

8.2 Participant disposition

For the Screened Set, the number and percentage of participants that are screen failures will be presented along with a summary of the primary reason for screening failure. Re-screened participants will only be counted once with the reason of their last screening failure. If the last screening was successful, the participant will not be considered a screen failure. A listing of participants that failed inclusion/exclusion criteria will also be presented.

The number of participants screened to each substudy overall, and the number of participants allocated to each dose level will be presented. The number and percentage of the following will be summarized based on the number of participants in the Safety Analysis Set:

Analysis sets:

- Safety Analysis Set
- Immunogenicity Analysis Set 1
- Immunogenicity Analysis Set 2

Disposition:

- Participants receiving Dose 1
- Participants receiving Dose 2
- Participants discontinuing treatment
- Trial completers
- Participants discontinuing trial
    - Participants discontinuing trial after Dose 1 and before Dose 2
    - Participants discontinuing trial after Dose 2 and before 1 month post-Dose 2
    - Participants discontinuing trial after 1 month post-Dose 2

Protocol deviations:

- Participants with important PDs
    - PD Category and sub-category

For each analysis set, the number and percentage of participants excluded from the analysis set will be presented, along with a summary of the reasons for exclusion based on the Screened Set. Non-Key PDs will only be presented in participant listings.

In addition, for participants who discontinued treatment and/or trial, a summary of the primary reason for treatment and/or trial discontinuation as reported in the electronic CRF will be summarized.

8.3 Baseline characteristics

8.3.1 Demographics and baseline characteristics

Demographics and baseline characteristics data will be summarized by the Safety Analysis Set.

Age (years) at time of enrollment will be summarized as continuous data. Sex at birth (male or female), childbearing potential (yes or no), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not reported, Unknown, Other and Multiracial) and Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported and Unknown) will be tabulated as categorical data.

Height (cm), weight (kg) and BMI (kg/m^2) will be summarized descriptively. BMI category (<18.5 kg/m^2, 18.5 - <25.0 kg/m^2, 25.0 - <30 kg/m^2, ≥ 30 kg/m^2) will be summarized with frequency counts and percentage.

8.3.2 Orthopoxvirus medical and vaccination history

Orthopoxvirus medical and vaccination history will be tabulated for the Safety Analysis Set.

The below variables will be summarized descriptively by number of participants and associated percentages:

- Was the participant's prior smallpox vaccination status collected? (Yes/No)
- Does the participant have any prior history of known or suspected mpox vaccination? (Yes/No/Unknown)
- Excluding mpox vaccination, does the participant have any prior history of known or suspected Orthopoxvirus-based vaccination (including vaccines using Orthopoxvirus vectors)? (Yes/No/Unknown)
- Does the participant have any medical record of smallpox vaccination? (Yes/No/Unknown)
- Is the smallpox vaccination characteristic scar present (Present/Absent)
- Anatomical Location of Scar (Left Arm/Right Arm)
- Infection History
  - Mpox (Yes/No)
  - Smallpox (Yes/No)
  - Vaccinia infection (Yes/No)

8.3.3 Prior and concomitant medications/Procedures/Non-drug therapies

Prior and concomitant medications/procedure, including prior vaccinations, will be defined using medication start and stop dates recorded, relative to the first dose of trial treatment.

A medication is considered prior if it started and ended before the date of the first dose of IMP. A medication is considered concomitant if it was ongoing at the time of the first IMP dose or if it was initiated after the first dose of IMP..

Medications will be coded using the World Health Organization Drug Dictionary (WHO DD) drug codes of version B3 March 2023 or later, resulting in Anatomical-Therapeutic-Chemical (ATC) codes indicating therapeutic classification for each medication.

The number and percentage of participants who had prior medications and concomitant medications will be summarized by ATC classification level 4 and preferred name for participants in the Safety Analysis Set. The tabulation will be presented alphabetically by ATC and preferred name within ATC.

Concomitant medications administered due to local and systemic reactions during time interval Day 1 to 7 days post each dose will be tabulated separately.

Concomitant procedures and non-drug therapies will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) coding system version 26.0 or later. Concomitant procedures and non-drug therapies will be listed only.

8.3.4 Medical history

Medical history will be coded using MedDRA® version 26.0 or later. The number and percentage of participants with each medical history and surgery will be tabulated by System Organ Class (SOC) and Preferred Term (PT) for participants in the Safety Analysis Set. The tabulation will be sorted alphabetically by SOC and PT within SOC.

8.4 Efficacy Analysis

There are no efficacy endpoints for this trial.

8.5 Safety Analysis

The primary objective for Substudies A, B and D is to describe the reactogenicity and safety after the first and after the second dose of the multivalent vaccine candidate.

The endpoints used for this are described in Sections 8.5.2, 8.5.2.2, 8.5.3 and 8.5.4 below.

Safety data that will be summarized includes solicited local reactions, solicited systemic reactions, unsolicited AEs, clinical safety laboratory assessments (including Hematology, Clinical chemistry), vital signs, and ECGs.

All safety analyses in Substudies A, B and D, will be based on the Safety Analysis Set. All safety data will be listed.

8.5.1 Extent of exposure

Trial IMP exposure data will be listed for participants in the Safety Analysis Set.

8.5.2 Local Reactions

8.5.2.1 Local Reactions

Local reactions assessed and reported in the e-diary are pain, erythema/redness, and induration/swelling at the injection site. The local reactions are assessed in the e-diary from Day 1 through Day 7 after each trial IMP dose, where Day 1 is the day of each IMP injection.

A participant is deemed to have had a local reaction if they report the reaction as “yes” on any day (Day 1 through Day 7).

Local reactions will be categorized as mild, moderate, severe or potentially life-threatening and graded from 1 to 4, as described in Table 9. The categories and grades are based on the United States Food and Drug Administration (FDA) Guidance for Industry: “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” (US FDA 2007).

Any local reaction of Grade 3 or higher will be confirmed by the investigator. Any assessment of erythema/redness and induration/swelling not captured in cm will be converted and rounded to 1 decimal place prior to severity grading in cm.

Table 9: Local reaction grading scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)[a]	Potentially life-threatening (Grade 4)[a]
Pain at the injection site	Does not interfere with activity	Interferes with Activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Erythema / redness	2.5 cm to 5.0 cm	>5.0 cm to 10.0 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration / swelling	2.5 cm to 5.0 cm	>5.0 cm to 10.0 cm	>10 cm	Necrosis

a Investigator or medically qualified person confirmation is required.
Source: Modified from the US FDA guidance (US FDA 2007)

For each local reaction mentioned in Table 9:

- The maximum severity grade is equal to the highest graded local reaction within the respective period. In case of a discrepancy between the participant and investigator assessment of severity, the confirmed assessment of the investigator will be used for analyses and a comment in the listings will be provided explaining the discrepancy.
- Duration is defined as (last day of last solicited reaction within 7 days post-dose – first day of first solicited reaction within 7 days post-dose + 1).
- For events that persist beyond Day 7, the duration of the reactogenicity event will be derived using the start and the end date of the AE (as recorded on the AE page).
- Onset day, defined as the first day of reporting any severity, will be derived for each recorded local reaction.

