PCA001 Protocol v5.0, 18Apr2024

Cover Page for ClinicalTrials.gov

Official Title:

A Phase 1/Phase 2 Trial to Evaluate Safety, Immunogenicity and PSA Response of VTP-850 Prostate Cancer Immunotherapeutic in Men with Biochemical Recurrence after Definitive Local Therapy for Prostate Cancer

NCT Number:

NCT05617040

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18 April 2024

TITLE PAGE

Protocol Title: A Phase 1/Phase 2 Trial to Evaluate Safety, Immunogenicity and PSA Response of VTP-850 Prostate Cancer Immunotherapeutic in Men with Biochemical Recurrence after Definitive Local Therapy for Prostate Cancer

Protocol Number: PCA001 Version 5.0 18 April 2024

EudraCT Number: 2022-001479-14

Compound: VTP-850 (ChAdOx1-PCAQ and MVA-PCAQ)

Short Title: Prime-boost Immunotherapeutic Trial in Men with Biochemical Recurrence after Definitive Local Therapy for Prostate Cancer

Trial Phase: Phase 1/Phase 2

Sponsor Name: Barinthus Biotherapeutics (UK) Ltd.

Legal Registered Address:

Units 6 to 10 Zeus Building

Rutherford Avenue

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OX11 0DF

Approval Date: 18-APR-2024

Sponsor Signatory:

[redacted] 18-APR-2024

VP Clinical Development Date

Medical Monitor Name and Contact Information will be provided separately.

INVESTIGATOR AGREEMENT

I, the undersigned, agree to conduct this study in accordance with this protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), the ethical principles set forth in the Declaration of Helsinki and with local regulatory requirements.

Signature Date

Printed Name

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1 PROTOCOL SUMMARY

1.1 Synopsis

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<tr><td>Sponsor:</td><td colspan="2">Barinthus Biotherapeutics (UK) Ltd.</td></tr>
<tr><td>Protocol Title:</td><td colspan="2">A Phase 1/Phase 2 Trial to Evaluate Safety, Immunogenicity and PSA Response of VTP-850 Prostate Cancer Immunotherapeutic in Men with Biochemical Recurrence after Definitive Local Therapy for Prostate Cancer</td></tr>
<tr><td>Short Title:</td><td colspan="2">Prime-boost Immunotherapeutic Trial in Men with Biochemical Recurrence after Definitive Local Therapy for Prostate Cancer</td></tr>
<tr><td>Trial Centres:</td><td colspan="2">Up to 30 centres worldwide</td></tr>
<tr><td rowspan="6">Objectives and Endpoints</td><td>Primary Objective</td><td>Primary Endpoints</td></tr>
<tr><td>To evaluate the safety of VTP-850 prime-boost regimens, with the booster dose administered either intramuscularly (IM) or intravenously (IV), and establish a recommended Phase 2 regimen (RP2R)</td><td>• Number and proportion of participants with adverse events (AEs), treatment--related AEs, ≥Grade 3 AEs, ≥Grade 3 treatment-related AEs, serious adverse events, and treatment-related serious adverse events
• Number and proportion of participants with clinically significant laboratory values
• Change from baseline for laboratory tests and vital sign measurements at each time point of collection</td></tr>
<tr><td>Secondary Objectives</td><td>Secondary Endpoints</td></tr>
<tr><td>To evaluate the prostate-specific antigen (PSA) response rate to VTP-850</td><td>• Percentage of participants with ≥50% reduction in serum PSA compared to baseline at any time, based on two consecutive measurements, at least 2 weeks apart</td></tr>
<tr><td>To evaluate the durable PSA response rate to VTP-850</td><td>• Percentage of participants with confirmed PSA response compared to baseline without having PSA progression on or before Month 8.</td></tr>
<tr><td>To evaluate the duration of PSA response to VTP-850 (for the subset of participants with PSA response)</td><td>• Duration of PSA response (for the subset of participants with PSA response), defined as time from date of first dose of VTP-850 to the date of PSA progression (i.e., an increase of ≥25% and an absolute increase of 0.2 ng/mL or more from nadir)</td></tr>
</table>

	To assess the Metastasis-free Survival (MFS) and Time to Metastases (TTM) of the subset of participants with PSA response	• MFS is defined as the time from date of first dose of VTP-850 until metastatic disease by conventional imaging (computed tomography [CT]/magnetic resonance imaging [MRI] and/or technetium-99 bone scan) or death from any cause, whichever occurs first • TTM is defined as the time from date of first dose of VTP-850 until metastatic disease by conventional imaging (CT/MRI and or technetium-99 bone scan) Note that MFS and TTM events do not include local progression events, e.g., progression in pelvic lymph nodes below the aortic bifurcation.
	To assess the time to start of androgen deprivation therapy (ADT) for the participants with PSA response	• Time from date of first dose of VTP-850 to the earliest of the start of ADT or the date when criteria to start ADT are met
	Exploratory Objectives	**Exploratory Endpoints**
	To characterise immunogenicity (including antigen-specific T cell magnitude, phenotype and functionality associated with each regimen)	CD4+ and CD8+ T cell response to the VTP-850 antigens in the peripheral blood as measured by multi-parameter flow cytometry and enzyme linked immunospot assays • Other immune responses to VTP-850
	To explore association of PSA response with biomarkers	Microsatellite instability-high (MSI-H) status, BReast CAncer gene (BRCA) mutations (and other molecular markers Expression level of the VTP-850 antigens (PSA, prostatic acid phosphatase [PAP], six-transmembrane epithelial antigen of prostate 1 [STEAP1], 5T4) in historic tumour samples • Circulating tumour DNA • Serum PSA-binding antibodies
	To look for evidence of resolution of lesions on prostate-specific membrane antigen (PSMA) scan after administration of VTP-850 (if documented at baseline), and association of resolution of such lesions with PSA response in the subset of participants who have lesions on baseline PSMA scan and who have a PSA response on trial	• PSMA scans (optional)

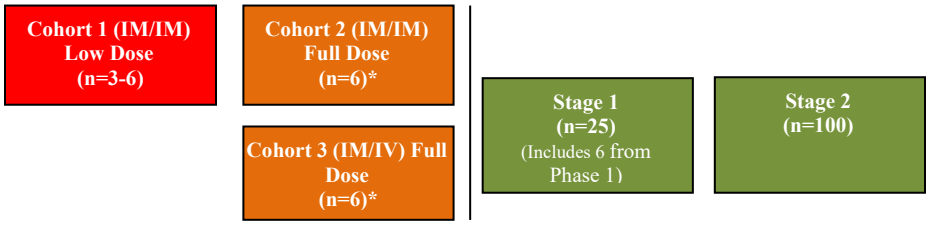
	To assess the MFS and TTM of all participants	• MFS is defined as the time from date of first dose of VTP-850 until metastatic disease by conventional imaging (CT/MRI and/or technetium-99 bone scan) or death from any cause, whichever occurs first • TTM is defined as the time from date of first dose of VTP-850 until metastatic disease by conventional imaging (CT/MRI and/or technetium-99 bone scan) Note that MFS and TTM events do not include local progression events, e.g., progression in pelvic lymph nodes below the aortic bifurcation
Trial Design:	This is a multicentre, Phase 1/2, open-label clinical trial of the VTP-850 prime-boost immunotherapeutic in men with biochemical recurrence after definitive local therapy for prostate cancer. Participants in all cohorts will receive the ChAdOx1-PCAQ component on Day 1 (prime) and the MVA-PCAQ component on Days 29 and 57 (boosts; Intervention Period). Participants will be followed until the Month 6 Visit or start of new therapy such as ADT or until development of unequivocal metastatic prostate cancer (Short-term Follow-up Period). Participants who have a PSA response will be followed for an additional 18 months, up to 24 months from first dose, or until start of new therapy such as ADT or development of unequivocal metastatic prostate cancer (Long-term Follow-up Period). . In the event that a participant experiences a confirmed PSA response but subsequently experiences PSA progression more than 2 months after their final dose of VTP-850, an additional dose of MVA-PCAQ may be offered to the participant. Phase 1 will determine the RP2R (dose level of both ChAdOx1-PCAQ and MVA-PCAQ, and route of administration of MVA-PCAQ) that will be used in Phase 2 and will follow a 3+3 design. The first 3 participants will be enrolled in Cohort 1. Enrolment of the first 3 participants in each cohort will be staggered by at least 9 days. The medical monitor will review the safety data for the previous participant, at least 7 days after the prime dose and after the first booster dose of VTP-850, before the corresponding dose is administered to the next participant. The safety review will include data from at least 7 days after each ChAdOx1-PCAQ prime dose; at least 7 days after the first booster MVA-PCAQ dose if administered IM; and at least 14 days after the first booster dose of MVA-PCAQ if administered IV. If 1 or more of the 3 participants has a dose limiting toxicity (DLT), 3 additional participants may be enrolled into Cohort 1. If there is no DLT after the first dose of VTP-850 in the first 3 participants, 3 participants will be enrolled into each of Cohorts 2 and 3 concurrently, with the first participants in Cohorts 2 and 3 staggered by at least 9 days to allow for medical review. If DLT is not seen in more than 1 participant in Cohort 2 after the first dose of VTP-850, then an additional 3 participants will be enrolled into Cohort 2. Safety data for the DLT period following each booster dose will be assessed by the medical monitor prior to the corresponding booster dose being administered to additional participants. If DLT is not seen after the first dose of VTP-850 in more than 1 participant in Cohort 3 then an additional 3 participants will be enrolled into Cohort 3. Safety data for the DLT period following each booster dose will be assessed by the medical monitor prior to the corresponding booster dose being administered to additional participants. A total of 6 participants in each of Cohorts 2 and 3 will be dosed with MVA-PCAQ on Day 29 and Day 57. Therefore, participants who withdraw before dosing, before completion of dosing or who have dose delays will be	

<table>
<tr><td></td><td>replaced (unless the reason for not completing dosing per protocol is related to a stopping rule criteria being met) If the safety of one or more cohorts is acceptable after all participants have been followed through the DLT period after the first booster dose of VTP-850, then a Phase 2 dosing regimen will be selected based on safety data, and recruitment to Phase 2 will be opened.

Phase 2 of the trial will consist of 2 sequential stages.

In Stage 1 of Phase 2, 19 additional participants will be enrolled at the chosen Phase 2 regimen. If 4 or more of the 25 participants at the RP2R (out of the 19 Phase 2 participants and the 6 Phase 1 participants who received the same dose regimen according to the dosing schedule) have a PSA response, Stage 2 will be opened to enrolment of up to 100 additional participants. If 3 or fewer of the 25 participants have a PSA response in Stage 1, no further participants will be enrolled. PSA response is defined as ≥50% reduction in serum PSA compared to baseline at any time, measured at two consecutive timepoints, at least 2 weeks apart.

The Safety Monitoring Committee (SMC) will make a recommendation whether 1) to enrol each cohort in Phase 1, 2) about the choice of RP2R after reviewing available safety data and whether to open enrolment in Phase 2 and 3) to open enrolment in Phase 2 Stage 2 after reviewing available safety and efficacy data after at least 4 participants have exhibited a PSA response.

Phase 1: Dose/Regimen Finding Phase Phase 2: Main Phase
 

Abbreviations: IM=intramuscular, IV=intravenous, *n=number of participants who have received their scheduled doses of MVA-PCAQ on Day 29 and Day 57,</td></tr>
<tr><td>Trial Intervention:</td><td>VTP-850 consists of 2 components: ChAdOx1-PCAQ and MVA-PCAQ. Participants in all cohorts will receive the ChAdOx1-PCAQ component on Day 1 and the MVA-PCAQ component on Days 29 and 57.

In the event that a participant experiences a confirmed PSA response but subsequently experiences PSA progression more than 2 months after their final dose of VTP-850, an additional dose of MVA-PCAQ may be offered to the participant.</td></tr>
<tr><td>Dose Levels</td><td>
<table>
<tr><th rowspan="2">Cohort</th><th rowspan="2">Number of participants</th><th colspan="2">Trial Intervention: VTP-850</th></tr>
<tr><th>ChAdOx1-PCAQ Day 1</th><th>MVA-PCAQ Days 29 and 57</th></tr>
<tr><td>1</td><td>3-6</td><td>5×10^9 vp IM</td><td>5×10^7 pfu IM</td></tr>
<tr><td>2</td><td>6</td><td>2.5×10^{10} vp IM</td><td>2×10^8 pfu IM</td></tr>
<tr><td>3</td><td>6</td><td>2.5×10^{10} vp IM</td><td>2×10^7 pfu IV</td></tr>
</table>
Abbreviations: IM=intramuscular, IV=intravenous, pfu=plaque forming units, vp=viral particles</td></tr>
<tr><td>Duration of Trial:</td><td>Maximum duration for each participant: Up to 24 months after first dose of VTP-850.
Duration of whole trial: Approximately 42 months (18 months recruitment + 24 months follow-up).</td></tr>
<tr><td>Participant Numbers:</td><td>A total of approximately 25 participants will be enrolled in Phase 1 (including replacement participants so that 6 participants in each of Cohorts 2 and 3 have received MVA-PCAQ at Days 29 and 57); 19 participants will be enrolled in Stage 1 of Phase 2, and 100 participants will be enrolled in Stage 2 of Phase 2.</td></tr>
</table>

