CV301-BLD-001

A Phase 2, Multicenter, Single-Arm Trial of CV301 in Combination with PD-1/L1 Blockade in Patients with Locally Advanced or Metastatic Urothelial Bladder Cancer

NCT03628716

Clinical Trial Protocol Edition 2.0

28-Mar-2019

Revision Chronology

Protocol Edition	Date	Version
Edition 1.0	16-Feb-2018	Original
Edition 2.0	28-Mar-2019	Amendment 1
Refer to Section 17.5 for details		

1 General Information

1.1 Investigator Signature Page

Herewith I agree that I have read and fully understand this protocol:

A Phase 2, Multicenter, Single-Arm Trial of CV301 in combination with PD-1/L1 blockade in Patients with Locally Advanced or Metastatic Urothelial Bladder Cancer

This protocol describes necessary information to conduct the trial. I agree that I will conduct the trial according to the instructions given within this protocol. Furthermore, I agree that I will conduct this trial according to International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), the 2013 version of the Declaration of Helsinki, as well as applicable local legal and regulatory requirements in the respective countries. I agree that all information revealed in this protocol is handled strictly confidentially.

Additionally, I will permit trial related monitoring, audits, Institutional Review Board (IRB) review and regulatory inspections, providing direct access to source data/documents.

(Date)	(Signature) [Name, Department]

1.2 Sponsor Signature Page

By signing the protocol:

A Phase 2, Multicenter, Single-Arm Trial of CV301 in combination with PD-1/L1 blocka in Patients with Locally Advanced or Metastatic Urothelial Bladder Cancer

The undersigned parties agree that the protocol was written according to international ethical a scientific quality standards (ICH-GCP), in compliance with the 2013 version of the Declaratio of Helsinki and applicable local legal and regulatory requirements in the respective countries.

Coordinating Author

[redacted]

Medical Monitor

Biostatistician

Immunology

Chief Medical Officer

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1.3 Responsibilities

Trial Number	CV301-BLD-001
Title	**A Phase 2, Multicenter, Single-Arm Trial of CV301 in Combination with PD-1/L1 Blockade in Patients with Locally Advanced or Metastatic Urothelial Bladder Cancer**
Sponsor and Product Supply Phone Fax Website	[redacted]
Project Leader Phone E-mail	
Medical Monitor Phone E-mail	
Pharmacovigilance Phone E-mail	

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List of Abbreviations

anti-TNF	anti-Tumor-Necrosis Factor
aPTT	Activated Partial Thromboplastin Time
AE	Adverse Event
AESI	Adverse Event of Special Interest
ADR	Adverse Drug Reaction
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BCG	Bacillus Calmette-Guérin
BN	Bavarian Nordic
BUN	Blood Urea Nitrogen
CEA	Carcinoembryonic Antigen
CI	Confidence Interval
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CRA	Clinical Research Associate
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte-associated Protein 4
DDMVAC	Dose-dense Methotrexate, Vinblastine, Doxorubicin and Cisplatin
dL	Deciliter
DILI	DrugInduced Liver Injury
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form

EDC	Electronic Data Capture
EE	Efficacy Evaluable Set
EMA	European Medicines Agency
EMR	Electronic Medical Record
EOT	End of Treatment
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	Formalin-fixed Paraffin-embedded
FPV	Fowlpox Virus
FU	Follow-Up
GC	Gemcitabine plus Cisplatin
GCP	Good Clinical Practice
g	Grams
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICAM-1	Intercellular Adhesion Molecule-1
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IMAEs	Immune-Mediated Adverse Events
IFN	Interferon
IL	Interleukin
IMP	Investigational Medicinal Product
Inf.U	Infectious Units
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine Device

IV	Intravenous
L	Liter
LA	Locally Advanced
LLN	Lower Limit of Normal
LDH	Lactate Dehydrogenase
LFA-3	Leukocyte Function-Associated Antigen 3
LTFU	Long Term Follow-up
M	Metastatic
MCH	Mean Corpuscular Hemoglobin
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Affairs
mg	Milligram
mL	Milliliter
mmol	Millimole
MMR	Mismatch repair
MP	Medical Product
MRI	Magnetic Resonance Imaging
MSI	Microsatellite instability
MUC-1	Mucin-1
MVA	Modified Vaccinia Ankara
MVAC	Methotrexate, Vinblastine, Doxorubicin, plus Cisplatin
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	NCI Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
OS	Overall Survival
OR	Objective Response
ORR	Objective Response Rate
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PD-1	Programmed Death 1
PD-L1	Programmed Death Ligand 1