A safety overview summary will include the participants with

- Any local reaction within 7 days post-dose
- Any local reaction with Grade ≥3 within 7 days post-dose
- Any local reaction within 7 days post-dose, overall, regardless of dose
- Any local reaction with Grade ≥3 within 7 days post-dose, overall, regardless of dose

The number and percentage of participants reporting local reactions (pain at the injection site, erythema/redness, induration/swelling) within 7 days after each dose will be tabulated by maximum severity and cumulatively across severity levels. The summary will include categories “Any”, “Grade 1”, “Grade 2”, “Grade 3”, and “Grade 4”.

The Safety Analysis Set will be used for local reaction summaries. Data will be summarized based on the number of participants who received the respective dose.

In addition, local reactions of at least Grade 1 will also be summarized (as continuous variables) by:

- Maximum duration (days) of each local reaction after each IMP injection, and overall, across all injections. The number of participants who have a reaction continuing past Day 7 will be presented.
- Onset day of each local reaction after each IMP injection, and overall, across all injections. Onset day is the first day the symptom is reported by the participant in relation to the Dose. For overall reporting, onset day is considered as the first day, regardless of Dose.

For analyses overall across all injections, the participant will only be counted once for each local reaction reported.

Bar charts with the number of participants for each local reaction throughout 7 days after each dose will be plotted. The bars will be divided into severity categories to highlight the number of participants by maximum severity.

Investigators will assess injection site reactogenicity symptoms occurring within 1 hour +/- 15 minutes of injection at the visits given in Section 10.4. Investigators will grade and record local reactions as described in Table 9.

A listing of participants in the Safety Analysis Set, with reported local reactions, will be provided. All participant and investigator data will be listed.

8.5.2.2 Systemic Reactions

The systemic reactions assessed and recorded in the e-diary are fever, chills, fatigue/tiredness, headache, new or worsened muscle pain, new or worsened joint pain, vomiting and diarrhea from Day 1 through Day 7 inclusive, where Day 1 is the day of each IMP injection.

Derivations for systemic reactions will be handled the same way as local reactions are handled for presence of reaction, severity level, duration, and onset day.

Fever is defined as an oral temperature ≥ 38.0°C. Any temperatures collected in degrees Fahrenheit (°F) will be converted to degrees Celsius (°C), and grading will be based upon Celsius as specified in Table 10. The highest oral temperature for each day will be recorded in the e-diary and the temperature from Day 1 through Day 7 will be graded as described in Table 10.

Systemic reactions will be categorized as mild, moderate, severe, or potentially life-threatening and graded from 1 to 4 as described in Table 10.

Any systemic reaction of Grade 3 or higher will be confirmed by the investigator. Any assessment of fever not captured in °C will be converted and rounded to 1 decimal place prior to severity grading in °C.

Systemic reactions (fever, chills, fatigue/tiredness, headache, new or worsened muscle pain, new or worsened joint pain, vomiting and diarrhea) reported within 7 days after each dose will be analyzed in the same manner as local reactions (see Section 8.5.2) using the Safety Analysis Set. Data will be summarized based on the number of participants who received the respective dose.

In addition, listing of participants in the Safety Analysis Set, with reported systemic reactions, will be provided. All participant and investigator data will be listed.

Table 10: Systemic reaction grading scale

	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially life-threatening (Grade 4)** [a]
Vomiting	1 to 2 times in 24 hours	>2 times in 24 hours	Requires intravenous hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Myalgia / muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe Muscle pain
Arthralgia/ Joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe joint pain

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life-threatening (Grade 4) [a]
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
Fever (oral temperature of ≥38.0°C/≥100.4°F)	38.0°C/100.4°F to 38.4°C/101.1°F	38.5°C/101.2°F to 38.9°C/102.0°F	39.0°C/102.1°F to 40.0°C/104.0°F	>40.0°C/>104.0°F

a Investigator or medically qualified person confirmation is required.
Source: Modified from the US FDA guidance (US FDA 2007)

If data regarding local and systemic reactions were not entered into the e-diary as planned, and instead were recorded on the AE CRF page, SDTM data reconstruction will be implemented to align with the FDA guidance outlined in "Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review" dated December 2019.

8.5.3 Adverse events

All unsolicited AE collection will start once informed consent is given and will continue until Visit 9 (1 month post-dose 2). After Visit 9 only adverse event of special interest (AESI) and serious adverse event (SAE) collection will continue until Visit 12 (1 year post-dose 2) or the end of participant participation in the trial.

Local and systemic reactions (i.e., reactogenicity events) that are recorded from trial participants' e-diaries should not be reported as unsolicited AEs unless the reaction meets criteria for an SAE or starts at Days 1 to 7 and continues past Day 7 post trial IMP dose. All solicited AEs will be considered related.

All AEs will be coded using the most recent version of MedDRA® coding system version 26.0 or later to get a SOC and PT for each AE and graded for severity using FDA Guidance for Industry: "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (US FDA 2007). In case a participant has an AE with missing relationship status, the event will be assumed to be related. No imputation for missing grades will be conducted.

If a participant reports multiple AEs by the same SOC, PT and time interval, the participant will be counted once for the SOC, PT and time interval under the maximum severity grade.

AEs are defined as related if the causality assessed by the investigator is reported as related to the trial investigational medicinal product (IMP).

All AE summary tables will be sorted alphabetically by SOC and PT within SOC.

The Safety Analysis Set will be used for analysis of adverse events. Data will be summarized based on the number of participants who received the respective dose for the analysis of the respective time intervals.

Overall summary of adverse events

The number and percentage of participants reporting the below events will be tabulated:

- Unsolicited AEs with onset date from Dose 1 to 28 days after Dose 1, from Dose 2 to 28 days after Dose 2 and overall, *regardless* of dose broken down by:
    - All
    - Related
    - Grade >=3
    - Related and Grade >=3

  Note that this includes all unsolicited AEs and solicited events that persisted 7 days beyond any dose or is an SAE.
- Solicited reactions that persisted beyond 7 days post-Dose 1, 7 days post-Dose 2 and 7 days post-dose, overall, regardless of dose broken down by:
    - All
    - Grade >=3

The number and percentage of participants with AEs leading to treatment discontinuation will be tabulated overall, regardless of dose.

The number and percentage of participants reporting any SAE, MAAE or AESI and separately by SAE, MAAE and AESI will be tabulated overall regardless of dose:

- Any
- Related
- Grade >=3
- Related and Grade >=3

Unsolicited AEs

The number and percentage of participants reporting unsolicited AEs occurring up to Day 28 post each dose for each dose level and overall, regardless of dose, will be summarized separately by grade nested within PT and SOC. This summary will be presented for all and related unsolicited AEs. Also, AEs with a missing grade will be presented in the summary table with a grade category of “Missing”.

Local and systemic reactions that continue longer than 7 days post-dose

The number and percentage of participants with any local or systemic reaction that continues longer than 7 days post each dose will be summarized in the same manner as unsolicited AEs above.

Unsolicited serious and non-serious AEs

SAEs occurring from Dose 1 to Day 201 post-Dose 1 and until the end of trial participation, will be summarized overall, regardless of dose, separately by grade nested within PT and SOC. This summary will be presented for all and related SAE.