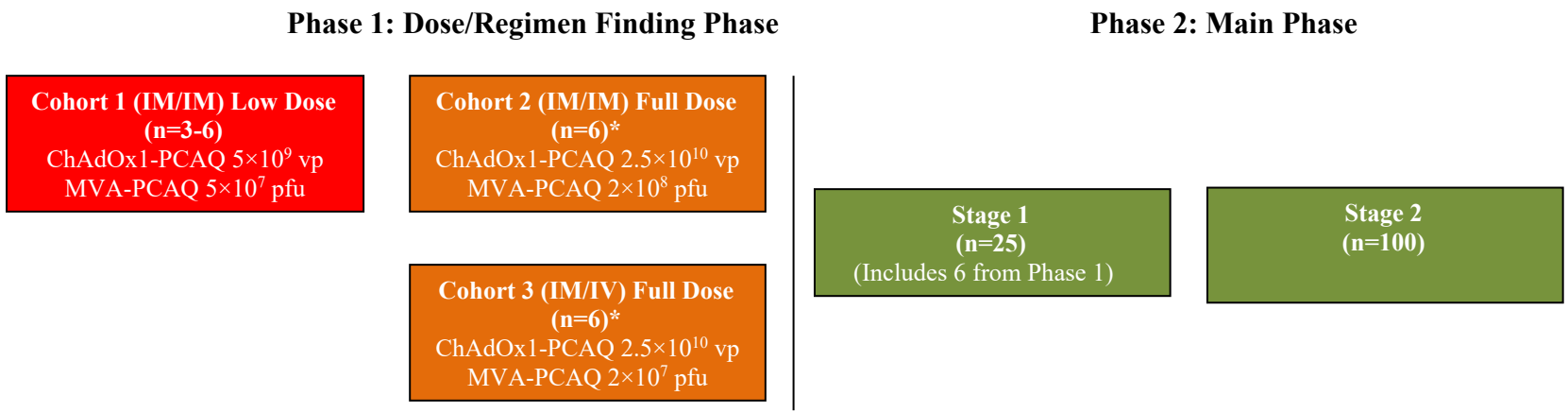
Inclusion Criteria:	**Age** 1. Males aged 18 years and above at the time of signing the informed consent. **Type of Participant and Disease Characteristics** 2. Histologically or cytologically confirmed adenocarcinoma of the prostate. 3. Has undergone primary therapy for prostate cancer (radical prostatectomy and/or definitive external beam radiation and/or brachytherapy). Salvage external radiation therapy (XRT) following radical prostatectomy >6 months prior to Day 1 is allowed. 4. No further local therapy to prostate or systemic therapy for prostate cancer and no metastasis-directed therapy for PSA-positron emission tomography (PET) positive lesions planned within 4 months after the first dose of VTP-850. 5. Serum testosterone >175 ng/dL. 6. Nonmetastatic (M0) disease and no evidence of prostatic bed recurrence verified by whole body bone scintigraphy and either CT or MRI. Note that a positive PSMA-PET does not exclude the participant if the conventional scans are negative. 7. Serum PSA of >0.3 ng/mL for participants with prior radical prostatectomy (with or without salvage radiotherapy), or serum PSA of 2 ng/mL above nadir for participants with prior external beam radiation or brachytherapy. 8. PSA doubling time ≤12 months. 9. Not planning to start ADT for at least 4 months after Day 1. 10. Eastern Cooperative Oncology Group (ECOG) Score 0 or 1. 11. Baseline laboratory parameters must meet the following criteria: • Haemoglobin ≥110 g/Le • White cell count ≥2.0×10^9/L • Absolute neutrophil count ≥1.5×10^9/L • Lymphocytes ≥0.9×10^9/L • Platelets ≥100×10^9/L • Creatinine ≤1.5×upper limit of normal (ULN) OR calculated creatinine clearance ≥50 mL/min by the Cockcroft Gault formula • Total bilirubin ≤1.5×ULN, (total bilirubin >1.5×ULN is acceptable if total bilirubin is fractionated and direct bilirubin <35%) • Alanine aminotransferase ≤1.5×ULN • Aspartate aminotransferase ≤1.5×UL • Troponin T within normal range • HbA1c <7 % **Sex and Contraceptive/Barrier Requirements** 12. Agrees to the following during the trial and for at least 65 days after the last dose of VTP-850: • Refrain from donating sperm PLUS, either • Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent OR

	• Agrees to use a male condom when having sexual intercourse with a woman of childbearing potential, and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak. **Other Inclusions** 13. Agrees to comply with all scheduled visits, VTP-850 administration plan, laboratory tests, lifestyle considerations and other trial procedures.
Exclusion Criteria	**Cancer History** 1. Any other prior malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years. **Medical Conditions** 2. Unstable medical condition, drug or alcohol abuse, or medical or psychiatric condition that in the opinion of the investigator would affect the safety of the participant or the evaluation of the data or interfere with adherence to the trial requirements. 3. Significant history of or current cardiovascular, respiratory, renal, gastrointestinal, endocrinological, haematological or neurological disorders constituting a risk when taking the trial intervention or interfering with the interpretation of data; cardiac event or heart failure in the previous 6 months. 4. Current or chronic history of liver disease. This includes but is not limited to: hepatitis virus infections, cirrhosis, drug- or alcohol-related liver disease, non-alcoholic steatohepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, primary biliary cholangitis, primary sclerosing cholangitis or any other liver disease considered clinically significant by the investigator. (Note that history of hepatitis C infection, Gilbert's syndrome or non-alcoholic fatty liver not associated with steatohepatitis are not exclusions. In line with Exclusion Criterion 10, active hepatitis C infection is exclusionary.) 5. Active autoimmune disease that has required systemic treatment in past 2 years with use of disease modifying agents, chronic corticosteroids (>14 days) or immunosuppressive drugs. Hormone replacement therapy (e.g., thyroxine, insulin or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is allowed. 6. History of severe allergy to eggs or history of severe reaction to any previous vaccination that required medical attention. 7. Medical history that could increase the participant's risk of reaction to a vaccine, including but not limited to capillary leak syndrome, transverse myelitis, multiple sclerosis, Guillain Barré syndrome, significant thrombocytopenia, thrombosis with thrombocytopenia syndrome (also termed vaccine-induced thrombotic thrombocytopenia), heparin-induced thrombocytopenia, or hereditary angioedema, acquired angioedema or idiopathic angioedema. 8. Any immunocompromised state, or history of solid organ or stem cell transplantation. 9. Active infection requiring parenteral antibiotic therapy or causing fever (temperature ≥38.0˚C) within 7 days prior to Day 1, or unexplained fever (temperature ≥38.0˚C) within 7 days prior to Day 1. 10. Known history of infection with hepatitis B virus, or human immunodeficiency virus, or active hepatitis C virus infection (antibody and RNA positive).

	Prior/Concomitant Therapy 11. Received XRT following radical prostatectomy within 6 months prior to Day 1. 12. Received ADT outside of the initial primary therapy 13. Prior chemotherapy or immunotherapy (including vaccines or checkpoint inhibitors) or experimental agent or participation in a clinical trial for prostate cancer with the exception of those taking part as primary treatment option. 14. Received a vaccine with adenovirus vector within 3 months prior to Day 1. 15. Received any live vaccine within 30 days prior to Day 1, or planned vaccination to occur within 3 months after Day 1. 16. Received any non-live/inactivated vaccine within 14 days of Day 1 or planned non-live vaccination to occur within 10 weeks after Day 1. 17. Administration of immunoglobulins and/or any blood products within 28 days prior to Day 1. 18. Condition requiring systemic treatment with corticosteroids or other immunosuppressive medications within 14 days of first dose of VTP-850. Note that adrenal replacement doses are permitted. Inhaled and topical corticosteroids are allowed. 19. Received an investigational product or investigational surgical procedure in the 3 months prior to Day 1 or planned use during the trial period, or participation at any time in clinical trial for prostate cancer with exception of those taking part as primary treatment. **Cardiovascular Risk Profile** 20. Any significant cardiovascular conditions per the investigator within 6 months before study entry including but not limited to: myocardial infarction, stroke, New York Heart Association class III or IV heart failure, thromboembolic events, major cardiovascular or cerebrovascular procedures, history of cardiac valvular disease or other structural heart disease or any other condition that in the investigator's opinion puts the participant at unacceptable risk to enter the study. 21. Participant with QT interval corrected for heart rate (QTc) determined using Fridericia's formula (QTcF; QTcF = QT/[R-R interval {RR}^0.33]) > 470 msec and any other ECG findings deemed clinically significant at screening 22. Uncontrolled hypertension that, in the opinion of the Investigator, puts participant at increased risk of a cardiovascular event at the time of screening. 23. Uncontrolled dyslipidemia that, in the opinion of the Investigator, puts participant at increased risk of cardiovascular event at the time of screening.

1.2 Schema

Figure 1 Trial Schematic



Abbreviations: IM=intramuscular, IV=intravenous, *n=number of participants who have received their scheduled doses of MVA-PCAQ on Day 29 and Day 57, pfu=plaque forming units, vp=viral particles

1.3 Schedule of Assessments

Table 1 Schedule of Assessments during the Screening and Intervention Periods

Optional schedule to be repeated for participants receiving a third dose of MVA-PCAQ after initial PSA response followed by progression. Schedule to be repeated for participants whose 2nd dose of MVA was delayed.¶

Visit/Call	Screening Period (42 d)[a]	Intervention Period (Days)												
		Day 1 Dosing Visit	Day 2 Telephone Call	Day 8 Telephone Call	Day 15 Clinic Visit	Day 29 Dosing Visit	Day 30 Telephone Call	Day 36 Clinic Visit	Day 43 Clinic Visit	Day 57 Dosing Visit [k]	Day 58 Telephone Call [k]	Day 64 Clinic Visit [k]	Day 71 Clinic Visit [k]	Day 91 Clinic Visit
Window[b]			1-2d post-dose	±1d	±2d	±2d	Up to 2d post-dose	±2d	±2d	±2d	Up to 2 d post-dose	±2d	±2d	±2d
Informed consent	X													
Baseline/eligibility variables														
Demographics	X													
Inclusion and exclusion criteria	X													
Full physical examination including height and weight	X													
Medical and disease history	X													
ECOG performance status	X													
Historic tumour sample collection[e]		X												
Laboratory eligibility and safety tests and investigations														
12-lead ECG[c]	X	X (pre-dose)			X	X (pre-dose)			X	X (pre-dose)			X	X
Echocardiogram[d]	X													

Optional schedule to be repeated for participants receiving a third dose of MVA-PCAQ after initial PSA response followed by progression. Schedule to be repeated for participants whose 2nd dose of MVA was delayed.¶

Visit/Call	Screening Period (42 d)[a]	Intervention Period (Days)												
		Day 1 Dosing Visit	Day 2 Telephone Call	Day 8 Telephone Call	Day 15 Clinic Visit	Day 29 Dosing Visit	Day 30 Telephone Call	Day 36 Clinic Visit	Day 43 Clinic Visit	Day 57 Dosing Visit [k]	Day 58 Telephone Call [k]	Day 64 Clinic Visit [k]	Day 71 Clinic Visit [k]	Day 91 Clinic Visit
Urinalysis	X													
Haematology	X	X			X	X		X	X	X		X	X	X
Biochemistry	X	X			X	X		X	X	X		X	X	X
Liver function tests	X	X			X	X		X	X	X		X	X	X
Troponin T[c,f]	X	X			X	X		X	X	X		X	X	X
CRP	X	X			X	X		X	X	X		X	X	X
Serum testosterone	X													
Intervention administration														
Enrolment /confirmation that eligibility requirements still met prior to dosing		X				X				X				
VTP-850 dose		ChAd				MVA				MVA				
Post-dose observation		X				X				X				
Other safety assessments														
Symptom-directed physical examination		X			X	X			X	X			X	X
Vital signs	X	X[g]			X	X[g]			X	X[g]			X	X
Medical occurrences	X													
Adverse events		←==========												==========→
Serious adverse events/AESIs[c]	X[h]	←==========												==========→

Optional schedule to be repeated for participants receiving a third dose of MVA-PCAQ after initial PSA response followed by progression. Schedule to be repeated for participants whose 2nd dose of MVA was delayed.¶

Visit/Call	Screening Period (42 d)[a]	Intervention Period (Days)												
		Day 1 Dosing Visit	Day 2 Telephone Call	Day 8 Telephone Call	Day 15 Clinic Visit	Day 29 Dosing Visit	Day 30 Telephone Call	Day 36 Clinic Visit	Day 43 Clinic Visit	Day 57 Dosing Visit [k]	Day 58 Telephone Call [k]	Day 64 Clinic Visit [k]	Day 71 Clinic Visit [k]	Day 91 Clinic Visit
Prior and concomitant medications	←==========													==========→
Efficacy assessments														
Serum PSA	X	X				X				X		X		X
Radiological assessment	X[i]													
Immunogenicity assessments														
Blood for PBMC assessment[j]		X				X		X		X		X		X
Blood for ctDNA assessment		X												X
Blood for PSA-binding antibody/anti-vector antibody/anti-antigen antibody assessment		X			X	X			X	X			X	X

Abbreviations: AESI – Adverse Event of Special Interest, C3=Cohort 3, ChAd=ChAdOx1-PCAQ, CRP=C-reactive protein, CT=computed tomography, ctDNA=circulating tumour DNA, d=day(s), ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, MVA=MVA-PCAQ, MRI=magnetic resonance imaging, PBMC=peripheral blood mononuclear cells, PET=positron emission tomography, PSA=prostate-specific antigen, SAE=serious adverse event

[a] If the screening period is longer than 42 days, the participant must be reconsented. Consult with the Medical Monitor for which assessments should be repeated.
[b] Windows during the intervention period are calculated from the date of the previous VTP-850 dose.
[c] If a cardiac event is reported, blood should be taken for an additional assessment of troponin T and the participant should undergo an additional ECG and echocardiogram at the earliest opportunity.
[d] Historic echocardiogram may be used if performed within 3 months of Day 1.
[e] May be retrieved at any time during the intervention period.
[f] If troponin T test result is abnormal, a re-test on the following day is required.
[g] Pre-dose and approximately 30 min post-dose.
[h] During the screening period, only SAEs that are causally related to a screening procedure should be collected.
[I] Historic CT/MRI/PET scans and bone scans may be used if performed within 3 months of Day 1. If no historic scan is available, a bone scan and a CT or MRI will be performed.

[j] Only required at sites qualified by Barinthus Biotherapeutics to perform PBMC isolation/processing.
[k] Optional schedule to be repeated for participants receiving a third dose of MVA-PCAQ after initial PSA response followed by progression. Schedule to be repeated for participants whose 2nd dose of MVA was delayed.

Table 2 Schedule of Assessments during the Follow-up Periods

Clinic Visit	Short-term Follow-up Period			Long-term Follow-up Period				
	Month 4 (Day 120)	**Month 5 (Day 150)**	**Month 6 /EOT[a] (Day 180)**	**Months 7/9/10/11/14/ 16/20/22 (Days 210/270 /300/330/420/ 480/600/660)**	**Month 8 (Day 240)**	**Month 12 (Day 360)**	**Month 18 (Day 540)**	**Month 24 (Day 720)/ EOT**
Window[b]	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±7d
Symptom-directed physical examination			X					X
12-lead ECG[c]			X					
Vital signs			X					X
Adverse events	←═══════════→							
Serious adverse events/ AESIs	←═══→							
Prior and concomitant medications	←═══→							
Laboratory safety tests								
Haematology			X					
Biochemistry			X					
Liver function tests			X					
Troponin T[c,d]			X					
Efficacy assessments								
Serum PSA	X	X	X	X	X	X	X	X
Radiological assessment			X (+/- 14 days)			X (+/- 14 days)	X (+/- 14 days)	X (+/- 14 days)
PSMA scan (optional)[e]	←═══→							

Clinic Visit	Short-term Follow-up Period			Long-term Follow-up Period				
	Month 4 (Day 120)	Month 5 (Day 150)	Month 6 /EOT[a] (Day 180)	Months 7/9/10/11/14/16/20/22 (Days 210/270/300/330/420/480/600/660)	Month 8 (Day 240)	Month 12 (Day 360)	Month 18 (Day 540)	Month 24 (Day 720)/ EOT
Immunogenicity assessments								
Blood for PBMC assessment[f]					X	X		
Blood for anti-antigen antibody assessment					X	X		

Abbreviations: AESIs- Adverse Events of Special Interest, d=days, EOT=End of Trial, PBMC=peripheral blood mononuclear cells, PSA=prostate-specific antigen, PSMA=prostate-specific membrane antigen

[a] Participants will only have 1 EOT visit at either Months 6 or 24 or earlier in the event of initiation of new therapy (such as ADT) or development of unequivocal metastatic prostate cancer. Participants with no PSA response in the first 6 months will not enter the Long-Term Follow-up Period. Participants with a PSA response through Month 6 will enter the Long-term Follow-up Period.
[b] Visits during the Follow-up Periods are from Day 1. Windows are relative to the target date of the visit.
[c] If a cardiac event is reported, blood should be taken for an additional assessment of troponin T and the participant should undergo an additional ECG and echocardiogram at the earliest opportunity
[d] If troponin T test result is abnormal, a re-test on the following day is required.
[e] PSMA scan can be performed at any time for participants who had a positive PSMA scan prior to screening and where a 50% reduction from baseline in PSA is observed.
[f] Only required at sites qualified by Barinthus Biotherapeutics to perform PBMC isolation/processing.