Unsolicited AEs leading to treatment discontinuation

The number and percentage of participants with unsolicited AEs leading to treatment discontinuation will be summarized overall, regardless of dose, separately by grade nested within PT and SOC. This summary will be presented for all and related unsolicited AEs. Also, AEs with a missing grade will be presented in the summary table with a grade category of "Missing".

Deaths, MAAEs and AESIs

The number and percentage of participants reporting AESIs occurring from Dose 1 to Day 201 post-Dose 1, AESIs occurring from Dose 1 until end of trial participation, and MAAEs occurring up to Day 28 post each dose will be summarized overall, regardless of dose, by grade nested within PT and SOC. These summaries will be presented for all and related AESIs/MAAEs.

All deaths and reasons for death for the participants in Safety Analysis Set will be listed displaying the days since last dose.

AE listings

All deaths, local and systemic reactions, AEs, SAEs, MAAEs, AESIs, unsolicited AEs leading to treatment discontinuation, and unsolicited AEs leading to death will be presented. Local and systemic reactions that persisted beyond 7 days will be flagged in all unsolicited AE listings.

8.5.4 Laboratory assessments

Hematology, clinical chemistry, urinalysis, immune response monitoring, follicle stimulating hormone (FSH), pregnancy tests and viral screening will be performed by a central laboratory. Summaries of key laboratory data, except urinalysis, will be summarized for the participants in the Safety Analysis Set.

For the purposes of summarizing and presentation in tables and listings, all laboratory values will be presented in System International (SI) units. If a laboratory value is reported using a non-numeric qualifier e.g., less than (<) a certain value, or greater than (>) a certain value, the given numeric value will be used in the summary statistics, ignoring the nonnumeric qualifier. The data as collected will be presented in the listings.

Absolute values in central clinical laboratory variables will be provided by timepoint and parameter using descriptive summary statistics for each parameter listed in the protocol. Additionally, absolute values and change from initial trial IMP baseline (trial baseline) to

each post-baseline visit by parameter will be summarized. Shift tables from the initial trial IMP baseline (trial baseline) to each post-baseline visit will be presented.

Categorical variables will be summarized using n and %.

Lab abnormalities severity will be determined based upon grading from FDA guidance for industry 'Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical trials' (US FDA 2007).

All central and local laboratory data will be presented in the data listings with associated toxicity grades and values that are below or above the normal reference ranges will be flagged.

8.5.5 Vital signs

Vital sign parameters to be summarized include systolic and diastolic blood pressure, pulse rate, respiratory rate and oral body temperature. Body temperature will be presented in degrees Celsius.

Absolute values for vital sign parameters at each visit and change from baseline to each post-baseline visit will be summarized using descriptive summary statistics for each parameter. Vital signs will be collected both pre- and post-IMP administration.

The evaluation of abnormal clinically significant, abnormal not clinically significant, and normal will be listed only.

All vital signs will be presented in data listings and abnormal values will be flagged.

8.5.6 12-Lead Electrocardiogram

12-Lead ECG parameters include Ventricular Heart Rate (beats/unit), PR Interval (millisecond [msec]), QRS Interval (msec), QT Interval (msec) and QTcF Interval (msec).

Absolute values collected at each time-point, and their change from baseline to each post-baseline time-point will be summarized using descriptive summary statistics. In addition, the investigators evaluation at each visit (Normal, Abnormal – not clinically significant and Abnormal – clinically significant) will be tabulated by visit.

All ECG data will be presented in data listings along with investigator evaluation.

8.5.7 Physical Examination

A complete physical examination will be performed at screening visit. At other visits, a symptom-directed examination will be performed.

The results from all physical examinations will be listed only.

8.6 Other analyses

8.6.1 E-diary Transmission

E-diary transmission will be tabulated for the participants in the Safety Analysis Set. The number and percentage of participants transmitting the e-diary each day and for the full 7 days will be presented by IMP dose. The number of participants who did not transmit the diary at all will also be presented.

8.6.2 Immunogenicity analysis

Immunogenicity analyses for secondary and exploratory endpoints will be summarized for each substudy by dose level (10, 30, or 60 µg) for both Immunogenicity Analysis Set 1, and Immunogenicity Analysis Set 2. Only samples that are collected within the pre-defined time windows (Appendix 5) will be included for analysis (see section 8.1). Visits to be analyzed for neutralizing antibody titers /antigen-specific antibody titers are marked as “X” in Table 11.

Table 111: Analysis visits

Visit	Substudy A			Substudy B			Substudy D		
	Antigen	MPXV	VACV	Antigen	MPXV	VACV	Antigen	MPXV	VACV
pre-Dose 1	X	X	X	X	X	X	X	X	X
1 wk after Dose 1	X			X					
2 wk after Dose 1	X			X					
pre-Dose 2	X	X	X	X	X	X	X	X	X
1 wk after Dose 2	X			X			X	X	X
2 wk after Dose 2	X	X	X	X	X	X	X	X	X
1 mo after Dose 2	X	X	X	X	X	X	X	X	X
3 mo after Dose 2	X	X	X	X	X	X	X	X	X
6 mo after Dose 2	X	X	X	X	X	X	X	X	X
1 yr after Dose 2	X	X	X	X	X	X	X	X	X

MPXV = Monkeypox virus; VACV = Vaccinia virus.

8.6.2.1 Monkeypox virus neutralizing antibody titers

Monkeypox virus (MPXV) neutralization measurements will be reported as 50% neutralizing titers. Titers above the lower limit of quantification (LLOQ) are considered accurate and their quantitated values will be reported. Antibody titers below the LLOQ will be set to 0.5 × LLOQ for all analysis if not specified otherwise. Titers above the upper limit of quantification (ULOQ) will be set to ULOQ. Missing data will not be imputed.

Geometric mean titer (GMT) will be computed along with associated 95% CI at each timepoint. Per trial group, the geometric mean of MPXV 50% neutralizing titers will be calculated as the mean of the assay results after taking the natural log scale transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of assay results, calculating the 95% CI with reference to Student's t-distribution, and then exponentiating the confidence limits.

Fold rise will be defined as the result after vaccination divided by the baseline result. GMFRs will be limited to participants with non-missing values at baseline and the protocol defined post-vaccination timepoints. GMFRs of antibody titers will be calculated as the mean of the difference of logarithmically transformed antibody titers (post-dose result minus pre-dose result) and exponentiating the mean. The associated 2-sided 95% CIs are obtained by constructing CIs using Student's t-distribution for the mean difference on the natural log scale and exponentiating the confidence limits.

The number of participants with valid assay results will be presented at baseline and each timepoint post vaccination.

In case a participant gets an Orthopoxvirus infection based on clinical or virological evidence during trial conduct, all tables based on Immunogenicity Analysis Set 2 of the respective substudy will be repeated including only samples of the respective participant that were taken before the Orthopox infection.

Bar charts with overlaid individual data points and line plots with mean and 95% CIs over time by dose level and treatment group for GMT and GMFR will be presented.