2 INTRODUCTION

2.1 Trial Rationale

VTP-850 is a prime-boost immunotherapeutic regimen consisting of 2 viral vectored components, ChAdOx1-PCAQ and MVA-PCAQ. ChAdOx1-PCAQ, the prime dose, consists of a recombinant nonreplicating chimpanzee adenovirus Oxford 1 (ChAdOx1) vector encoding 4 prostate cancer antigens: prostate-specific antigen (PSA), prostatic acid phosphatase (PAP), six-transmembrane epithelial antigen of prostate 1 (STEAP1), and 5T4, an oncofoetal antigen. MVA-PCAQ, the component used for the booster doses, consists of a replication-deficient recombinant Modified Vaccinia virus Ankara (MVA) vector encoding the same prostate cancer antigens as ChAdOx1-PCAQ.

ChAdOx1 and MVA have been incorporated as vectors in different prophylactic vaccines and immunotherapeutics for infectious diseases and cancers. They have both demonstrated immunogenicity in nonclinical and clinical studies for these various indications.

VTP-800 was an earlier immunotherapeutic for prostate cancer that used the same ChAdOx1/MVA heterologous prime/boost platform as VTP-850 but included only one antigen, 5T4. VTP-800 was studied in prostate cancer patients in 2 trials at the University of Oxford.

The VANCE trial in newly diagnosed prostate cancer patients demonstrated immunogenicity and safety of VTP-800. 5T4-specific T cell responses were seen in 25 of the 39 patients (64%), and the median peak for responders was 198 spot forming cells/million.[1] In the ADVANCE trial in metastatic castration-resistant prostate cancer, VTP-800 was administered with nivolumab, and 5 of 23 patients (22%) had a >50% reduction in PSA level at any time point compared to baseline. Three of the responders had measurable lesions at baseline and also had partial response according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1. However, 3 of the PSA responses were transient.

Barinthus Biotherapeutics (formerly known as Vaccitech) designed VTP-850 to induce a broader immune response than VTP-800 by encoding multiple antigens to reduce the ability of cancer cells to evade the immune response by mutating or losing expression of any one antigen.

Trial PCA001 is the first-in-human trial of VTP-850. The aim of this trial is to evaluate the safety, immunogenicity, and the rate and duration of PSA response of VTP-850 in patients with biochemical recurrence after definitive local therapy for prostate cancer. The efficacy of VTP-850 will be assessed by the PSA response rate. In addition, the quality of the responses will be characterised by determining the duration of PSA response and by following the responders to establish whether the responders require new treatment for prostate cancer or develop metastases during long term follow-up. During the Dose/Regimen Finding Phase, different dose levels of each component will be evaluated, with the MVA-PCAQ component evaluated in different cohorts as either an intramuscular (IM) injection or an intravenous (IV) infusion.

2.2 Background

Prostate cancer is the second most frequent cancer diagnosis in men and the fifth leading cause of cancer-related deaths in men worldwide.[2] In 2018, approximately 1.3 million new cases were diagnosed, and approximately 360,000 deaths occurred. The incidence and mortality of prostate cancer increase with age, with the average age of diagnosis being 66 years.[2] Furthermore, the incidence of prostate cancer is expected to increase due to longer life expectancy and lifestyle factors. The rates are highest in North America, Australia, and northern and central Europe, and lowest in south-eastern and south-central Asia and northern Africa.[2]

The serum concentration of PSA is usually elevated in men with prostate cancer and is used to monitor the progression of prostate cancer in men who have already been diagnosed with the disease. About 90% of patients with prostate cancer have localised or regional disease at the time of diagnosis. Localised or regional prostate cancer can be treated with radiation or surgical removal of the prostate. These localised therapies can be curative, but the cancer recurs in approximately 20% to 30% of patients. Patients with localised prostate cancer may also receive androgen deprivation therapies (ADTs), as androgens stimulate the growth of prostate cancer cells. Patients with recurrent disease are typically offered ADT when they present with symptomatic local disease progression, proven metastases or a PSA doubling time of less than 3 months.[3] If a patient has evidence that their cancer is progressing despite ADT, such as increasing PSA in their blood or new bone metastases, it signifies that their disease is castration-resistant.[4]

Once prostate cancer becomes metastatic, it is considered incurable. Current treatment options for metastatic prostate cancer include androgen receptor inhibitors, such as enzalutamide and abiraterone; chemotherapy including docetaxel and cabazitaxel; a radioactive isotope radium-223; lutetium vipivotide tetraxetan, a radiopharmaceutical, and sipuleucel-T, a patient-specific immunotherapeutic. All of these treatments have been shown to improve survival, but once the cancer is castration-resistant, the median overall survival is less than 3 years.

Recent Phase 3 clinical studies have shown that drugs such as enzalutamide, apalutamide, abiraterone and docetaxel can provide a survival advantage when used earlier in a patient's course of treatment, but the optimal sequence for the different treatment types has yet to be determined.

Patients with prostate cancer have few options once metastatic disease is evident. Targeting the disease earlier in its development may be an effective strategy to prevent or delay the development of metastases and may allow patients to delay or avoid ADT and other therapies. VTP-850 is designed as a potentially low-toxicity immunotherapeutic intervention to treat prostate cancer, prior to metastases forming, while the disease is still considered castration sensitive, but with rising PSA values.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of VTP-850 may be found in the Investigator's Brochure (IB).

2.3.1 Risk Assessment

A summary of potential risks for VTP-850 administration is included in Table 3.

Table 3 Summary of Potential Risks for VTP-850 Administration

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Trial Intervention (VTP-850)		
A potential signal of cardiac risk has been identified and assessed following administration of VTP-850 in the trial population	In the first 14 participants treated, a potential cardiac-related death has been reported together with non-serious adverse events of dyspnoea, and dyspnoea exertional and atrial fibrillation in two further participants. These events have a possible temporal relationship to trial intervention, occurring within a similar timeframe after the first MVA-PCAQ boost.	Participants with a history of cardiac events that put them at risk will be excluded from the trial. In addition, cardiac monitoring (ECG and laboratory blood tests) will be performed at pre-defined timepoints during the first 6 months of the trial and a baseline echocardiogram will be performed to exclude participants with any clinically significant abnormalities.
Potential for local reactions (injection site redness, injection site swelling and injection site pain) and systemic reactions (including fever, chills, feverishness and headache) following IM administration.	These are common reactions seen with other products that use the same viral vectors as are used in VTP-850. Further details are provided in the current IB.	The investigator site will contact the participant one day after the administration of each component of VTP-850 7 days after the administration of ChAdOx1-PCAQ, and the participant will return to the clinic 7 days after each administration of MVA-PCAQ, at which times the trial staff will record AEs
With any immunotherapeutic there is a rare risk of anaphylaxis which can be fatal.	-	Participants will be dosed in a clinical area where appropriate drugs and medical equipment to treat acute anaphylactic reactions are immediately available for the management of such adverse reactions in the immediate post-administration period. Participants are observed in the clinic for at least 30 min post-dose. Participants with history of anaphylaxis to previous vaccination are excluded.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential risk of elevated liver function tests following IV MVA-PCAQ.	Transient laboratory abnormalities including increases in liver function tests following IV dosing were observed in clinical studies with an MVA-vectored vaccine for malaria. These abnormalities were without clinical symptoms or signs and returned toward baseline values over time. The clinical significance of these observations is unknown.	Safety labs at 7 and 14 days after each IV administration of MVA-PCAQ. The first 3 participants who receive IV MVA-PCAQ will be staggered so that the second and third participants do not receive MVA-PCAQ until the laboratory results following the previous participant's initial MVA-PCAQ dosing have been assessed.
Unknown AEs and laboratory abnormalities with a novel immunotherapeutic.	This trial is the first time VTP-850 will be administered to humans.	Routine safety laboratory testing (including haematology, chemistry, liver function tests) and clinical assessments will be obtained during the Intervention and Follow-up Periods to monitor for expected and unexpected AEs. A Safety Monitoring Committee (SMC) will review safety data during the trial.
Potential very rare adverse events that have occurred in people who have received a different ChAdOx1-vectored product.	There have been very rare events of thrombosis with thrombocytopenia, Guillain Barré Syndrome, and capillary leak syndrome with the ChAdOx1-vectored vaccine Vaxzevria, which is authorised in many parts of the world. It is not known if these are related to the ChAdOx1 vector. Such events have not been detected with other ChAdOx1-vectored products to date, and it is not known if they will occur with ChAdOx1-PCAQ.	Participants with previous history of thrombosis with thrombocytopenia, Guillain Barré Syndrome, and capillary leak syndrome have been excluded from the trial because it is possible that they may be at higher risk.
Trial Procedures		
Venipuncture will be performed during the trial.	There is the risk of bleeding, bruising, haematoma formation and infection at the venipuncture site.	Only appropriately qualified personnel would perform the blood draw.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Bone scans and radiographic assessments will be performed during the trial.	There is a low risk of allergic reaction to contrast material. Bone scans and CT scans involve exposure to small amounts of radiation.	Only appropriately qualified personnel would perform radiographic procedures.

Abbreviations: AE=adverse event, CT=computed tomography, IM=intramuscular, IV=intravenous

2.3.2 Benefit Assessment

Potential benefits to individual participants may include:

Receipt of a potentially efficacious immunotherapeutic for prostate cancer. However, as this is an early development trial with no previous efficacy data, there may be no such benefit to trial participants.

The participants will receive additional monitoring of their prostate cancer compared to the standard of care.

- Contributing to research to help others. Participation in this trial may contribute to the development of a treatment for prostate cancer.

2.3.3 Overall Benefit-Risk Conclusion

Taking into account the measures taken to minimise risk to participants participating in this trial, the potential risks identified in association with VTP-850 are justified by the anticipated benefits that may be afforded to participants with prostate cancer.

3 OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Endpoints
To evaluate the safety of VTP-850 prime-boost regimens, with the booster dose administered either IM or IV, and establish an RP2R	• Number and proportion of participants with AEs, treatment-related AEs, ≥Grade 3 AEs, ≥Grade 3 treatment-related AEs, serious adverse events, and treatment-related serious adverse events • Number and proportion of participants with clinically significant laboratory values • Change from baseline for laboratory tests and vital sign measurements at each time point of collection
Secondary Objectives	**Secondary Endpoints**
To evaluate the PSA response rate to VTP-850	• Percentage of participants with ≥50% reduction in serum PSA compared to baseline at any time, based on two consecutive measurements, at least 2 weeks apart
To evaluate the durable PSA response rate to VTP-850	• Percentage of participants with confirmed PSA response compared to baseline without having PSA progression on or before Month 8.
To evaluate the duration of PSA response to VTP-850 (for the subset of participants with PSA response)	• Duration of PSA response (for the subset of participants with PSA response), defined as time from date of first dose of VTP-850 to the date of PSA progression (i.e., an increase of ≥25% and an absolute increase of 0.2 ng/mL or more from nadir)
To assess the Metastasis-free Survival (MFS) and Time to Metastases (TTM) of the subset of participants with PSA response	• MFS is defined as the time from date of first dose of VTP-850 until metastatic disease by conventional imaging (CT/MRI and/or technetium-99 bone scan) or death from any cause, whichever occurs first • TTM is defined as the time from date of first dose of VTP-850 until metastatic disease by conventional imaging (CT/MRI and/or technetium-99 bone scan) Note that MFS and TTM events do not include local progression events, e.g., progression in pelvic lymph nodes below the aortic bifurcation.
To assess the time to start of ADT for the participants with PSA response	• Time from date of first dose of VTP-850 to the earliest of the start of ADT or the date when criteria to start ADT are met
Exploratory Objectives	**Exploratory Endpoints**
To characterise immunogenicity (including antigen-specific T cell magnitude, phenotype and functionality associated with each regimen)	CD4+ and CD8+ T cell response to the VTP-850 antigens in the peripheral blood as measured by multi-parameter flow cytometry and enzyme linked immunospot assays • Other immune responses to VTP-850

To explore association of PSA response with biomarkers	Microsatellite instability-high status (MSI-H), Breast Cancer gene (BRCA) mutations and other molecular markers Expression level of the VTP-850 antigens (PSA, prostatic acid phosphatase [PAP], six-transmembrane epithelial antigen of prostate 1 [STEAP1], 5T4) in historic tumour samples • Circulating tumour DNA • Serum PSA-binding antibodies
To look for evidence of resolution of lesions on PSMA scan after administration of VTP-850 (if documented at baseline), and association of resolution of such lesions with PSA response in the subset of participants with baseline PSMA scan who have a PSA response on trial	• PSMA scans (optional)
To assess the MFS and TTM of all participants	• MFS is defined as the time from date of first dose of VTP-850 until metastatic disease by conventional imaging (CT/MRI and/or technetium-99 bone scan) or death from any cause, whichever occurs first • TTM is defined as the time from date of first dose of VTP-850 until metastatic disease by conventional imaging (CT/MRI and/or technetium-99 bone scan) Note that MFS and TTM events do not include local progression events, e.g., progression in pelvic lymph nodes below the aortic bifurcation

Abbreviations: ADT=androgen deprivation therapy, CT=computed tomography, IM=intramuscular, IV=intravenous, MFS=Metastasis-free Survival, MRI=magnetic resonance imaging, PSA= prostate-specific antigen, PSMA=prostate-specific membrane antigen, RP2R=recommended Phase 2 regimen, TTM=Time to Metastases

4 TRIAL DESIGN

4.1 Overall Trial Design

This is a multicentre, Phase 1/2, open-label clinical trial of the VTP-850 prime-boost immunotherapeutic in men with biochemical recurrence after definitive local therapy for prostate cancer. The trial will be conducted in up to 30 centres worldwide.

Participants in all cohorts will receive the ChAdOx1-PCAQ component on Day 1 (prime) and the MVA-PCAQ component on Days 29 and 57 (boosts). Participants will be followed until the Month 6 Visit or start of new therapy such as ADT or until development of unequivocal metastatic prostate cancer. Participants who have a PSA response will be followed for an additional 18 months, up to 24 months from first dose, or until start of new therapy such as ADT or development of unequivocal metastatic prostate cancer. In the event that a participant experiences a confirmed PSA response but subsequently experiences PSA progression more than 2 months after their final dose of VTP-850, an additional dose of MVA-PCAQ may be offered to the participant.

4.1.1 Phase 1 – Dose/Regimen Finding Phase

Phase 1 will determine the recommended Phase 2 regimen (RP2R; dose level of both ChAdOx1-PCAQ and MVA-PCAQ, and route of administration of MVA-PCAQ) that will be used in Phase 2 and will follow a 3+3 design.

Participants will be dosed according to Table 1 during the Screening and Intervention PeriodsTable 5. The first 3 participants will be enrolled in Cohort 1. Enrolment of the first 3 participants in each cohort will be staggered by at least 9 days. The medical monitor will review the safety data for the previous participant, at least 7 days after the prime dose and after the first booster dose of VTP-850, before the corresponding dose is administered to the next participant. The safety review will include data from at least 7 days after each ChAdOx1-PCAQ prime dose; at least 7 days after the first booster MVA-PCAQ dose if administered IM; and at least 14 days after the first booster dose of MVA-PCAQ if administered IV. If 1 or more of the 3 participants has a dose limiting toxicity (DLT), 3 additional participants may be enrolled into Cohort 1. If there is no DLT after the first dose of VTP-850 in the first 3 participants, 3 participants will be enrolled into each of Cohorts 2 and 3 concurrently, with the first participants in Cohorts 2 and 3 staggered by at least 9 days to allow for medical review.

If DLT is not seen in more than 1 participant in Cohort 2 after the first dose of VTP-850, then an additional 3 participants will be enrolled into Cohort 2. Safety data for the DLT period following each booster dose will be assessed by the medical monitor prior to the corresponding booster dose being administered to additional participants.

If DLT is not seen after the first dose of VTP-850 in more than 1 participant in Cohort 3, then an additional 3 participants will be enrolled into Cohort 3. Safety data for the DLT period following each booster dose will be assessed by the medical monitor prior to the corresponding booster dose being administered to additional participants.

A total of 6 participants in each of Cohorts 2 and 3 will be dosed with MVA-PCAQ on Day 29 and Day 57. Therefore, participants who withdraw before dosing, before completion of dosing or who have dose delays will be replaced (unless the reason for not completing dosing per protocol is related to a stopping rule criteria being met).

If the safety of one or more cohorts is acceptable after all participants have been followed through the DLT period after the first booster dose of VTP-850, then a Phase 2 dosing regimen will be selected based on safety data, and recruitment to Phase 2 will be opened.

A Safety Monitoring Committee (SMC) consisting of the Medical Monitor, sponsor physician, a prostate cancer physician not participating in the trial, and at least 2 investigators will review cumulative safety data and decide whether to enrol each cohort in Phase 1 and whether to open enrolment in Phase 2, and will also choose the RP2R. The SMC will evaluate all events that meet the DLT criteria, taking into consideration the outcome and recovery time of each event.

The DLT evaluation period ends 7 days after each IM injection and 14 days after each IV injection of MVA-PCAQ.

A DLT is defined as any of the following toxicities that occur during the DLT evaluation period and are considered related to trial intervention (Grading is per CTCAE Version 5.0):

- Grade 4 or fatal AE
- Grade 3 or greater hematologic AE that does not recover to Grade 1 or baseline Grade within 72 hours
- Grade 3 or greater hepatic and renal dysfunction that does not improve to ≤ Grade 2 within 7 days

Grade 3 or greater AE affecting heart, lung or Central Nervous System (CNS) of any duration (including encephalopathy as defined by Immune Effector Cell Encephalopathy [ICE] or Immune Effector Cell -Associated Encephalopathy criteria [ICAN])

- Grade 3 or greater cytokine release syndrome (CRS) that does not improve to ≤ Grade 2 within 72 hours
- Grade 3 or greater clinical AE other than heart, lung or CNS toxicity, hepatic or renal dysfunctions, not resolving to <Grade 2 within 72 hours

4.1.2 Phase 2 – Main Phase

Phase 2 of the trial will consist of 2 sequential stages.

In Stage 1 of Phase 2, 19 additional participants will be enrolled at the chosen Phase 2 regimen. If 4 or more of the 25 participants at the RP2R (out of the 19 Phase 2 participants and the 6 Phase 1 participants who received the same dose regimen according to the dosing schedule) have a PSA response, Stage 2 will be opened to enrolment. If 3 or fewer of the 25 participants receiving the RP2R have a PSA response, no further participants will be enrolled. PSA response is defined as ≥50% reduction in serum PSA compared to baseline at any time, measured at two consecutive timepoints, at least 2 weeks apart. The decision to open recruitment in Stage 2 will be made by the SMC after reviewing available safety and efficacy data after at least 4 participants have exhibited a PSA response.

4.1.3 Selection of Phase 2 Regimen

This trial will test 2 dose levels of ChAdOx1-PCAQ and 2 dose levels of MVA-PCAQ delivered IM and one dose level of MVA-PCAQ delivered IV.

Based on previous experience with vaccines and immunotherapeutics made with the ChAdOx1 vector, it is expected that the higher dose level of ChAdOx1-PCAQ (2.5×10^{10} viral particles [vp]; Cohorts 2 and 3) will be more immunogenic and therefore will be chosen over the lower dose if both have acceptable safety. Similarly, for IM administration of MVA-PCAQ, the higher of the 2 IM doses (2×10^{8} plaque forming units [pfu] IM; Cohort 2) is expected to be more immunogenic and will be chosen over the lower dose if both have acceptable safety.

Based on previous preclinical and clinical experience with vaccines and immunotherapeutics made with the MVA vector used as a booster, it is expected that the IV route of administration will result in enhanced T cell responses and better delivery of T cells to tissues, resulting in better efficacy. Therefore, the IV route of administration of MVA-PCAQ (Cohort 3) will be chosen over the IM route if both have acceptable safety.

4.1.4 Duration of Trial for Participants

The trial consists of the following periods:

- Screening Period: Up to 42 days from informed consent until VTP-850 prime dose.
- Intervention Period: From VTP-850 prime dose until the Day 91 Clinic Visit.

Short-term Follow-up Period: All participants will be followed monthly from the end of the intervention period until the Month 6 Visit or until start of new therapy such as ADT or development of unequivocal metastatic prostate cancer, if sooner. If a participant does not have a PSA response by their Month 6 visit, they will complete their EoT visit and will not enter the Long-term Follow-up Period.

Long-term Follow-up Period: Participants who have PSA response will be followed for an additional 18 months, up to 24 months from first dose, or until start of new therapy such as ADT or development of unequivocal metastatic prostate cancer, if sooner. Clinic visits will be monthly to Month 12 and bimonthly thereafter. If a participant has a significant decrease in PSA but does not meet the criteria for a PSA responder e.g., the confirmatory measurement is not yet performed, discuss with the Medical Monitor whether the participant should continue follow-up.

4.1.5 Safety Review During the Trial

The Medical Monitor will review the trial data throughout the trial.

The SMC will review the trial data periodically and make recommendations as detailed in Appendix A1.5.

4.1.6 Pausing/Stopping Rules

The trial will be temporarily paused and there will also be an unscheduled review of trial data by the SMC in the event of one or more of the following at any time during the trial:

A CTCAE Grade 4 or 5 AE that is considered related to either component of VTP-850

An SAE that is considered related to either component of VTP-850

Death that occurs within 30 days of receiving either component of VTP-850

The regulatory authority and independent ethics committee (IEC)/institutional review board (IRB) will be notified of a temporary halt according to local requirements. If, following review of data, a recommendation is made by the SMC to resume trial enrolment and VTP-850 administration, the SMC will record their judgment in a memorandum to the trial file. The SMC memorandum will be forwarded to the investigators.

If the trial is terminated early, the regulatory authority and IEC/IRB will be notified according to local requirements.

4.1.7 Progression after Initial PSA Response

In the event that a participant experiences a confirmed PSA response but subsequently experiences PSA progression more than 2 months after their final dose of VTP-850, an

additional dose of MVA-PCAQ may be offered to the participant if the investigator believes it may be in the participant's best interest, after discussion with the medical monitor and agreement of the SMC. In this case, the participant will have an additional dosing visit which will include the events done on the Day 57 Dosing Visit in the Schedule of Assessments (SoA; see Table 1). Additional follow-up visits 1, 7, and 14 days after the additional dose will include the assessments done on the Day 58, Day 64, and Day 71 Visits in the SoA,. Subsequently they will continue to follow the SoA from the Day 91 Clinic Visit for their remaining time on trial (Section 1.3). Participants will be followed up to the Month 6 visit following the additional dose of VTP-850 or, if a PSA response is seen, for up to 24 months following the first dose of VTP-850, or until start of new therapy such as ADT or development of unequivocal metastatic prostate cancer, at which point an End of Trial (EOT) visit will be performed.

In order to perform sufficient follow-up post dose, the latest a participant can qualify for an additional MVA-PCAQ dose is using the blood test taken at the Month 18 visit.

4.2 Justification for Dose

The doses/regimens chosen for evaluation in this trial are provided in Table 4.

The doses of each component and the dosing intervals chosen for this trial are based on historical data from previous studies of other products made with the same vectors. MVA boosts and prolongs the CD4+ and CD8+ T cells induced by ChAdOx1. This heterologous prime/boost immunotherapeutic regimen has been safe and immunogenic when used with products for other indications. ChAdOx1, including doses up to 5×10^{10} vp, and MVA, including doses up to 2.5×10^{8} pfu IM and up to 1×10^{9} pfu IV, were evaluated in various indications.[6-9,12]

4.2.1 Selection of ChAdOx1-PCAQ Target Dose

The target ChAdOx1-PCAQ dose level selected for this trial is 2.5×10^{10} vp, based on the review of doses employed in other programs employing the ChAdOx1 platform in which this dose level, or higher, of ChAdOx1-based products has been safely administered:

This is the same dose as the ChAdOx1 component of VTP-800, a prostate cancer immunotherapeutic that was made with the same ChAdOx1/MVA platform as VTP-850 and which included only the 5T4 oncofoetal antigen. It was safely administered in 2 clinical trials at University of Oxford.

Two dose levels of ChAdOx1-HBV were studied in trial HBV001 (2.5×10^{9} vp and 2.5×10^{10} vp). Safety data were reviewed from HBV001 by the SMC, and the higher dose was chosen to use in trial HBV002.

- Over one billion people have been immunised with a ChAdOx1-vectored COVID-19 vaccine at a dose of 5×10^{10} vp.[13]

Safety and immunogenicity data from an additional clinical trial, MERS001 (NCT03399578), using the ChAdOx1 vector at this dose, also helped inform dose selection.

4.2.2 Selection of MVA-PCAQ Doses and Regimen

The target MVA-PCAQ doses selected for this trial are 2×10^8 pfu for IM administration and 2×10^7 pfu for IV administration, based on the review of historical data from previous studies in other programs employing the MVA platform.

- In the completed studies of VTP-800, the prostate cancer immunotherapeutic that was made with the same ChAdOx1/MVA platform as VTP-850 and which included only the 5T4 oncofoetal antigen, booster doses of MVA.5T4 were safely administered IM in 2 clinical trials at University of Oxford at a dose of 1.2×10^8 pfu in the first trial, in patients with early phase prostate cancer, and at a dose of 2×10^8 pfu in the second trial, in patients with advanced prostate cancer.
- One dose level of MVAHBV fixed at 1×10^8 pfu is being administered IM in the ongoing HBV002 trial.

A dose of 1.5×10^8 pfu MVA was administered IM to nearly 2,000 healthy participants in influenza studies conducted by Oxford University and Barinthus Biotherapeutics .

An MVA-vectored smallpox vaccine was approved in the US in 2019. JYNNEOS (IMVANEX, IMVAMUNE) is a vaccine produced from the strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN). Each 0.5 mL dose is formulated to contain 0.5×10^8 to 3.95×10^8 infectious units of MVA-BN live virus. The overall clinical trial program included 22 studies and a total of 7859 individuals 18 through 80 years of age who received at least 1 dose of JYNNEOS.

4.2.3 Justification for Intravenous Administration of MVA-PCAQ

In addition to IM dosing, which has been used in the studies described in the previous section, the booster doses of MVA-PCAQ will also be administered IV to investigate whether this route of administration might lead to increased efficacy.

Preclinical studies have demonstrated that IV administration of some vaccines, including MVA-based constructs, can induce superior immunogenicity compared with subcutaneous or IM routes. Studies of a prophylactic vaccine for malaria (ChAd63-ME-TRAP/MVA-ME-TRAP) in mice, which used a similar prime-boost vaccination regimen, showed that changing the route of administration of the booster vaccine from IM to IV resulted in delivery of higher numbers of resident memory T-cells to the liver and improvement of efficacy against sporozoite challenge. A clinical trial of this vaccine at University of Oxford, in which participants received the booster vaccine intravenously, showed enhanced T cell responses to the malaria antigens in the vaccine (personal communication).

In a first-in-human trial at the National Institutes of Health Clinical Center [12], 13 cancer patients received IV MVA-BN-brachyury-TRICOM, an MVA vector-based therapeutic cancer vaccine designed to induce an immune response against brachyury, which is overexpressed in many solid tumours. The maximum administered dose was 1×10^9 infectious units every 3 weeks for 3 doses. No DLTs were observed, and no SAEs were attributed to the vaccine. The maximum tolerated dose was not reached. One patient achieved a partial response.

4.3 Scientific Rationale for Trial Design

Barinthus Biotherapeutics is developing a prime-boost immunotherapeutic strategy using 2 non-replicating viral vectors to deliver immunogens in various indications: ChAdOx1 followed by boosting with a heterologous vector, MVA, containing the same immunogens. These vectors have been shown to induce high magnitude CD4+ and CD8+ T-cell responses and to generate lasting cell-mediated immunity.[5-9]

Adenoviral vectors are exceptional priming vectors but there is a concern that anti-vector immunity could interfere with boosting the immune response when the ChAdOx1 vector is used repeatedly at short intervals. For this reason, product developers often use a different vector (known as a heterologous prime-boost) to augment the levels of the induced T cells.[10,11]

Previous studies have shown that heterologous prime-boost regimens employing different vectors tend to produce more potent T-cell responses in nonhuman primates and humans than do homologous prime-boost regimens.

VTP-850 has been designed following a Phase 1/2 clinical trial with VTP800, a prime-boost regimen with ChAdOx1 and MVA but encoding 5T4 only. Barinthus Biotherapeutics designed VTP-850 to induce a broader immune response by encoding multiple antigens (PSA, PAP, STEAP1, 5T4) to reduce the ability of cancer cells to evade the immune response by mutating or losing expression of any one antigen. These components are known as ChAdOx1-PCAQ and MVA-PCAQ.

The dose escalation design including a small number of participants used in the dose/regimen finding phase is standard in first-in-human studies to minimise exposure to ineffective or poorly tolerated doses.

Both ChAdOx1-PCAQ and MVA-PCAQ will be administered by IM injection. MVA-PCAQ will also be administered IV in one dose regimen cohort because preclinical data and previous clinical data suggest that boosting by the IV route might lead to increased efficacy.

5 TRIAL POPULATION

Prospective approval of protocol deviations to eligibility criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the trial only if all of the following criteria apply:

Age

1. Males aged 18 years and above at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Histologically or cytologically confirmed adenocarcinoma of the prostate.
3. Has undergone primary therapy for prostate cancer (radical prostatectomy and/or definitive external beam radiation and/or brachytherapy). Salvage external radiation therapy (XRT) following radical prostatectomy >6 months prior to Day 1 is allowed.