8.6.2.2 Vaccinia virus neutralizing antibody titers

Vaccinia virus (VACV) neutralization measurements will be reported as 50% neutralizing titers. This endpoint will be summarized in similar manner to section 8.6.2.1.

8.6.2.3 Electrochemiluminescence assay of BNT166a four antigen-specific antibody titers

An electrochemiluminescence (ECL) assay will measure antibody titers to the four antigens of the candidate vaccine BNT166a (A35, B6, M1, and H3), and results will each be reported in arbitrary units (AU/ml). This endpoint will be summarized in similar manner to section 8.6.2.1. Antibody responses will be presented individually for each of the four antigens.

8.6.2.4 Seroresponse

Seroresponse of each assay (MPXV neutralization, VACV neutralization, or antigen-specific antibody titers) is defined as a ≥2-fold increase from baseline (Visit 1) for participants with a titer above LLOQ at baseline. If the baseline measurement is below LLOQ, measurements will be set to 0.5 x LLOQ and seroresponse will be defined as a rise above LLOQ.

The percentage of participants achieving seroresponse of VACV or MPXV neutralizing antibody or vaccine antigen-specific binding antibody titers will be calculated per trial group and per timepoint, and the associated 2-sided 95% CIs will be obtained by constructing CIs using the Clopper-Pearson method.

The above analysis will be repeated as a sensitivity analysis for the Immunogenicity Analysis Set 2 only using the following definition of seroresponse (for each assay):

A ≥4-fold increase from baseline (Visit 1) for participants with a titer above LLOQ at baseline. If the baseline measurement is below LLOQ, seroresponse will be defined as a rise above 2*LLOQ.

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In case a participant gets an Orthopoxvirus infection based on clinical or virological evidence during trial conduct, all tables based on Immunogenicity Analysis Set 2 of the respective substudy will be repeated including only samples of the respective participant that were taken before the Orthopoxvirus infection.

8.6.3 Additional research analyses

Note in case of further exploratory analysis including additional biomarker analyses respective documentation of these analyses will be generated.

9 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline E3: Note for Guidance on Structure and Content of Clinical Trial Reports (CPMP/ICH/137/95), July 1996. Retrieved on 30 January 2018 from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/96), March 1998. Retrieved on 21 April 2019 from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf
3. Clopper, CJ and Pearson, ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26: 404-413, 1934
4. FDA Guidance 2007. US FDA Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.
5. Pittman PR, Hahn M, Lee HS, et al. Phase 3 Efficacy Trial of Modified Vaccinia Ankara as a Vaccine against Smallpox. N Engl J Med. 2019;381(20):1897-1908.
6. FDA Guidance 2019. US FDA Guidance for Industry. Submitting Study Datasets for Vaccines to the Office of Vaccines Research and Review.

10 SUPPORTING DOCUMENTATION

10.1 Appendix 1: Changes to protocol-planned analyses

For MPXV and VACV specific neutralizing antibody levels, changes to the analysis visits from the protocol planned analysis visits have been detailed in section 8.6.2.

10.2 Appendix 2: List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
AU	Arbitrary Units
BMI	Body Mass Index
CI	Confidence Interval
cm	centimeters
CRF	Case Report Form
CSR	Clinical Study Report
d	Day(s)
DP	Drug Product
ECG	Electrocardiogram
ECL	Electrochemiluminescence
EDC	Electronic Data Collection
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
h	Hour
HIV	Human Immunodeficiency Virus
IM	Intramuscular
IMP	Investigational medicinal product
IRC	Internal Review Committee
IRT	Interactive Response Technology
kg	Kilogram
LNP	Lipid nanoparticle
LLOQ	Lower Limit of Quantification
m2	Meter square
MAAE	Medically Attended Adverse Event
max	Maximum

MedDRA®	Medical Dictionary for Regulatory Activities
min	Minimum
ml	Milliliter
mpox	Monkeypox
MPXV	Monkeypox Virus
msec	millisecond
N	Number of Participants
n	Number of Observations
PD	Protocol Deviation
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Deviation
SoA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedures
TMF	Trial Master File
ULOQ	Upper Limit of Quantification
VACV	Vaccinia virus
WHO DD	World Health Organization Drug Dictionary
%	Percentage
°C	Degrees Celsius
°F	Degrees Fahrenheit

10.3 Appendix 3: Reporting conventions

SAS version 9.4, or higher, will be used to produce all tables, listings, and figures.

For summary statistics, the mean and median will be displayed to one decimal place greater than the original value and the measure of variability (e.g., SD) will be displayed to two decimal places greater than the original value. Minimum and maximum will be reported to the same decimal places as the original value. Percentages (%) will be displayed with one decimal place and 95% CIs will be displayed with one decimal place greater than the original value, unless otherwise stated in the programming notes of the shells.

Dose level in the Table 12 will be used for the Tables/Figures/Listings display as appropriate:

Table 122: Planned Treatment descriptors

Substudy	Treatment Group	Dose Level Label	Dose	Treatment Code
A	A1	BNT166a 10 µg	10 µg	1
	A2	BNT166a 30 µg	30 µg	2
	A4	BNT166a 60 µg	60 µg	4
B	B1	BNT166a 30 µg	30 µg	2
D	D1	BNT166a 60 µg[a]	60 µg [a]	4[a]

a) The dose was selected based on the Substudy A and Substudy B data.
Note: These are the planned treatment descriptors but changes to this table will not require an SAP amendment and will be reflected in the programming shells.

10.4 Appendix 4: Schedule of activities

Table 13 to Table 15 lists all the assessments to be performed in the trial for Substudy A, B and D respectively.

Table 13: Schedule of activities – Substudy A

Visit (V)	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Visit description	**Screening**	**Dose 1 (D1)**	**3 d after D1**	**1 wk after D1**	**2 wk after D1**	**Dose 2 (D2)**	**3 d after D2**	**1 wk after D2**	**2 wk after D2**	**1 mon after D2**	**3 mon after D2**	**6 mon after D2**	**1 yr after D2 or Early Term.[n]**
Visit day/window:	**1 to 28 d pre-D1**												
- relative to D 1		**1**	**3-4**	**8-10**	**13-17**	**29-33**							
- relative to D 2							**3-4**	**8-10**	**13-17**	**29-33**	**86-96**	**171-191**	**356-376**
Collect informed consent	X												
Inclusion / exclusion criteria	X	X (review)											
Medical history incl. prior medication and smallpox vaccination status, and history of mpox, smallpox or vaccinia infection	X	X (update)											
Physical examination	X	X	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]			
Vital signs [b]	X	X (pre- and ~1 h post-dose)	X	X	X	X (pre- and ~1 h post-dose)	X	X	X	X			
Height & body weight	X												
12-lead ECG	X	X	X	X	X	X	X	X	X				

Visit (V)	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Visit description	**Screening**	**Dose 1 (D1)**	**3 d after D1**	**1 wk after D1**	**2 wk after D1**	**Dose 2 (D2)**	**3 d after D2**	**1 wk after D2**	**2 wk after D2**	**1 mon after D2**	**3 mon after D2**	**6 mon after D2**	**1 yr after D2 or Early Term.[n]**
Visit day/window:	**1 to 28 d pre-D1**												
- relative to D 1		**1**	**3-4**	**8-10**	**13-17**	**29-33**							
- relative to D 2							**3-4**	**8-10**	**13-17**	**29-33**	**86-96**	**171-191**	**356-376**
Urine for clinical laboratory [d]	X												
Blood for viral screen (~14 mL) [e]	X												
Blood for clinical laboratory (9 mL) [f]	X	X [g]		X		X [g]		X		X			
Pregnancy test for VOCBP [h]	X	X				X							
Counsel/remind participants to perform contraception	X	X	X	X	X	X	X	X	X	X	X		
Blood for humoral response assessments (30 mL) [i]		X [g]		X	X	X [g]		X	X	X	X	X	X
Randomization / allocation to trial treatment		X											
Vaccination and 1 h observation period [c]		X				X							
Injection site assessment		X (pre- and 1 h post-dose)	X	X		X (pre- and 1 h post-dose)	X	X					
Participant hotline availability	Start	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	End

Visit (V)	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Visit description	**Screening**	**Dose 1 (D1)**	**3 d after D1**	**1 wk after D1**	**2 wk after D1**	**Dose 2 (D2)**	**3 d after D2**	**1 wk after D2**	**2 wk after D2**	**1 mon after D2**	**3 mon after D2**	**6 mon after D2**	**1 yr after D2 or Early Term.[n]**
Visit day/window:	**1 to 28 d pre-D1**												
- relative to D 1		**1**	**3-4**	**8-10**	**13-17**	**29-33**							
- relative to D 2							**3-4**	**8-10**	**13-17**	**29-33**	**86-96**	**171-191**	**356-376**
Issue, train, and collect participant e-diaries [j]		Issue, train				Re-train		Collect [j]					Collect (in case of early termination) [j]
Participants report local reactions and systemic events (incl. oral body temperature) daily for 7 d after each IMP dose using an e-diary		Start after Dose 1	=>	End after 7 d reporting		Start after Dose 2	=>	End after 7 d reporting					
Investigators review e-diary data daily		Start	=>	End		Start	=>	End					
Record AEs, MAAEs, AESI, and SAEs since last visit		X	X	X	X	X	X	X	X	X	X [k]	X [k]	X [k]
Record pregnancies		X	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	End
Record concomitant medication since last visit		X	X	X	X	X	X	X	X	X	X [l]	X [l]	X [l]
Wellbeing phone call		X [m]				X [m]							
Total volume of blood drawn per visit	**23 mL**	**39 mL**	**0 mL**	**39 mL**	**30 mL**	**39 mL**	**0 mL**	**39 mL**	**30 mL**	**39 mL**	**30 mL**	**30 mL**	**30 mL**

a Brief (symptom-directed) physical examination.

b Vital signs: systolic/diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature. On days with IMP dosing, before and at 1 h (±15 minutes) after dosing.

c Participants will be monitored by trial site personnel for adverse reactions for at least 1 h after each IMP dose.

d Dipstick urine analysis. Microscopic urinalysis: if warranted by dipstick results, urine sediment will be microscopically examined.

e Viral screen: screen for human immunodeficiency virus (HIV) 1 and 2, Hepatitis B, and Hepatitis C.

f Clinical laboratory tests: chemistry, hematology. Obtain FSH at Visit 0 only if postmenopausal status needs to be confirmed. Troponin will only be measured in the Screening (V0) sample.

g On dosing days, blood draws should be done pre-dose.

h VOCBP: The serum beta human chorionic gonadotropin pregnancy test at Visit 0 will be performed using the sample collected for clinical laboratory tests. Before each dosing, urine pregnancy tests will be performed using a commercial kit and the trial participants will be counseled about the need for the correct use of a highly effective method of contraception.

i If justified by the collected data, the listed blood draw days and the draw volumes may be adapted if not increasing the total number of draw days or the total volume drawn. Leftover blood after completion of the immunogenicity assessments may be used for additional biomarker analyses.

j Trial site personnel will remind the participants to record the oral body temperature and the worst grade for each symptom in the e-diary at approximately the same time every evening on the day of IMP dosing and then every day in the evening for a total of seven consecutive days. Also, remind the participant to contact the site if they experience any severe or potentially life-threatening reactogenicity events. At V1 assist the participant with downloading the e-diary application, or issue provisioned device; at V7 or Early Termination visit, collect e-diary or help the participant to delete application.

k Only record SAEs and AESI since last visit.

l Starting with Visit 10, only prohibited concomitant medications will be recorded.

m Trial participants contacted by phone will be asked non-leading wellbeing questions at >5 h after IMP administration on the day of dosing and at 24±4 h after each IMP dose.

n At the Early Termination Visit, if possible, all assessments planned for the actual week or day of that visit and which are not included in the Early Termination Visit should also be performed.

Notes:

If, for any reason, participants are permanently discontinued from the trial before completing all scheduled visits, participants will complete an Early Termination Visit. If possible, all assessments planned for the actual week or day of that visit as listed in the SoA and which are not included in the Early Termination Visit should also be performed. The only exception will be pregnant women, who will not have further research blood draws, but will otherwise complete planned assessments, if required including pregnancy follow-up.

The total blood volume drawn over any 8-week period in any group will always be less than 550 mL. Additional blood samples may be taken, e.g., for safety assessments after AEs or SAEs.

As long as the absolute volume of blood drawn does not change per participant overall, the volume of individual blood draws may be adapted if required, e.g., due to unforeseen shortage of specific tubes. Leftover or back up clinical sample aliquots of a participant, which have the exact same collection times, intended to a particular assessment can be used for another assay than that stated on the label if both assessments are described in the SoA and, the participant has consented to all. This is only possible if a primary sample has been used first for its original purpose and it is confirmed that no re-testing is required. Samples can only be used interchangeably if the sample characteristics, collection, shipment, and storage conditions are the same.

Abbreviations: AE = adverse event; CMI = cell-mediated immunity/immune response; d = day(s); D = dose; ECG = 12-lead electrocardiogram; = follow-up (visit); FSH = follicle stimulating hormone; h = hour(s); IMP = investigation medicinal product; mon = month(s); MAAE = medically attended adverse event; SAE = serious adverse event; SoA = schedule of activities; V = visit; VOCBP = volunteers of childbearing potential; wk = week(s); yr = year(s)

Table 144: Schedule of activities – Substudy B

Visit (V)	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Visit description	**Screening**	**Dose (D) 1**	**3 d after D1**	**1 wk after D1**	**2 wk after D1**	**Dose (D) 2**	**3 d after D2**	**1 wk after D2**	**2 wk after D2**	**1 mon after D2**	**3 mon after D2**	**6 mon after D2**	**1 yr after D2 or Early Termination [n]**
Visit day/window:	**1 to 28 d pre-D1**												
- relative to Dose 1		**1**	**3-4**	**8-10**	**13-17**	**29-33**							
- relative to Dose 2							**3-4**	**8-10**	**13-17**	**29-33**	**86-96**	**171-191**	**356-376**
Collect informed consent	X												
Inclusion/exclusion criteria	X	X (review)											
Medical history incl. prior medication and smallpox vaccination status, and history of mpox, smallpox or vaccinia infection	X	X (update)											
Physical examination	X	X	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]			
Vital signs [b]	X	X (pre- and ~1 h post-dose)	X	X	X	X (pre- and ~1 h post-dose)	X	X	X	X			
Height & body weight	X												
12-lead ECG	X	X	X	X	X	X	X	X	X				
Urine for clinical laboratory [d]	X												