4. No further local therapy to prostate or systemic therapy for prostate cancer and no metastasis-directed therapy for PSA-positron emission tomography (PET) positive lesions planned within 4 months after the first dose of VTP-850.
5. Serum testosterone >175 ng/dL.
6. Nonmetastatic (M0) disease and no evidence of prostatic bed recurrence verified by whole body bone scintigraphy and either computed tomography (CT) or magnetic resonance imaging (MRI). Note that a positive PSMA PET does not exclude the participant if the conventional scans are negative.
7. Serum PSA of >0.3 ng/mL for participants with prior radical prostatectomy (with or without salvage radiotherapy), or serum PSA of 2 ng/mL above nadir for participants with prior external beam radiation or brachytherapy.
8. PSA doubling time ≤12 months.
9. Not planning to start ADT for at least 4 months after Day 1.
10. Eastern Cooperative Oncology Group (ECOG) Score 0 or 1.
11. Baseline laboratory parameters must meet the following criteria:
    - Haemoglobin ≥110 g/L
    - White cell count $\geq 2.0 \times 10^9$/L
    - Absolute neutrophil count $\geq 1.5 \times 10^9$/L
    - Lymphocytes $\geq 0.9 \times 10^9$/L
    - Platelets $\geq 100 \times 10^9$/L
    - Creatinine ≤1.5×upper limit of normal (ULN) OR calculated creatinine clearance ≥50 mL/min by the Cockcroft Gault formula
    - Total bilirubin ≤1.5×ULN, (total bilirubin >1.5×ULN is acceptable if total bilirubin is fractionated and direct bilirubin < 35%)
    - Alanine aminotransferase ≤1.5×ULN
    - Aspartate aminotransferase ≤1.5×ULN
    - Troponin T within normal range
    - HbA1c <7 %

Sex and Contraceptive/Barrier Requirements

12. Agrees to the following during the trial and for at least 65 days after the last dose of VTP-850:
    - Refrain from donating sperm

PLUS, either

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

OR

- Agrees to use a male condom when having sexual intercourse with a woman of childbearing potential, and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak

Other Inclusions

Agrees to comply with all scheduled visits, VTP-850 administration plan, laboratory tests, lifestyle considerations and other trial procedures.

5.2 Exclusion Criteria

Participants are excluded from the trial if any of the following criteria apply:

Cancer History

1. Any other prior malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.

Medical Conditions

2. Unstable medical condition, drug or alcohol abuse, or medical or psychiatric condition that in the opinion of the investigator would affect the safety of the participant or the evaluation of the data or interfere with adherence to the trial requirements.
3. Significant history of or current cardiovascular, respiratory, renal, gastrointestinal, endocrinological, haematological or neurological disorders constituting a risk when taking the trial intervention or interfering with the interpretation of data; cardiac event or heart failure in the previous 6 months.
4. Current or chronic history of liver disease. This includes but is not limited to: hepatitis virus infections, cirrhosis, drug- or alcohol-related liver disease, non-alcoholic steatohepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, primary biliary cholangitis, primary sclerosing cholangitis or any other liver disease considered clinically significant by the investigator. (Note that history of hepatitis C infection, Gilbert's syndrome or non-alcoholic fatty liver not associated with steatohepatitis are not exclusions. In line with Exclusion Criterion 10, active hepatitis C infection is exclusionary.)
5. Active autoimmune disease that has required systemic treatment in past 2 years with use of disease modifying agents, chronic corticosteroids (>14 days) or immunosuppressive drugs. Note that hormone replacement therapy (e.g., thyroxine, insulin or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is allowed.
6. History of severe allergy to eggs or history of severe reaction to any previous vaccination that required medical attention.
7. Medical history that could increase the participant's risk of reaction to a vaccine, including but not limited to capillary leak syndrome, transverse myelitis, multiple sclerosis, Guillain Barré syndrome, significant thrombocytopenia, thrombosis with thrombocytopenia syndrome (also termed vaccine-induced thrombotic thrombocytopenia), heparin-induced thrombocytopenia, or hereditary angioedema, acquired angioedema or idiopathic angioedema.

8. Any immunocompromised state, or history of solid organ or stem cell transplantation.
9. Active infection requiring parenteral antibiotic therapy or causing fever (temperature ≥38.0˚C) within 7 days prior to Day 1, or unexplained fever (temperature ≥38.0˚C) within 7 days prior to Day 1.
10. Known history of infection with hepatitis B virus, or human immunodeficiency virus, or active hepatitis C virus infection (antibody and RNA positive).

Prior/Concomitant Therapy

11. Received XRT following radical prostatectomy within 6 months prior to Day 1.
12. Received ADT outside of the initial primary therapy.
13. Prior chemotherapy or immunotherapy (including vaccines or checkpoint inhibitors) or experimental agent or participation in a clinical trial for prostate cancer with the exception of those taking part as primary treatment option.
14. Received a vaccine with adenovirus vector within 3 months prior to Day 1.
15. Received any live vaccine within 30 days prior to Day 1, or planned vaccination to occur within 3 months after Day 1.
16. Received any non-live/inactivated vaccine within 14 days of Day 1 or planned non-live vaccination to occur within 10 weeks after Day 1.
17. Administration of immunoglobulins and/or any blood products within 28 days prior to Day 1.
18. Condition requiring systemic treatment with corticosteroids or other immunosuppressive medications within 14 days of first dose of VTP-850. Note that adrenal replacement doses are permitted. Inhaled and topical corticosteroids are allowed.
19. Received an investigational product or investigational surgical procedure in the 3 months prior to Day 1 or planned use during the trial period, or participation at any time in clinical trial for prostate cancer with exception of those taking part as primary treatment.

Cardiovascular Risk Profile

20. Any significant cardiovascular conditions per the investigator within 6 months before study entry including but not limited to: myocardial infarction, stroke, New York Heart Association class III or IV heart failure, thromboembolic events, major cardiovascular or cerebrovascular procedures, history of cardiac valvular disease or other structural heart disease or any other condition that in the investigator's opinion puts the participant at unacceptable risk to enter the study.
21. Participant with QT interval corrected for heart rate (QTc) determined using Fridericia's formula (QTcF; QTcF = QT/[R-R interval {RR}^0.33]) > 470 msec and any other ECG findings deemed clinically significant at screening.
22. Uncontrolled hypertension that, in the opinion of the Investigator, puts participant at increased risk of a cardiovascular event at the time of screening.
23. Uncontrolled dyslipidemia that, in the opinion of the Investigator, puts participant at increased risk of cardiovascular event at the time of screening.

5.3 Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical trial is not subsequently entered in the trial. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE causally related to a screening procedure.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened after discussion with the medical monitor.

5.4 End of Trial Definition

The end of the trial is defined as the date of the last visit of the last participant in the trial.

6 TRIAL INTERVENTIONS AND CONCOMITANT THERAPIES

6.1 Identity of Investigational Products

Details of the components of VTP-850 are provided in Table 4.

Table 4 Interventions Administered

Intervention Name	ChAdOx1-PCAQ	MVA-PCAQ
Investigational Medicinal Product Type	Biologic (Immunotherapeutic)	Biologic (Immunotherapeutic)
Dose Formulation	Suspension in a glass vial 10 mM TRIS, 10 mM L-histidine, 75 mM NaCl, 5% sucrose (w/v), 1 mM $MgCl_2$, 0.02% Polysorbate 80 (w/v), 0.1 mM ethylenediaminetetraacetic acid, 0.5% ethanol (v/v), water for injections to 0.7 mL, pH 7.4	Suspension in a glass vial sucrose 50 g/L, 50 mM NaCl, 10 mM TRIS, 10 mM sodium glutamate, pH 8.0
Route of Administration	IM injection	IM injection **or** Slow injection and flushing into IV line
Use	Experimental (Prime vaccination)	Experimental (Booster vaccination)
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labelling	Will be provided in glass vials. Secondary packaged in a cardboard carton, with tamperproof seal. Each carton and vial will be labelled as per country requirement.	Will be provided in glass vials. Secondary packaged in a cardboard carton, with tamperproof seal. Each carton and vial will be labelled as per country requirement.
Target Concentration per Vial	5.0×10^{10} vp/mL	4.0×10^{8} pfu/mL

Abbreviations: IM=intramuscular, IV=intravenous, pfu=plaque forming units, TRIS=Tris (hydroxymethyl) aminomethane, v=volume, vp=viral particles, w=weight

6.2 Dose Levels Administered

The doses/regimens chosen for evaluation in this trial are provided in Table 5.

Table 5 Phase 1 Trial Cohorts

Cohort	Number of Participants completing MVA-PCAQ dosing at Day 29 and 57	Trial Intervention	
		ChAdOx1-PCAQ Day 1	MVA-PCAQ Days 29 and 57
1	3-6	5×10^9 vp IM	5×10^7 pfu IM
2	6	2.5×10^{10} vp IM	2×10^8 pfu IM
3	6	2.5×10^{10} vp IM	2×10^7 pfu IV

Abbreviations: IM=intramuscular, IV=intravenous, pfu=plaque forming units, vp=viral particles

6.3 Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit and storage for all trial intervention received, and any discrepancies are reported and resolved before use of the trial intervention. Any excursions from the storage conditions of the trial intervention as described in the label should be reported to Barinthus Biotherapeutics upon discovery along with any actions taken. The site should actively pursue options for returning the trial intervention to the storage conditions described in the labelling, as soon as possible. Once an excursion is identified, the trial intervention must be quarantined and not used until Barinthus Biotherapeutics provides permission to use the trial intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the pharmacy manual.

Only participants enrolled in the trial may receive trial intervention, and only authorised site staff may supply or administer trial intervention. All trial intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution or the head of the medical institution (where applicable) is responsible for trial intervention accountability, reconciliation and record maintenance (i.e., receipt, reconciliation and final disposition records). Copies of these records will be provided to the sponsor for filing in the trial master file.

Detailed instructions on administration of the components of VTP-850 are provided in the pharmacy manual.

Further guidance and information for the final disposition of unused trial interventions are provided in the pharmacy manual.

6.4 Measures to Minimise Bias: Randomisation and Blinding

Not applicable. This is an open-label trial with no randomisation or blinding.

6.5 Trial Intervention Compliance

All participants will be dosed at the site and will receive trial intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and electronic case report form (eCRF).

6.6 Dose Modification

No dose modifications of VTP-850 for individual participants are planned.

6.7 Continued Access to Trial Intervention after the End of the Trial

VTP-850 will not be made available to the participants after the trial is completed, as immunotherapeutic regimens of this type are intended to produce long-lasting immune responses and are not meant to require chronic use.

6.8 Overdose or Incorrect Administration

For this trial, any dose of VTP-850 greater than 50% above the intended dose is considered an overdose.

An overdose or incorrect administration of either component of VTP-850 is not an AE unless it results in untoward medical effects.

In the case of overdose the participant should be monitored for evidence of toxicity and standard supportive treatment provided based on any signs or symptoms experienced. There is no rescue medication. In the event of an overdose or other significant medication error that might impact the safety of the participant, the investigator should:

Contact the medical monitor immediately

Closely monitor the participant for any AE/SAE and laboratory abnormalities

- Record any overdose or incorrect administration of VTP-850 in the eCRF as part of the administration information

6.9 Rescue Medicine

There is no rescue medication for VTP-850.

6.10 Prior and Concomitant Medications

Any medication (including ADT, over-the-counter or prescription medicines, recreational drugs, vitamins and/or herbal supplements) that the participant receives from 30 days prior to Day 1 until the End of Trial Visit should be recorded, along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

All vaccines that the participant received any time from 6 months prior to enrolment and any time during the trial should be recorded. Any prior adenoviral-vectored vaccine administered at any time should be recorded (e.g., Covid-19 vaccines made by Janssen/Johnson & Johnson or by AstraZeneca).

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Concurrent administration of certain agents might confound efficacy and safety assessments. These agents include:

- Immunosuppressants (such as cyclosporin, mycophenolate mofetil, tacrolimus).
- Immunomodulators used in autoimmune conditions (such as rituximab, anti-tumour necrosis factor inhibitors).

High-dose systemic steroids at greater than physiological replacement dose (typically >10 mg/day prednisone or equivalent). However, inhaled, otic and ophthalmic corticosteroids or localised injections (e.g., intra-articular, intrabursal) are typically not a problem.

Medications should not be withheld if they are required for a participant's medical care. Use of these drugs during the trial should be discussed with the medical monitor.

Note: any condition requiring systemic treatment with corticosteroids or other immunosuppressive medications within 14 days of the first dose of VTP-850, other than inhaled and topical corticosteroids, are exclusionary (exclusion criterion 18, Section 5.2).

Vaccines may interfere with the response to each other if administered too closely together. The following restrictions apply unless the investigator considers a vaccine to be medically indicated for the participant. Exceptions to these restrictions should be discussed with the medical monitor so that optimal timing of the vaccine in relation to VTP-850 can be discussed.

Live vaccines should not be administered within 30 days before or after either component of VTP-850

Inactivated or non-live vaccines (e.g., mRNA vaccines) should not be administered within 14 days of either component of VTP-850

Adenoviral-vectored vaccines should not be administered within 3 months before or after the ChAdOx1-PCAQ component of VTP-850

6.11 Contraindications/Delay to Dosing

If the participant has an acute illness (moderate or severe illness with or without fever) or a fever (temperature ≥38.0°C) at the scheduled time or within 48 h before VTP-850 is to be administered, administration of the relevant component should be temporarily delayed. Trial intervention may be administered to that participant once the condition(s) has/have resolved, even if subsequent administration of components of VTP-850 will fall outside of the visit windows specified in the relevant SoA (Table 1). Delays in VTP-850 administration should be discussed with the Medical Monitor so that the optimal timing of administration and subsequent assessments can be agreed upon. See Section 7.1 for permanent discontinuation of trial intervention.

6.12 Delay to Dosing Due to Study Pause

Participants whose scheduled dosing of MVA-PCAQ is delayed due to a study pause during the Phase 1 portion of the study will be offered to recommence dosing and follow the SoA from Day 57. These participants will also be replaced to ensure that 6 participants are dosed in each of Cohorts 2 and 3, to allow for a meaningful assessment at the end of Phase 1.

7 DISCONTINUATION OF TRIAL INTERVENTION AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Discontinuation of specific sites or of the trial as a whole are detailed in Appendix 1.

7.1 Discontinuation of Trial Intervention

It may be necessary for a participant to permanently discontinue trial intervention. Trial participants who present with at least one of the following VTP-850 discontinuation criteria listed below will be withdrawn from further trial intervention but will remain in the trial to be evaluated for safety, immunogenicity and efficacy, according to their PSA response and SoA (Section 1.3).

Ulceration, abscess or necrosis at the site of injection of trial VTP-850

Any CTCAE $\geq$ Grade 3 AE considered related to VTP-850 and persisting continuously at $\geq$ Grade 3 for >72 h, with the exception of Grade 3 laboratory test abnormalities that improve to Grade 1 or baseline grade within 14 days

- An SAE considered related to VTP-850
- Acute allergic reaction attributed to the administration of VTP-850

If the participant requests discontinuation of further dosing with VTP-850, it must be documented on the appropriate eCRF and in the medical records whether the participant is discontinuing also from trial procedures, post-intervention trial follow-up, and/or future collection of additional information.

7.2 Participant Discontinuation/Withdrawal from the Trial

A participant may withdraw from the trial at any time at his own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, disease-management (for example, in the case of rapid PSA progression, a participant may need to discontinue the trial to consider other treatment options) or compliance reasons.

At the time of discontinuing from the trial, if possible, an End of Trial visit should be conducted, as shown in the SoA (Section 1.3).

The participant will be permanently discontinued from the trial intervention and the trial at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the trial, he may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up on the date of latest successful contact if he repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a participant fails to return to the clinic for a required trial visit:

The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the trial.

Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he will be considered to have withdrawn from the trial.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants enrolled, including those who did not get trial intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 TRIAL ASSESSMENTS AND PROCEDURES

- Trial procedures and their timing are summarised in the SoA (Section 1.3)

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the informed consent form (ICF) may be utilised for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the timeframe defined in the SoA

8.1 Intervention Assessments

Participants will receive the relevant VTP-850 dose for their visit based on their Phase/cohort allocation, administered according to the pharmacy manual.

All participants will be observed in the clinic for at least 30 min post-dose in case of immediate AEs. The first participant in each Cohort should be observed for at least 60 min post each dose.

The following will be performed post-dose:

- Vital signs (pulse rate, blood pressure and temperature) will be measured at approximately 30 min post-dose
- The participant will be assessed for local or systemic reactions (e.g., change in vital signs, occurrence of pain or swelling at the injection site)

8.2 Efficacy Assessments

8.2.1 Serum Prostate-Specific Antigen

Blood samples for high-sensitivity serum PSA will be assessed at the central laboratory.

8.2.2 Tumour Imaging

To assess eligibility (Inclusion Criterion #6, see Section 5.1), historic CT or MRI scans and bone scans may be used if performed within 3 months of Day 1. If no historic scan is available, a bone scan and a CT or MRI will be performed.

Participants will be assessed by whole body bone scintigraphy and either CT or MRI at least approximately every 6 months on trial. The optimal type of radiographic assessment for each participant will be determined by the investigator.

Specific imaging of the prostate bed is not required for every participant. If there is a question of locally persistent or recurrent disease, a directed MRI of the prostate or prostate bed and/or biopsy of the site is recommended. Participants with evidence of prostatic bed recurrence will be excluded from trial participation.

Metastasis-free Survival (MFS) will be determined based on the Prostate Cancer Working Group 3 (PCWG-3) criteria. If radiographic progression occurs, it should be recorded whether it was manifested by lesions in bone and/or nodes and/or viscera.

8.2.2.1 Technetium-99 Bone Scan

The use of 99mTc-methylene diphosphonate radionuclide bone scintigraphy is the standard for bone imaging to assess the presence or absence of metastasis.

8.2.2.2 CT or MRI of Chest, Abdomen and Pelvis

Imaging of the chest, abdomen and pelvis using a contrast-enhanced CT scan with ≤5 mm axial slices is advised. For those intolerant of contrast, a cross-sectional MRI scan of the abdomen and pelvis, with a noncontrast CT scan of the chest, may be considered.

If there is a question of locally persistent or recurrent disease, a directed MRI of the prostate or prostate bed and/or biopsy of the site is recommended.

Extraskeletal disease should be assessed by RECIST 1.1. To establish nonmetastatic (M0) status, per PCWG3 criteria.

It is recommended that the same standard imaging modalities (e.g., bone scan, CT and/or MRI) used to determine eligibility be used for monitoring the participant on trial.

8.2.3 Assessment of Progression to Metastatic Disease Based on PCWG3 Criteria

Tumour progression will be based on the PCWG3 criteria for nonmetastatic disease. MFS is defined as the time from date of first dose of VTP-850 until unequivocal metastatic disease by conventional imaging (CT/MRI and/or technetium-99 bone scan) or death from any cause, whichever occurs first. Note that MFS events do not include local progression events, e.g., progression in pelvic lymph nodes below the aortic bifurcation.

Bone

Bone lesions will be assessed by bone scintigraphy commonly performed with technetium-99. Documentation of radiographic evidence of metastatic disease should include the time of the unequivocal development of new sites on bone scintigraphy. Confirmation of additional lesions (2+2) is not required.

Lymph Nodes

Lymph nodes that were previously normal in size (<1.0 cm) or pathologic in size must have grown by at least 5 mm in the short axis from baseline or nadir and be ≥1.0 cm in the short axis to be considered to have progressed. If the node progresses to ≥1.5 cm in the short axis, it is pathologic and measurable. Nodes that have progressed to between 1.0 and <1.5 cm are pathologic subject to clinical discretion and are nonmeasurable.

Visceral

The date of first metastasis is the date on which an unequivocal visceral lesion by RECIST 1.1 is determined. No confirmatory scan is required. Visceral disease should be reported as being with or without other patterns of spread (node, bone).

8.3 Exploratory Assessments

8.3.1 Cellular Immune Response

Immunogenicity samples (peripheral blood mononuclear cells; PBMCs) will be taken for planned and potential exploratory analyses at each of the timepoints according to the SoA (Section 1.3). These samples will not be required at sites not qualified to process PBMCs.

Immunogenicity studies will include (but are not limited to) analysis of samples *ex vivo* by multiparameter flow cytometry (including Mean Fluorescence Intensity measurements) and *ex vivo* IFN-γ enzyme linked immunospot assays (ELISpot) assays. The latter may be used for specific epitope mapping. Additional immunogenicity assessments may be performed.

Prostate cancer-specific CD4+, CD8+ and T cell subsets within PBMCs will be further defined by phenotypic markers of activation, differentiation, memory and functionality using multiparameter flow cytometry assays such as intracellular cytokine staining. Peripheral blood mononuclear cells will also be used in IFN-γ ELISpot assays to determine the breadth of prostate

cancer-specific T cell responses (defined by number of peptide pools or individual peptides recognised). These data may be used to build immunologic models of the immune system.

Left over immunology blood samples may, with participant consent, be retained for future research related to ChAdOx1-PCAQ and MVA-PCAQ. This additional consent is optional, will not be required for participation in the trial and may be withdrawn at any time.

8.3.2 Biomarkers

Biomarker samples will only be analysed after Phase 2 Stage 2 is opened following the SMC's review of efficacy and safety data after at least 4 PSA responses have been confirmed among the 25 participants treated at the RP2R. If 3 or fewer of the 25 participants have a PSA response at the RP2R in Stage 1, biomarker sample analysis may not be performed.

The investigator should attempt to collect an historical prostate tumour sample for assessment of:

- Microsatellite instability-high status, BRCA and other molecular markers
- Expression level of the VTP-850 antigens (PSA, PAP, STEAP1, 5T4) in tumour samples

Blood will be taken for the assessment of biomarkers including:

- Circulating tumour DNA
- Serum PSA-binding antibodies
- Anti-antigen antibodies

8.3.3 Serum PSA-binding and anti-antigen Antibodies

Serum PSA-binding and anti-antigen antibodies will be evaluated in blood samples collected from all participants according to the SoA (Section 1.3), using a validated assay method.

8.3.4 PSMA scan

PSMA scans are not required at baseline, but if a participant has had a PSMA scan in the previous 3 months or if they have ever had a PSMA scan showing lesions, the result of the PSMA scan should be collected in the eCRF. Optional PSMA scans will be performed to assess lesions in the subset of participants who had lesions on PSMA scan at baseline and who have a 50% reduction in PSA from baseline on trial. The optional PSMA scan may be performed at any time during the trial after a PSA response is documented.

If a participant has a PSMA scan on trial and it shows progression, the participant should also be assessed by standard radiography to confirm progression.

8.4 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.4.1 Vital Signs

Vital signs will be performed as per the SoA

- Vital signs will include temperature, systolic and diastolic blood pressure, and pulse. Blood pressure and pulse will be measured in a sitting position after 3 min rest

8.4.2 Physical Examinations

A complete physical examination will be performed at screening and will include, at a minimum, assessments of the cardiovascular, gastrointestinal and lymphatic systems. Height and weight will also be measured and recorded

A symptom-directed physical examination will be performed as per the SoA

Investigators should pay special attention to clinical signs related to previous serious illnesses and any symptoms or signs potentially pertaining to cardiotoxicity

Results will be recorded as normal, abnormal and not clinically significant, or abnormal and clinically significant

8.4.3 Clinical Laboratory Assessments

Scheduled clinical laboratory assessments will be performed and samples will be sent to a central laboratory, with the exception of troponin T which will be performed by local laboratories.

- Unscheduled or emergency laboratory assessments may be performed using a local laboratory if needed to ensure rapid delivery of test results, otherwise unscheduled study laboratory assessments will be done at the central laboratory.
- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the trial as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal after the first dose with VTP-850 in the trial should be repeated until the values return to normal or to baseline grade or are no longer considered to be required by the investigator or medical monitor.

If clinically significant abnormal safety laboratory values do not return to normal/baseline grade within a period of time judged reasonable by the investigator, the aetiology should be identified, and discussed with the Medical Monitor.

- If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.4.4 Electrocardiograms

12-lead ECG(s) will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTc intervals. The investigator should review the result and assess as normal or abnormal; if abnormal, it should be assessed as clinically significant or not clinically significant.

8.4.5 Echocardiogram

An echocardiogram will be obtained as outlined in the SoA (Section 1.3). The Investigator should review the result and, at screening, assess if the participant is eligible for dosing. If a cardiac event is reported during the trial period, an additional echocardiogram should be performed at the earliest opportunity.

8.4.6 Pregnancy

- If the partner of a participant becomes pregnant within 2 months of a participant receiving a dose of VTP-850, the partner will be asked to provide signed informed consent for the collection of details of the pregnancy and outcome.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor after obtaining the necessary signed informed consent from the female partner.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the pregnant female partner and the neonate, and the information will be forwarded to the sponsor.

- Any post-trial pregnancy-related SAE considered reasonably related to the trial intervention by the investigator will be reported to the sponsor as described in Appendix 3. While the investigator is not obligated to actively seek this information in former pregnant female partners, he or she may learn of an SAE through spontaneous reporting.

8.4.7 Other Safety Assessments

On the day of each dose, during the telephone calls the day following administration of each component of VTP-850 and 7 days following the administration of ChAdOx1-PCAQ and at the 7-day post-dose visits following administration of MVA-PCAQ, the investigator will assess the injection/IV site and ask the participant how they are feeling since receiving VTP-850.

- If a participant experiences necrosis or exfoliative dermatitis at the injection site or requires an Emergency Room visit or hospitalisation for severe injection site pain, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the trial intervention, further administration will be discontinued in that participant (see Section 7.1).
- To allow participants to obtain information on fever when not at site, they will be given a thermometer with instructions on how to measure temperature at home. Temperature will be measured at any time during the trial when fever is suspected. Fever is defined as a temperature of ≥38.0°C.

9 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, ADVERSE EVENTS OF SPECIAL INTEREST AND OTHER SAFETY REPORTING

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate or the participant's legally authorised representative).

The investigator and any qualified designees are responsible for detecting, documenting and recording events that meet the definition of an AE, adverse event of special interest (AESI), or SAE and remain responsible for following up all AEs and SAEs that are considered related to the VTP-850 administration or trial procedures, or that caused the participant to discontinue VTP-850 or the trial.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE/AESI reports are provided in Appendix 3.

9.1 Time Period and Frequency for Collecting AE, SAE and AESI Information

Adverse Events

All AEs will be collected from the start of the first VTP-850 administration, continuing until the Month 6 Visit (see Table 1 and Table 2).

Serious Adverse Events and Adverse Events of Special Interest During the Trial Intervention and Follow-up Periods

SAEs and AESIs (see Section 9.5) will be collected from the start of the first VTP-850 administration until the last trial visit. All SAEs and AESIs will be recorded and reported to the sponsor or designee within 24 h, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 h of its being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the trial participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the trial, and he/she considers the event to be reasonably related to the trial intervention or trial participation, the investigator must promptly notify the sponsor.

Medical Occurrences Prior to First Dose of VTP-850

This trial enrols participants who are not receiving other therapy for their prostate cancer. There is no required washout period, and there is no prolonged screening period, or invasive or unusual

procedures required during the screening period. Therefore, collection of AEs or SAEs prior to dosing in this trial would not help the sponsor monitor the safety of the participants or understand the safety profile of the trial intervention. Medical occurrences that begin before the start of trial intervention but after obtaining informed consent will be considered part of the participant's medical history/current medical conditions. However, any medical occurrence that begins before the start of trial intervention but after obtaining informed consent that meets the criteria for seriousness (Appendix 3) and is causally related to a screening procedure should be reported to the sponsor or designee following the SAE/AESI reporting procedure within 24 h.

9.2 Follow-up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs that occur after the first VTP-850 administration will be followed until resolution, stabilisation, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3.

9.3 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a trial intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IECs/IRBs, and investigators.

An investigator who receives an individual case safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Individual case safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

9.4 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Progression of prostate cancer including radiographic evidence of progression will be captured as an endpoint and does not need to be reported as an AE or SAE.

9.5 Adverse Events of Special Interest

The following events have been identified as adverse events of special interest (AESI) for the purpose of expedited reporting to Sponsor during the conduct of this trial::

- any cardiac event

- shortness of breath / dyspnoea
- abnormal cardiac investigation or examination

If a cardiac event is reported, blood should be taken for assessment of troponin T and C-reactive protein (CRP) and the participant should undergo an ECG and echocardiogram at the earliest opportunity along with any other appropriate assessments as determined by the Investigator.

10 PHARMACOKINETICS

Pharmacokinetic parameters are not evaluated in this trial.

11 STATISTICAL CONSIDERATIONS

The statistical analysis plan (SAP) will be finalised prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

11.1 Statistical Objectives

The primary objective is to demonstrate that VTP-850 has a reasonable safety and tolerability profile. No formal hypothesis will be tested.

The secondary objectives include evaluating the presence and durability of PSA response to VTP-850. Estimated response rates and durability may be used for power and sample size purposes in subsequent trials.

11.1.1 Multiplicity Adjustment

The analyses associated with this trial are primarily descriptive in nature, and multiplicity adjustments have not been specified.

11.1.2 Analysis sets

- The intent-to-treat analysis set (full analysis set) will consist of all participants who are enrolled into the trial and who received at least one dose of VTP-850
- The safety analysis set will consist of all participants who receive at least one dose of VTP-850 (data will be summarised according to the dose levels and regimens actually received)
- The per-protocol analysis set will consist of all participants in the safety analysis set who received the correct trial intervention and who had no major protocol deviations that would potentially bias the trial's analyses
- The immunogenicity analysis set will consist of all participants who have available immunogenicity data to evaluate the immunogenicity endpoints and do not have any major protocol deviations that would impact the results of the immunological analysis

Assignment of participants to the analysis sets (and whether any participant or specific data from a participant will be excluded) will be determined at the pre-database-lock Data Review meeting.

11.2 Statistical Analyses

11.2.1 General Considerations

Most analyses will be descriptive in nature. Unless stated otherwise, continuous variables will be summarised using descriptive statistics (number of participants, mean, standard deviation, median, minimum and maximum values), and the number and percentage of participants will be presented for categorical variables. Data will be summarised by trial cohort and, where appropriate, overall. Immunogenicity and efficacy data may have additional statistical analysis, which will be detailed in the trial's SAP.

The SAP will describe and account for the occurrence of and extent of missing data and its possible impact on the trial analysis.

11.2.2 Primary Endpoint Analysis

Safety data will be summarised descriptively. Adverse Events are defined as those occurring after trial intervention administration.

11.2.2.1 Adverse Events

All AEs will be listed, including the verbatim description and the Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) and system organ class (SOC).

All AEs will be summarised by SOC and PT over the course of AE follow-up, as well as during the 28-day period following each administration of VTP-850. The incidence of AEs will be based on the numbers and percentages of participants with events. AEs will be further summarised by severity and relationship to trial intervention.

An overall summary of AE incidence will also be presented by trial cohort and overall to include the number and percentage of participants with at least one: AE, treatment-related AE, Grade 3 to Grade 5 AE, death, SAE, treatment-related SAE, AE leading to trial intervention discontinuation and AE leading to trial discontinuation.

Narratives will be written for any deaths, other SAEs, AESIs, AEs leading to trial intervention discontinuation and AEs leading to trial discontinuation.