Visit (V)	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**
Visit description	**Screening**	**Dose (D) 1**	**3 d after D1**	**1 wk after D1**	**2 wk after D1**	**Dose (D) 2**	**3 d after D2**	**1 wk after D2**	**2 wk after D2**	**1 mon after D2**	**3 mon after D2**	**6 mon after D2**	**1 yr after D2 or Early Termination** [n]
Visit day/window:	**1 to 28 d pre-D1**												
- relative to Dose 1		**1**	**3-4**	**8-10**	**13-17**	**29-33**							
- relative to Dose 2							**3-4**	**8-10**	**13-17**	**29-33**	**86-96**	**171-191**	**356-376**
Blood for viral screen (~14 mL) [e]	X												
Blood for clinical laboratory (9 mL) [f]	X	X [g]		X		X [g]		X		X			
Pregnancy test for VOCBP [h]	X	X				X							
Counsel/remind participants to perform contraception	X	X	X	X	X	X	X	X	X	X	X		
Blood for humoral response assessments (30 mL) [i]		X [g]		X	X	X [g]		X	X	X	X	X	X
Randomization / allocation to trial treatment		X											
Vaccination and 1 h observation period [c]		X		X		X	X						
Injection site assessment		X (pre- and 1 h post-dose)	X	X		X (pre- and 1 h post-dose)	X	X					

Visit (V)	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**
Visit description	**Screening**	**Dose (D) 1**	**3 d after D1**	**1 wk after D1**	**2 wk after D1**	**Dose (D) 2**	**3 d after D2**	**1 wk after D2**	**2 wk after D2**	**1 mon after D2**	**3 mon after D2**	**6 mon after D2**	**1 yr after D2 or Early Termination** [n]
Visit day/window: **- relative to Dose 1**	**1 to 28 d pre-D1**	**1**	**3-4**	**8-10**	**13-17**	**29-33**							
- relative to Dose 2							**3-4**	**8-10**	**13-17**	**29-33**	**86-96**	**171-191**	**356-376**
Participant hotline availability	Start	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	End
Issue, train, and collect participant e-diaries [j]		Issue, train				Re-train		Collect					Collect (in case of early termination)
Participants report local reactions and systemic events (incl. oral body temperature) daily for 7 d after each IMP dose using an e-diary		Start after Dose 1	=>	End after 7 d reporting		Start after Dose 2	=>	End after 7 d reporting					
Investigators review e-diary data daily		Start	=>	End		Start	=>	End					
Record AEs, MAAEs, AESIs, and SAEs since last visit		X	X	X	X	X	X	X	X	X	X [k]	X [k]	X [k]
Record pregnancies		X	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	End
Record concomitant medication since last visit		X	X	X	X	X	X	X	X	X	X [l]	X [l]	X [l]
Wellbeing phone call		X [m]				X [m]							

Visit (V)	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Visit description	**Screening**	**Dose (D) 1**	**3 d after D1**	**1 wk after D1**	**2 wk after D1**	**Dose (D) 2**	**3 d after D2**	**1 wk after D2**	**2 wk after D2**	**1 mon after D2**	**3 mon after D2**	**6 mon after D2**	**1 yr after D2 or Early Termination [n]**
Visit day/window:	**1 to 28 d pre-D1**												
- relative to Dose 1		**1**	**3-4**	**8-10**	**13-17**	**29-33**							
- relative to Dose 2							**3-4**	**8-10**	**13-17**	**29-33**	**86-96**	**171-191**	**356-376**
Total volume of blood drawn per visit	**23 mL**	**39 mL**	**0 mL**	**39 mL**	**30 mL**	**39 mL**	**0 mL**	**39 mL**	**30 mL**	**39 mL**	**30 mL**	**30 mL**	**30 mL**

a Brief (symptom-directed) physical examination.

b Vital signs: systolic/diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature. On days with IMP dosing, before and at 1 h (±15 minutes) after dosing.

c Participants will be monitored by trial site personnel for adverse reactions for at least 1 h after each IMP dose.

d Dipstick urine analysis. Microscopic urinalysis: if warranted by dipstick results, urine sediment will be microscopically examined.

e Viral screen: screen for human immunodeficiency virus (HIV) 1 and 2, Hepatitis B, and Hepatitis C.

f Clinical laboratory tests: chemistry, hematology. Obtain FSH at Visit 0 only if postmenopausal status needs to be confirmed. Troponin will only be measured in the Screening (V0) sample.

g On dosing days, blood draws should be done pre-dose.

h VOCBP: The serum beta human chorionic gonadotropin pregnancy test at Visit 0 will be performed using the sample collected for clinical laboratory tests. Before each dosing, urine pregnancy tests will be performed using a commercial kit and the trial participants will be counseled about the need for the correct use of a highly effective method of contraception.

i If justified by the collected data, the listed blood draw days and the draw volumes may be adapted if not increasing the total number of draw days or the total volume drawn. Leftover blood after completion of the immunogenicity assessments may be used for additional biomarker analyses.

j Trial site personnel will remind the participants to record the oral body temperature and the worst grade for each symptom in the e-diary at approximately the same time every evening on the day of IMP dosing and then every day in the evening for a total of seven consecutive days. Also, remind the participant to contact the site if they experience any severe or potentially life-threatening reactogenicity events. At V1 assist the participant with downloading the e-diary application, or issue provisioned device; at V7 or Early Termination visit, collect e-diary or help the participant to delete application.

k Only record SAEs and AESI since last visit.

l Starting with Visit 10, only prohibited concomitant medications will be recorded.

m Trial participants contacted by phone will be asked non-leading wellbeing questions >5 h after IMP administration on the day of dosing and at 24±4 h after each IMP dose.

n At the Early Termination Visit, if possible, all assessments planned for the actual week or day of that visit and which are not included in the Early Termination Visit should

also be performed.

Notes:

If, for any reason, participants are permanently discontinued from the trial before completing all scheduled visits, participants will complete an Early Termination Visit. If possible, all assessments planned for the actual week or day of that visit as listed in the SoA and which are not included in the Early Termination Visit should also be performed. The only exception will be pregnant women, who will not have further research blood draws, but will otherwise complete planned assessments, if required including pregnancy follow-up.

The total blood volume drawn over any 8-week period in any group will always be less than 550 mL. Additional blood samples may be taken, e.g., for safety assessments after AEs or SAEs.

As long as the absolute volume of blood drawn does not change per participant overall, the volume of individual blood draws may be adapted if required, e.g., due to unforeseen shortage of specific tubes. Leftover or back up clinical sample aliquots of a participant, which have the exact same collection times, intended to a particular assessment can be used for another assay than that stated on the label if both assessments are described in the SoA and, the participant has consented to all. This is only possible if a primary sample has been used first for its original purpose and it is confirmed that no re-testing is required. Samples can only be used interchangeably if the sample characteristics, collection, shipment, and storage conditions are the same.