11.2.2.2 Laboratory Safety Tests

Severity grading using CTCAE Version 5.0 will be assigned to laboratory safety values where applicable. Laboratory results in reported units and International System of Units (SI) units will be listed, including high and low flags, severity grades where applicable, the corresponding normal range and clinical significance.

Safety laboratory tests summaries will be based on results in SI units. Absolute and change from baseline results, including the worst change for each parameter for each participant, will be summarised using descriptive statistics.

Treatment-emergent, out-of-range results with the corresponding severity grade, normal ranges, baseline results and clinical significance will be listed separately. Shift tables of the CTCAE grades will be used to show changes from baseline at each timepoint and the worst change in each participant. The number of participants showing shifts of at least 2 severity grades will be summarised.

The number of participants with treatment-emergent clinically significant safety laboratory test results and safety laboratory test results of Grade 3 or 4 will be summarised.

11.2.2.3 Vital Signs

Absolute and change from baseline vital sign results, including the worst change for each variable for each participant will be summarised using descriptive statistics. Treatment-emergent, out-of-range results with the corresponding normal ranges, baseline results and clinical significance will be listed separately. The number of participants with treatment-emergent, clinically significant results will be summarised.

11.2.3 Secondary Endpoint Analyses

11.2.3.1 PSA Response to VTP-850

The number, proportion, and 90% confidence interval (CI) of participants with a PSA response, defined as ≥50% reduction in serum PSA compared to baseline and measured twice consecutively, will be summarised by timepoint and overall. This will be further broken down by whether the participants had prior radical prostatectomy or prior external beam radiation. The maximum PSA reduction from baseline will be summarised, as well as by whether participants had prior radical prostatectomy, external beam radiation or brachytherapy.

11.2.3.2 Durable PSA Response to VTP-850 at Month 8

The number, proportion and 90% CI of participants with a durable PSA response at Month 8 will be summarised, among all participants and among those with a response by Month 6. Durable PSA response is defined as having follow-up through Month 8 and a confirmed PSA response without having PSA progression (i.e., an increase relative to nadir of ≥25% and an absolute increase of 0.2 ng/mL or more) on or before Month 8. This will be further summarised by whether the participants had prior radical prostatectomy, external beam radiation or brachytherapy.

11.2.3.3 Duration of PSA Response to VTP-850

Among those participants who experienced a PSA response, the duration of PSA response, defined as the time from first dose of VTP-850 to the date of PSA progression, will be summarised (n, median, interquartile range, minimum, maximum) and presented using a

Kaplan-Meier plot. Participants whose PSA response is ongoing upon the completion of follow-up will be censored at the time of their last follow-up visit with a non-missing PSA evaluation. An additional analysis will evaluate duration of PSA response, defined as the time from observation of PSA reduction of at least 50% to the date of PSA progression.

This endpoint will be further summarised by whether the participants had prior radical prostatectomy, external beam radiation or brachytherapy.

11.2.3.4 Metastasis-Free Survival and Time to Metastases

The duration of MFS, defined as the time from first dose of VTP-850 to detection of metastatic disease or all-cause mortality, will be summarised (n, median, interquartile range, minimum, maximum) and presented using a Kaplan-Meier plot. Participants who have survived without development of metastatic disease by the end of follow-up will be censored at the time of their last follow-up visit with an evaluable assessment of metastatic disease.

The duration of TTM, defined as the time from first dose of VTP-850 to detection of metastatic disease, will be summarised (n, median, interquartile range, minimum, maximum) and presented using a Kaplan-Meier plot. Participants who have not developed metastatic disease by the end of follow-up will be censored at the time of their last follow-up visit with an evaluable assessment of metastatic disease.

These endpoints will be further summarised by whether the participants had prior radical prostatectomy, external beam radiation or brachytherapy. These endpoints will be further summarised for participants who experienced a PSA response.

11.2.3.5 Time to Start of ADT for Participants with PSA Response

Among those participants who experienced a PSA response, the time to initiation of ADT treatment (or when they have met the criteria to initiate ADT) will be summarised (number of participants, median, interquartile range, minimum, maximum) and presented using a Kaplan-Meier plot. Responders who have not started ADT or met the criteria to start ADT by the end of follow-up will be censored at the time of their last follow-up visit.

This endpoint will be further summarised by whether the participants had prior radical prostatectomy or external beam radiation. This endpoint will be further summarised for participants who experienced a PSA response.

11.2.4 Exploratory Endpoint Analyses

Exploratory endpoints and planned analyses will be described in detail within the SAP.

11.2.5 Other Analyses

11.2.5.1 Disposition

Participant disposition (such as the number screened, screen failed, treated, completed, discontinued from treatment and discontinued from trial), including reasons for withdrawal, if applicable, will be summarised descriptively.

11.2.5.2 Protocol Deviations

Protocol deviations will be listed including the nature (e.g., missed procedure(s), early or late procedure(s), missed visits, visit performed out of protocol defined window, prohibited medication taken, trial intervention dosing deviation, inclusion/exclusion criteria deviations, participants not withdrawn but meeting withdrawal criteria, biological sample handling error, other) and major or minor classification.

11.2.5.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be listed and summarised descriptively for participants in the safety analysis set.

11.2.5.4 Prior and Concomitant Medications and Procedures

Concomitant medications and procedures will be summarised by Anatomic Therapeutic Chemical classification. Both prior and concomitant medications and procedures will be listed.

11.2.5.5 Medical History

Medical history will be listed, including the verbatim description and associated MedDRA PT and SOC.

11.3 Interim Analysis

Two interim reviews of trial data are planned.

The first is a preliminary assessment of data from the 25 participants who received the RP2R through Stage 1 of Phase 2 to determine whether the trial has provided sufficient evidence of PSA response to warrant enrolment of an additional 100 participants in Phase 2, Stage 2. Enrolment in Stage 2 will begin following the SMC's review of efficacy and safety data after at least 4 PSA responses have occurred among the 25 participants.

In addition to this and other data reviews performed by the SMC (refer to Section 4.1.1), an interim analysis will be conducted once all participants enrolled in the Phase 2 portion of the trial have been followed through at least the Month 3 visit. The results from this interim analysis will solely be used for the purpose of planning future clinical trials and will not impact the conduct of this trial, i.e., the sample size of the ongoing trial will not expand as a result of this review. Further, given this is an open-label trial without a control arm, and the trial's endpoints will only be evaluated in a descriptive manner upon trial completion, this interim look will not result in a penalty on any pre-planned alpha level. All secondary endpoints described above will be included in the interim analysis.

11.4 Sample Size Determination

A total of approximately 144 participants will be enrolled. A sample size of approximately 125 participants will be eligible for inclusion in the Phase 2 efficacy evaluation.

Twenty-five participants are to be included in the preliminary Stage 1 assessment to expand into Stage 2 of Phase 2 (i.e., the first 19 participants enrolled in Stage 1 and the 6 participants from Phase 1 receiving the RP2R according to the dosing schedule). If the true response rate (where response is defined as ≥50% reduction in serum PSA at any 2 consecutive post-baseline timepoints at least 2 weeks apart) associated with VTP-850 administration is ≥20%, 25 participants will yield a 76.6% chance (i.e., power) of observing 4 or more responders.

One hundred and twenty-five participants (combined Stage 1 enrolment as described above and Stage 2 enrolment in Phase 2) will yield the following 90% and 95% Confidence Intervals (CIs) for the true response rate based on the example observed response rates in Table 6. This Phase 2 sample size has 89.3% power to rule out a null proportion of PSA responders of 10% using a two-sided exact test with a target significance level of 0.05 assuming a true response percentage of 20%. The null hypothesis response rate of 10% will be rejected if at least 20 PSA responders (16%) are observed amongst the 125 participants.

The observed response rate and associated CIs will facilitate decision-making regarding whether to continue the program as well as the appropriate sample size for subsequent trials.

Table 6 Confidence Intervals for True Serum PSA Response Rate Based on Observed Response Rate (n=125)

Observed Response Rate (%)	90% Confidence Interval	95% Confidence Interval
0.10	(0.059, 0.156)	(0.054, 0.166)
0.15	(0.100, 0.213)	(0.092, 0.225)
0.20	(0.143, 0.268)	(0.134, 0.281)
0.25	(0.187, 0.322)	(0.177, 0.335)
0.30	(0.233, 0.375)	(0.221, 0.388)

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12.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

A1.1. REGULATORY AND ETHICAL CONSIDERATIONS

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the trial is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to trial participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

A1.2. FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

A1.3. INFORMED CONSENT PROCESS

The investigator or his representative will explain the nature of the trial, including the risks and benefits, to the participant and answer all questions regarding the trial.
Participants must be informed that their participation is voluntary. Participants will be required to

sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or trial centre.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the trial and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the trial.
- A copy of the ICF(s) must be provided to the participant.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 42 days from the previous ICF signature date, or there is a new ICF including updated safety or trial information.

A1.4. DATA PROTECTION

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
The participant must be informed that his personal trial-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
The participant must be informed that his medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A1.5. SAFETY MONITORING COMMITTEE

Participant safety will be continuously monitored by the SMC.
The SMC, consisting of the sponsor trial physician, the Medical Monitor, a prostate cancer physician not participating in the trial, and at least 2 investigators will be appointed to review the trial data periodically or when needed and make recommendations concerning the continuation, modification or termination of the trial.

- The timings of SMC meetings will be defined in a trial-specific SMC Charter.
- The SMC will make recommendations about:
  - Opening each cohort in Phase 1
  - Choosing the regimen for Phase 2 and opening enrolment in Phase 2
  - Opening recruitment in Stage 2 of Phase 2, after reviewing available safety and efficacy data after at least 4 PSA responders have been identified
  - Altering the dose/ regimen (e.g., dropping back a dose level or dropping the second booster dose)
  - Pausing or stopping the trial
  - The institution of additional safety measures, if considered to be required

A1.6. DISSEMINATION OF CLINICAL TRIAL DATA

- Barinthus Biotherapeutics will share anonymised trial data on a publicly available database, as per local regulations.

Clinical Trial Reports (CSRs), periodic safety reports, and clinical trial summary reports will be disclosed after review by regulatory authorities. This includes access to Clinical Trial Reports from studies with negative outcomes and from terminated development programs.

A1.7. DATA QUALITY ASSURANCE

All participant data relating to the trial will be recorded on eCRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- Guidance on completion of eCRFs will be provided.

The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
Monitoring details describing strategy, including definition of trial critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote or on-site monitoring) will be described in the monitoring plan.
The sponsor or designee is responsible for the data management of this trial, including quality checking of the data.

- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organisations).

Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator for 25 years after trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A1.8. SOURCE DOCUMENTS

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.
Definition of what constitutes source data and its location will be agreed with the sites and documented.
The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete and verifiable from source documents; that the safety and rights of participants are being

protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP and all applicable regulatory requirements.

A1.9. TRIAL AND SITE CLOSURE

The sponsor or designee reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

The investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by the sponsor or investigator may include but are not limited to:

For trial termination:

- Discontinuation of further trial intervention development

For site termination:

Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures or GCP guidelines

- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the trial is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities and any contract research organisation(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

A1.10. PUBLICATION POLICY

The final trial report will be made available to the investigator for purposes of publications. The investigator and trial team must send all manuscripts, abstracts and presentations using data from this trial to the sponsor for review prior to their submission. The sponsor reserves the right to publish first or to delete any part or parts of the investigator's materials deemed to be confidential or proprietary.

12.2 Appendix 2: Clinical Laboratory Tests – Analytes and Laboratory Locations

- The tests detailed in Table 7 will be performed by the central laboratory with the exception of troponin T which will be performed by local laboratories.

Except for troponin T, local laboratory results are only required if the central laboratory results are not available in time for either trial intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a trial intervention decision or response evaluation, the results must be recorded.

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations.

Table 7 Protocol-Required Laboratory Safety Tests

Laboratory Tests	Parameters		
Haematology	Platelet count Red blood cell (RBC) count Haemoglobin Haematocrit	RBC indices: Mean corpuscular volume (MCV) Mean corpuscular haemoglobin (MCH) %Reticulocytes	White blood cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Biochemistry	Blood urea nitrogen (BUN) Calcium Creatinine Glucose (non-fasting) Potassium Sodium Total protein		
Liver function tests	Alanine aminotransferase (ALT) Alkaline phosphatase (ALP) Aspartate aminotransferase (AST) Total and direct bilirubin		
Markers for cardiac dysfunction or inflammatory response	Troponin T C-reactive protein (CRP)		
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick (read locally) • Microscopic examination (if blood or protein is abnormal)		

Investigators must document their review of each laboratory safety report.

12.3 Appendix 3: AEs, AESIs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

A3.1. DEFINITION OF AE

AE Definition
• An AE is any untoward medical occurrence in a participant or clinical investigation subject administered the investigational product and which does not necessarily have to have a causal relationship with this treatment. • An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of trial intervention, whether considered related to the investigational product.

Events Meeting the AE Definition
• Any clinically significant worsening of a pre-existing condition • An AE occurring from overdose of an investigational or marketed product, whether accidental or intentional • An AE occurring from abuse (e.g., use for non-clinical reasons) of an investigational or marketed product An event related to a medical procedure or associated with the discontinuation of the previous use of an investigational or marketed product required by protocol (protocol related AE) • Not all vital sign or laboratory abnormalities will be considered an AE. Usually these will be considered as an AE: o If CTCAE Grade 3 (severe) or greater in severity o If judged to be clinically significant by the investigator o If accompanied by clinical symptoms o If meeting the definition of an SAE o If resulting in dose interruption or discontinuation of trial intervention o If requiring specific treatment

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition • The disease/disorder being studied (prostate cancer) or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that

leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen

Recording Medical Occurrences Prior to Trial Dosing

- Any medical occurrence that occurs after the participant has given their informed consent and prior to the start of the first dose of VTP-850, including clinically significant abnormalities found in screening assessments, will be considered part of the participant's medical history.

A3.2. DEFINITION OF AESI

AESI Definition

An AESI is defined as:

- any cardiac event
- shortness of breath / dyspnoea
- abnormal cardiac investigation or examination

A3.3. DEFINITION OF SAE

An SAE is defined as any untoward medical occurrence that meets one of more of the criteria listed that occurs after the start of the first dose of VTP-850, or occurs after informed consent has been provided and is causally related to a trial procedure:

Results in death (i.e., the adverse event caused or led to the fatality). Serious does not describe an event which hypothetically might have caused death if it were more severe

a. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

b. Requires inpatient hospitalisation or prolongation of existing hospitalisation

It required inpatient hospitalisation or prolonged hospitalisation beyond the expected length of stay. Hospitalisations for scheduled treatments and elective medical/surgical procedures related to a pre-existing condition that did not increase in severity or frequency following receipt of trial intervention, are not serious by this criterion. Hospitalisation is defined as a hospital admission or an emergency room visit for a period greater than 24 h

- Hospitalisation for social reasons or for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

c. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

d. Is a congenital anomaly/birth defect (i.e., an adverse finding in a child or foetus of a participant exposed to the trial intervention prior to conception or during pregnancy).

Other **medically significant events:**

- An adverse finding that may not result in death, threaten life or require hospitalisation (i.e., the adverse event does not meet any of the above serious criteria) may be considered an SAE when, based on appropriate medical judgment, they may jeopardise the participant and require medical or surgical intervention to prevent one of the serious outcomes listed in these criteria (e.g., allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalisation, or the development of drug dependency or drug abuse).