Abbreviations: AE = adverse event; CMI = cell-mediated immunity/immune response; d = day(s); D = dose; ECG = 12-lead electrocardiogram; = follow-up (visit); FSH = follicle stimulating hormone; h = hour(s); IMP = investigation medicinal product; MAAE = medically attended adverse event; mon = month(s); SAE = serious adverse event; SoA = schedule of activities; V = visit; VOCBP = volunteers of childbearing potential; wk = week(s); yr = year(s).

Table 15: Schedule of activities – Substudy D

Visit (V)	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Visit description	**Screening**	**Dose 1 (D1)**	**1 d after D1**	**3 d after D1**	**1 wk after D1**	**2 wk after D1**	**Dose 2 (D2)**	**1 d after D2**	**3 d after D2**	**1 wk after D2**	**2 wk after D2**	**1 mon after D2**	**3 mon after D2**	**6 mon after D2**	**1 yr after D2 or Early Term.[n]**
Visit day/window: **- relative to D 1**	**1 to 28 d pre-D1**	**1**	**2**	**3-4**	**8-10**	**13-17**	**29-33**								
- relative to D 2							**1**	**2**	**3-4**	**8-10**	**13-17**	**29-33**	**86-96**	**171-191**	**356-376**
Collect informed consent	X														
Inclusion / exclusion criteria	X	X (review)													
Medical history incl. prior medication and smallpox vaccination status, and history of mpox, smallpox or vaccinia infection	X	X (update)													
Physical examination	X	X	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]
Vital signs [b]	X	X (pre- and ~1 h post-dose)	X	X	X	X	X (pre- and ~1 h post-dose)	X	X	X	X	X			
Height & body weight	X														
12-lead ECG	X	X		X	X	X	X		X	X	X				

Visit (V)	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Visit description	**Screening**	**Dose 1 (D1)**	**1 d after D1**	**3 d after D1**	**1 wk after D1**	**2 wk after D1**	**Dose 2 (D2)**	**1 d after D2**	**3 d after D2**	**1 wk after D2**	**2 wk after D2**	**1 mon after D2**	**3 mon after D2**	**6 mon after D2**	**1 yr after D2 or Early Term.[n]**
Visit day/window:	**1 to 28 d pre-D1**														
- relative to D 1		**1**	**2**	**3-4**	**8-10**	**13-17**	**29-33**								
- relative to D 2							**1**	**2**	**3-4**	**8-10**	**13-17**	**29-33**	**86-96**	**171-191**	**356-376**
Urine for clinical laboratory	X														
Blood for viral screen (~14 mL) [e]	X														
Blood for clinical laboratory (9 mL) [f]	X	X [g]			X		X [g]			X		X			
Pregnancy test for VOCBP [h]	X	X					X								
Blood for HLA typing (5 mL)		X [g]													
Blood for humoral response assessments (15 mL) [i]		X[g] (30 mL)					X [g]			X	X	X (30 mL)	X (30 mL)	X	X
Blood for CMI research (80 mL)		X [g]					X [g]			X		X	X	X	X
Blood for transcriptome analysis (5 mL)		X [g]	X	X			X [g]	X	X	X					
Blood for cytokine assessment (5 mL)		X [g]	X	X			X [g]	X	X						
Allocation to trial treatment		X													

Visit (V)	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Visit description	**Screening**	**Dose 1 (D1)**	**1 d after D1**	**3 d after D1**	**1 wk after D1**	**2 wk after D1**	**Dose 2 (D2)**	**1 d after D2**	**3 d after D2**	**1 wk after D2**	**2 wk after D2**	**1 mon after D2**	**3 mon after D2**	**6 mon after D2**	**1 yr after D2 or Early Term.[n]**
Visit day/window:	**1 to 28 d pre-D1**														
- relative to D 1		**1**	**2**	**3-4**	**8-10**	**13-17**	**29-33**								
- relative to D 2							**1**	**2**	**3-4**	**8-10**	**13-17**	**29-33**	**86-96**	**171-191**	**356-376**
Vaccination and 1 h observation period [c]		X				X									
Injection site assessment		X (pre- and >1 h post-dose)	X	X	X		X (pre- and >1 h post-dose)	X	X	X					
Issue, train, and collect participant e-diaries [j]		Issue, train			Collect		Re-train			Collect [j]					Collect (in case of early termination) [j]
Participants report local reactions and systemic events (incl. oral body temperature) daily for 7 d after each IMP dose using an e-diary		Start after Dose 1	=>	=>	End after 7 d reporting		Start after Dose 2	=>	=>	End after 7 d reporting					
Investigators review e-diary data daily		Start	=>	=>	End		Start	=>	=>	End					
Record AEs, MAAEs, AESI, and SAEs		X	X	X	X	X	X	X	X	X	X	X	X [k]	X [k]	X [k]

Visit (V)	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14
Visit description	**Screening**	**Dose 1 (D1)**	**1 d after D1**	**3 d after D1**	**1 wk after D1**	**2 wk after D1**	**Dose 2 (D2)**	**1 d after D2**	**3 d after D2**	**1 wk after D2**	**2 wk after D2**	**1 mon after D2**	**3 mon after D2**	**6 mon after D2**	**1 yr after D2 or Early Term.[n]**
Visit day/window: **- relative to D 1**	**1 to 28 d pre-D1**	**1**	**2**	**3-4**	**8-10**	**13-17**	**29-33**								
- relative to D 2							**1**	**2**	**3-4**	**8-10**	**13-17**	**29-33**	**86-96**	**171-191**	**356-376**
Record pregnancies		X	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	End
Record concomitant medication since last visit		X	X	X	X	X	X	X	X	X	X	X	X[l]	X[l]	X[l]
Counsel/remind participants to perform contraception	X	X	X	X	X	X	X	X	X	X	X	X	X		
Participant hotline availability	Start	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	=>	End
Wellbeing phone call		X[m]					X[m]								
Total volume of blood drawn per visit	**23 mL**	**134 mL**	**10 mL**	**10 mL**	**9 mL**	**0 mL**	**114 mL**	**10 mL**	**10 mL**	**109 mL**	**15 mL**	**119 mL**	**110 mL**	**95 mL**	**95 mL**

a Brief (symptom-directed) physical examination.

b Vital signs: systolic/diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature. On days with IMP dosing, before and at 1 h (±15 minutes) after dosing.

c Participants will be monitored by trial site personnel for adverse reactions for at least 1 h after each IMP dose.

e Viral screen: screen for human immunodeficiency virus (HIV) 1 and 2, Hepatitis B, and Hepatitis C.

f Clinical laboratory tests: chemistry, hematology. Obtain FSH at Visit 0 only if postmenopausal status needs to be confirmed. Troponin will only be measured in the Screening (V0) sample.

g On dosing days, blood draws should be done pre-dose.

h VOCBP: The serum beta human chorionic gonadotropin pregnancy test at Visit 0 will be performed using the sample collected for clinical laboratory tests. Before each

dosing, urine pregnancy tests will be performed using a commercial kit and the trial participants will be counseled about the need for the correct use of a highly effectivmethod of contraception.i If justified by the collected data, the listed blood draw days and the draw volumes may be adapted if not increasing the total number of draw days or the total volume drawn. Leftover blood after completion of the immunogenicity assessments may be used for additional biomarker analyses.

j Trial site personnel will remind the participants to record the oral body temperature and the worst grade for each symptom in the e-diary at approximately the same time every evening on the day of IMP dosing and then every day in the evening for a total of seven consecutive days. Also, remind the participant to contact the site if they experience any severe or potentially life-threatening reactogenicity events. At V1 assist the participant with downloading the e-diary application, or issue provisioned device; at V9 or Early Termination Visit, collect e-diary or help the participant to delete application.k Only record SAEs and AESI since last visit.

l Starting with Visit 12, only prohibited concomitant medications will be recorded.

m Trial participants contacted by phone will be asked non-leading wellbeing questions at >5 h after IMP administration on the day of dosing

n At the Early Termination Visit, if possible, all assessments planned for the actual week or day of that visit and which are not included in the Early Termination Visit should also be performed.