A3.4. RECORDING AND FOLLOW-UP OF AE AND/OR SAE

AE and SAE Recording

- All AEs are recorded in the eCRF at all telephone and clinic visits until the Month 6 visit. All AEs will be reported using a recognised medical term or diagnosis that accurately reflects the event.
- Adverse events will be assessed by the investigator, or a medically qualified trial team member, for severity, relationship to VTP-850, action taken, outcome and whether the event meets criteria as an SAE according to the guidelines in this appendix.

Assessment of Intensity

- The severity of AEs and laboratory values will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The scale shown in Table 8 will be used to assess severity of AEs not listed in the CTCAE.

Table 8 Severity Grading of Adverse Events not listed in CTCAE

Grade	Severity[1]	
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated.

2	Moderate	Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)[2].
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self care ADL[3].
4	Lifethreatening	Life-threatening consequences; urgent intervention indicated.
5	Fatal	Death related to this AE

[1] A semi-colon indicates 'or' within the description of the grade

[2] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[3] Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.

A change in severity of an AE will be recorded as a new AE with the outcome of the event prior to the change in severity stated as "change in severity". The onset and resolution dates will encompass the duration of each severity.

Note: It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section A3.3.

Assessment of Causality

For all AEs reported in the eCRF, the investigator will determine a **causal relationship** to VTP-850.

A number of factors will be considered in making this assessment, including: 1) the temporal relationship of the event to the administration of VTP-850, 2) whether an alternative aetiology has been identified and 3) biological plausibility.

Causality of all adverse events should be assessed by the investigator using the following question:

"Is there a reasonable possibility that the adverse event may have been caused by VTP-850"

- **YES (related):** There is a reasonable possibility that VTP-850 contributed to the AE
- **NO (not related):** There is no reasonable possibility that the AE is causally related to the administration of VTP-850. There are other, more likely causes and administration of VTP-850 is not suspected to have contributed to the AE

The investigator is required to provide an assessment of relationship of AEs to VTP-850 or trial procedures and determine causality. The sponsor and Medical Monitor can add another causality assessment to the investigator's causality. If the sponsor or the Medical Monitor disagrees with the investigator's causality assessment, the opinion of both the investigator, the sponsor and the Medical Monitor should be provided with the report.

Every effort should be made by the investigator to determine the existence of any pre-existing conditions (e.g., headache on trial Day 1 with onset prior to VTP-850 administration) that must be taken into consideration when assessing causal relationship of an AE. Pre-existing conditions should be recorded in the eCRF as medical history and substantiated by appropriate source documentation. Intermittent conditions such as headaches may be present on trial Day 1 but may

represent an AE if the intensity or duration of the event is worse than usual following trial intervention.

Assessment of Outcome

The outcome of the AE will be assessed as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Not recovered/resolved
- Unknown
- Fatal
- Change in severity

Follow-up of AEs and SAEs

Treatment of any AEs will be determined by the investigator using their best medical judgment and according to current clinical practice guidelines. All applied measures as well as follow-up will be recorded in the appropriate eCRF.

The investigator will continue follow-up on AEs, including laboratory abnormalities, until the event has resolved, stabilised, is otherwise explained, the participant completes the trial or is lost to follow-up. The resolution date will be recorded on the eCRF as the last date on which the participant experienced the AE. If an AE resolution date is uncertain the investigator should estimate the completion date based on medical judgment and interview of the participant. Approximate dates of resolution from phone or other communications may be taken as AE resolution dates. Some examples of estimation of adverse event resolution are: 1) an asymptomatic laboratory abnormality on one visit that has not been followed up between visits but has resolved by the next visit may be assumed to have resolved by the midpoint of the inter-visit interval; 2) A resolved AE that was treated may be assumed to have been resolved by the end of treatment.

Adverse events that are still present at the end of the trial should be recorded as ongoing.

Information recorded on the eCRF must be substantiated in the source documents. If an AE evolves into a condition that becomes "serious," it will be designated as serious on the AE eCRF, and a supplemental SAE report form will be completed.

Follow-up for SAEs will be attempted until resolution or stabilisation and the outcome reported to the sponsor, even if this extends beyond the SAE reporting period.

A3.5. REPORTING OF SAES AND/OR AESIS

All SAEs/AESIs are reported to the sponsor or designee until the end of the trial. Suspected unexpected serious adverse reactions are reported even after the trial is over, if the investigator becomes aware of them. The trial centre will be provided with specific reporting procedures including the SAE/AESI Report form and any supplemental reporting forms to be used.

SAEs/AESIs will be reported on the SAE/AESI form and the AE eCRF using a recognised medical term or diagnosis that accurately reflects the event.

SAEs/AESIs will be assessed for severity, causal relationship to VTP-850 or alternative aetiology by the sponsor and investigator. The onset and resolution dates of the event and medical care taken in response to the event will be documented. If the event has not resolved by the end of the trial, it will be documented as "ongoing" on the eCRF, however, follow-up of the SAE/AESIs should be attempted until resolved or the condition has stabilised. Information recorded on the eCRF must be substantiated in the source documents.

The SAE form should be completed with all information known at the time and reported per the SAE/AESIs reporting guidelines.

Likewise, fatal or life-threatening SAEs will have to be reported per the SAE reporting guidelines. If the Medical Monitor is required by the protocol or chooses to suspend enrolment, they shall immediately create a written memorandum for record to the trial file and telephonically notify the sponsor of this act.

Contact information for all safety personnel is contained in the Team Contact List, which will be stored at the trial centre in the Investigator Site File and maintained by the trial sponsor.

Investigators must not wait to collect additional information to fully document the event before notifying the Medical Monitor of an SAE/AESI. The initial notification should include the following (at a minimum):

- Protocol number and name and contact number of the investigator
- Participant identification
- Investigational product
- Event term

All SAEs/AESIs must be recorded on the SAE/AESI Report Form and sent to [redacted] via email [redacted] within 24 hours of awareness. Additionally, the investigator must submit any updated SAE data to Precision Safety within 24 hours of awareness.

Initial notification via telephone or email does not replace the need for the Investigator to complete, sign, and return the SAE/AESI report form within the designated reporting time frames.

12.4 Appendix 4: Contraceptive and Barrier Guidance

Participants should refrain from donating sperm during the trial for at least 65 days after the last dose of VTP-850

PLUS, either

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

OR

- Agree to use a male condom when having sexual intercourse with a woman of childbearing potential, and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak

12.5 Appendix 5: Abbreviations and Definitions

List of Abbreviations

ABBREVIATION	DEFINITION
ADT	androgen deprivation therapy
AE	adverse event
AESI	Adverse event of special interest
BRCA	BReast CAncer gene
ChAdOx1	chimpanzee adenovirus Oxford 1
CI	confidence interval
CRP	C-reactive protein
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CNS	Central Nervous System
DLT	dose limiting toxicity
eCRF	electronic case report form
ELISpot	enzyme linked immunospot assay
IB	Investigator's Brochure
ICF	informed consent form
IEC	independent ethics committee
IM	intramuscular(ly)
IRB	institutional review board
IV	intravenous(ly)
MedDRA	The Medical Dictionary for Regulatory Activities
MFS	metastasis-free survival
MRI	magnetic resonance imaging
MVA	Modified Vaccinia virus Ankara
MVA-BN	Modified Vaccinia Ankara-Bavarian Nordic
PAP	prostatic acid phosphatase
PBMC	peripheral blood mononuclear cells
PCWG3	Prostate Cancer Working Group 3
PET	positron emission tomography
pfu	plaque forming units
PSA	prostate-specific antigen
PSMA	prostate specific membrane antigen
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumours
RP2R	recommended Phase 2 regimen
SAE	serious adverse event
SAP	statistical analysis plan
SI	International System of Units
SMC	Safety Monitoring Committee
SoA	Schedule of Assessments

ABBREVIATION	DEFINITION
SOC	system organ class
STEAP1	six-transmembrane epithelial antigen of prostate 1
TTM	Time to Metastases
ULN	upper limit of normal
vp	viral particles
XRT	external radiation therapy

List of Definitions

TERM	DEFINITION
Enrolment	The point at which a participant has met all entry criteria and is eligible for dosing.
VTP-850	A prime-boost immunotherapeutic regimen consisting of 2 viral vectored components, ChAdOx1-PCAQ and MVA-PCAQ

12.6 Appendix 6: Changes made in Protocol Amendment

This is Version 5.0 of the protocol. The original protocol (Version 1.0) was issued on 22 April 2022, Version 2.0 was issued on 01 July 2022, Version 3.0 was issued on 06 December 2022 and Version 4.0 was issued on 04 March 2024.

Summary of changes:

Version 5.0 18 April 2024
Summary and Justification of Change
The following changes were made in response to the request from the US Central IRB to minimise potential cardiac risks for trial participants: • Schedule of Assessments: addition of screening echocardiogram. A historic echocardiogram can be used if performed within 3 months of the first dose of VTP-850 • Table 3 Section 2.3.1: addition of echocardiogram in the cardiac risk statement • Addition of Section 8.4.5: echocardiogram • Section 9.5: included echocardiogram in the assessments that should be performed in the event of a cardiac-related event
Version 4.0 04 March 2024
Summary and Justification of Change
The following changes were made to increase participant safety, to minimise potential cardiac risks and to monitor cardiac status subsequent to safety review: Cardiac safety: • Inclusion criterion 11: addition of inclusion criteria regarding troponin T and HbA1c • Exclusion criterion 12: increased exclusion of prior ADT from within 6 months prior to Day1 to outside of the primary prostate cancer therapy • Exclusion criterion 13: clarification that of the exclusion of receipt of experimental agents for prostate cancer includes participation in any clinical trials for prostate cancer with the exception of as being part of primary treatment options • Exclusion Criterion 19: addition of exclusion of participation in prior clinical trials to include previous participating in any clinical trials for prostate cancer with the exception of those as part of the primary treatment • Addition of exclusion criterion 20 detailing exclusionary cardiovascular conditions • Addition of exclusion criterion 21 detailing exclusionary ECG findings • Addition of exclusion criterion 22 specifying exclusion of uncontrolled hypertension

• Schedule of Assessments: Addition of on trial monitoring of ECGs • Schedule of Assessment and Appendix 2: addition of troponin T and CRP analysis • Schedule of Assessments, Section 9 (including addition of Section 9.5) and Appendix 3: Addition of classifying cardiac events as AESI and associated reporting • Table 3 Section 2.3.1: Addition of cardiac risk statement • Section 8.4.2: Addition that investigators should pay special attention to any symptoms or signs potentially pertaining to cardiotoxicity • Section 8.4.3 and Appendix 2: clarification that Troponin T samples will be analysed in local laboratories Other safety parameters: • Addition of monitoring of anti-antigen antibodies
The following changes were made to increase homogeneity of participants and data collection: Clarification of prostate cancer history: • Inc 4 addition of "or systemic therapy for prostate cancer" • Inc 6 addition of "and no evidence of prostatic bed recurrence" Data consistency: • Inc 6 removal of " An existing PSMA=PET scan showing no metastatic lesions may be used instead to confirm M0 status" • Addition of a PSA collection at Day 91 • Section 4.1: addition that a total of 6 participants in each of cohorts 2 and 3 will be required to be dosed with MVA-PCAQ on Day 29 and Day 57 so participants whose dosing was delayed will be replaced (unless dosing not to be completed for pause of stopping rule criteria being met) • Section 6.12: addition to detail how recommencement of dosing for participants whose dosing was delayed in Phase 1 due to a study pause will be managed
Clarification of the requirement to qualify sites for the collection of PBMCs as part of exploratory analyses: • The collection of PBMC samples has changed from being required for all participants to only required at those sites that are qualified by Barinthus Biotherapeutics to process PBMC samples
The following changes were made for clarification: • Exclusion criterion 4: clarification that history of Hep C infection is not exclusionary but in line with Ex 10 active Hepatitis C infection is exclusionary. • Exclusion criterion 10: Updated to clarity that only active hepatitis C virus infection is exclusionary • Update to SoA and associated footnotes following additional assessments

• Secondary Endpoint: rewording of endpoint regarding PSA response to ensure clarity • Exploratory endpoint: moving "other immune responses" from the objective around PSA response to the objective around immunogenicity. • Section 4.1 and Synopsis: clarification of the situation around when a participant could be offered an additional dose of MVA-PCAQ • Section 4.1.2: clarification that if 3 or fewer of the 25 participants at the RP2R in Phase 1/ Phase 2 Stage 1 have a PSA response then no further participants will be enrolled in the trial • Section 4.1.4: clarification that if a participant does not have a PSA response by their Month 6 visit they will not enter the Long-term Follow-up Period of the trial • Section 4.1.7: clarification of how any additional MVA-PCAQ doses will be managed. • Section 6.10: clarification that systemic treatment with corticosteroids or other immunosuppressive medications within 14 days of the first dose of VTP-850 are exclusionary. • Section 7.2: clarification that disease management for example in the case of rapid PSA progression is a reason that the participant may need to discontinue from the trial to consider other treatment options. • Section 8.2.2 clarification that participants with evidence of prostatic bed recurrence will be excluded from trial participation • Section 8.3.2: clarification that biomarker samples will only be analysed after Phase 2 Stage 2 is opened. If Phase 2 Stage 2 is not opened then biomarker sample analysis may not be performed. • Section 9.3: correction of "investigator safety report" to "individual case safety report" in bullets 3 and 4 • Section 11: minor updates to enhance clarity • Section 11.3: addition of statement documenting the review of data of the 25 participants receiving RP2P to determine whether Phase 2 Stage 2 will be opened. • Appendix 5: updated to include new abbreviations • Administrative amendments to ensure internal consistency and correct typographical errors
In addition, Vaccitech (UK) Limited changed its name to Barinthus Biotherapeutics (UK) Limited on 06 November 2023. Consequent updates have also been made.

Version 3.0, 06 December 2022
Summary and Justification of Change
The following changes and clarification were made in response to FDA requests:

Addition of assessment of TTM in the subset of participants with PSA response to the secondary objectives and endpoints Addition of assessment of MFS and TTM as exploratory objectives and endpoints • Revision of DLT criteria • Clarification of the staggering of enrolment during Phase 1
Following feedback on current treatment paradigms in this population inclusion criterion 7 was amended so that participants who had prior prostatectomy should have a Serum PSA of >0.3 ng/mL at screening
Administrative amendments to ensure internal consistency and correct typographical errors

Version 2.0, 01 July 2022
Summary and Justification of Change
Changes were made to: • Amend inclusion criterion 3 to include participants that had undergone primary therapy for prostate cancer with brachytherapy. • Amend inclusion criterion 7 to document that participants that had prior brachytherapy should have a serum PSA of 2ng/mL above nadir. • Section 4.1.1 to reorder and slightly reword DLT criteria to improve clarity • Include Investigator Agreement within the protocol Remove previous legal registered address of sponsor (current legal address was already listed) Section 8.3.1 included statement that left over immunology blood samples may, with participant consent, be retained for future research related to ChAdOx1-PCAQ and MVA-PCAQ, confirming that this additional consent is optional, will not be required for participation in the trial and may be withdrawn at any time. Clarified that SMC will also contain a prostate cancer physician who is not participating in the trial • Add summary of changes Appendix 6
Administrative amendments to ensure internal consistency and correct typographical errors