Notes:

If, for any reason, participants are permanently discontinued from the trial before completing all scheduled visits, participants will complete an Early Termination Visit. If possible, all assessments planned for the actual week or day of that visit as listed in the SoA and which are not included in the Early Termination Visit should also be performed. The only exception will be pregnant women, who will not have further research blood draws, but will otherwise complete planned assessments, if required including pregnancy follow-up as described in Section 10.5.3. The total blood volume drawn over any 8-week period in any group will always be less than 550 mL. Additional blood samples may be taken, e.g., for safety assessments after AEs or SAEs. As long as the absolute volume of blood drawn does not change per participant overall, the volume of individual blood draws may be adapted if required, e.g., due to unforeseen shortage of specific tubes. Leftover or back up clinical sample aliquots of a participant, which have the exact same collection times, intended to a particular assessment can be used for another assay than that stated on the label if both assessments are described in the SoA and the participant has consented to all. This is only possible if a primary sample has been used first for its original purpose and it is confirmed that no re-testing is required. Samples can only be used interchangeably if the sample characteristics, collection, shipment, and storage conditions are the same.

Abbreviations: AE = adverse event; CMI = cell-mediated immunity/immune response; d = day(s); D = dose; ECG = 12-lead electrocardiogram; Early Term. = early termination; FSH = follicle stimulating hormone; h = hour(s); HLA = human leukocyte antigens; IMP = investigation medicinal product; mon = month(s); MAAE = medically attended adverse event; SAE = serious adverse event; SoA = schedule of activities; V = visit; VOCBP = volunteers of childbearing potential; wk = week(s); yr = years

10.5 Appendix 5: Visit Windowing

Further details on the windowing for exploratory endpoints for Substudy D will be updated in Table 16 below in the next version of the SAP.

Table 166: Sampling outside CTP windows

Substudy	Visit number	Relative to dose	Visit relative to dose	Window per CTP (visit days)	Additional grace period without impact on immunogenicity = include in immunogenicity analysis (visit days)
A and B	V1	1	Pre-dose 1	n/a	n/a
	V3	1	1 week post-dose 1	Day 8-10	±1 day (Day 7-11)
	V4	1	2 weeks post-dose 1	Day 13-17	±1 days (Day 12-18)
	V5	1	Pre-dose 2	Day 29-33	±2 days (Day 27-35) Sample date time is prior to dose 2 administration.
	V7	2	1 week post-dose 2	Day 8-10 post-dose 2	±1 day (Day 7-11 post-dose 2)
	V8	2	2 weeks post-dose 2	Day 13-17 post-dose 2	±1 day (Day 12-18 post-dose 2)
	V9	2	1 month post-dose 2	Day 29-33 post-dose 2	±2 days (Day 27-35 post-dose 2)
	V10	2	3 months post-dose 2	Day 86-96 post-dose 2	±7 days (Day 79-103) post-dose 2)
	V11	2	6 months post-dose 2	Day 171-191 post-dose 2	±7 days (Day 164-198 post-dose 2)
	V12	2	1 year post-dose 2	Day 356-376 post-dose 2	±14 days (Day 342-390) post-dose 2)

Substudy	**Visit number**	**Relative to dose**	**Visit relative to dose**	**Window per CTP (visit days)**	**Additional grace period without impact on immunogenicity = include in immunogenicity analysis (visit days)**
	Early Termination	1 or 2	Early termination	na	n/a
D	V1	1	Pre-dose 1	n/a	n/a
	V6	1	Pre-dose 2	Day 29-33	±2 days (Day 27-35) Sample date time is prior to dose 2 administration.
	V9	2	1 week post-dose 2	Day 8-10 post-dose 2	±1 day (Day 7-11 post-dose 2)
	V10	2	2 weeks post-dose 2	Day 13-17 post-dose 2	±1 day (Day 12-18 post-dose 2)
	V11	2	1 month post-dose 2	Day 29-33 post-dose 2	±2 days (Day 27-35 post-dose 2)
	V12	2	3 months post-dose 2	Day 86-96 post-dose 2	±7 days (Day 79-103 post-dose 2)
	V13	2	6 months post-dose 2	Day 171-191 post-dose 2	±7 days (Day 164-198 post-dose 2)
	V14	2	1 year post-dose 2	Day 356-376 post-dose 2	±14 days (Day 342-390 post-dose 2)
	Early Termination	1 or 2	Early termination	n/a	n/a

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PPD Security Level: Email, Account Authentication (Required), Login with SSO	Signiert von: PPD Name des Unterzeichners: PPD Signiergrund: Ich genehmige dieses Dokument Signierzeit: 21-Apr-2026 | 10:17:21 BST PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD Signed using mobile With Signing Authentication via Docusign password With Signing Reasons (on each tab): Ich genehmige dieses Dokument	Sent: 20-Apr-2026 | 16:16 Viewed: 21-Apr-2026 | 10:17 Signed: 21-Apr-2026 | 10:17
Electronic Record and Signature Disclosure: Accepted: 21-Apr-2026 | 10:17 ID: PPD		
PPD Security Level: Email, Account Authentication (Required)	Signed by: PPD Signer Name: PPD Signing Reason: I approve this document Signing Time: 21-Apr-2026 | 05:44:03 BST PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via Docusign password With Signing Reasons (on each tab): I approve this document	Sent: 20-Apr-2026 | 16:16 Viewed: 21-Apr-2026 | 05:43 Signed: 21-Apr-2026 | 05:44
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Electronic Record and Signature Disclosure: Accepted: 20-Apr-2026 | 16:19 ID: PPD		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	20-Apr-2026 | 16:16
Certified Delivered	Security Checked	20-Apr-2026 | 16:19
Signing Complete	Security Checked	20-Apr-2026 | 16:20
Completed	Security Checked	21-Apr-2026 | 10:17
Payment Events	**Status**	**Timestamps**
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ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

I understand that my electronic signature is equivalent to my handwritten signature and is therefore legally binding. My electronic signature will remain unique to me and, under no circumstances, am I allowed to disclose my password to any individual which may allow unauthorised access to the system. I understand that I am accountable and responsible for all actions associated with my electronic signature.