PE	Physical Examination
PFS	Progression-Free Survival
PHI	Protected Health Information
PI	Principal Investigator
PR	Partial Response
PSA	Prostate Specific Antigen
PT	Prothrombin Time
PV	Pharmacovigilance
RBC	Red Blood Cells
RDW	Red Blood Cell Distribution Width
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SADR	Serious Adverse Drug Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
SC	Subcutaneous
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SMT	Safety Monitoring Team
SOP	Standard Operating Procedure
T3	Triiodothyronine
T4	Thyroxine
TAA	Tumor-Associated Antigen
$TCID_{50}$	Tissue Culture Infectious Dose
TCR	T cell Receptor
TEAE	Treatment Emergent Adverse Event
TIL	Tumor-Infiltrating-Lymphocytes
TNF	Tumor Necrosis Factor
Trial Vaccine	MVA-BN-CV301 and FPV-CV301
Trial Medication	Atezolizumab
Trial Product	MVA-BN-CV301, FPV-CV301, and Atezolizumab
TRICOM™	Triad of Costimulatory Molecules
TSH	Thyroid –Stimulating Hormone

TURBT	Transurethral Resection of Bladder Tumor
µL	Microliter
µm	Micrometer
UC	Urothelial Cancer
ULN	Upper Limit of Normal
US	United States
USA	United States of America
USPI	United States Prescribing Information
UTI	Urinary Tract Infection
WBC	White Blood Cell
WOCBP	Women of child-bearing potential

1.4 Protocol Synopsis

Title	A Phase 2, Multicenter, Single-Arm Trial of CV301 in Combination with PD-1/L1 Blockade in Patients with Locally Advanced or Metastatic Urothelial Bladder Cancer
Clinical phase	Phase 2
Sponsor	Bavarian Nordic A/S [redacted]
Number of sites	Approximately 12
Vaccination dose, schedule and administration route	Prime with MVA-BN-CV301 (nominal titer 1.6 x 10^9 Inf.U) given subcutaneously (SC) on Day 1 and Day 22. One dose = four 0.5 mL injections. One injection = nominal titer 4 x 10^8 Inf.U in 0.5 mL. Boost with FPV-CV301 (nominal titer of 1 x 10^9 Inf.U in 0.5 mL, given SC every 21 days for 4 doses (on days 43, 64, 85, and 106), followed by boosts every 6 weeks until 6 months on trial (i.e., days 148 and 190), then every 12 weeks until completion of 2 years. One dose = one 0.5 mL injection. Atezolizumab fixed dose of 1200 mg intravenous on Day 1 of each 21-day cycle. No dose reduction permitted.
Trial duration	Approximately 104 weeks before starting the long term follow up.
Trial Population	Patients with Locally Advanced or Metastatic Urothelial Cancer (UC) including bladder, ureter, renal pelvis and urethra. Cohort 1: Ineligible for cisplatin-containing chemotherapy (first-line treatment) Cohort 2: Previously treated with standard first-line cisplatin-based chemotherapy, PD-1/L1 Naïve (second-line treatment)
Number of Subjects:	Approximately up to 68
Primary objectives	Objective Response Rate (ORR; Complete Response [CR] + Partial Response [PR] Rate) as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1)

Secondary objectives	Progression-Free Survival (PFS) Overall Survival (OS) Duration of Response Safety of the treatment combination of CV301 with atezolizumab
Exploratory objectives	Analysis of biopsy tissue for differences between pre- and post-treatment samples correlation to patient survival e.g.: • T cell receptor (TCR) clonality • Tumor-Infiltrating-Lymphocytes (TILs) • Protein expression for e.g. Programmed Death Ligand 1 (PD-L1) and other biomarkers • Gene expression profiling for molecular subtyping Analysis of tumor DNA for Tumor mutational burden; DNA damage response gene mutations, MSI status, MMR deficiency status Analysis of peripheral blood mononuclear cells (PBMCs) / serum for differences between pre- and post-treatment samples correlation to patient survival e.g.: • Antigen-specific immune responses to carcinoembryonic antigen (CEA) and mucin-1 (MUC-1) as well as to other tumor-associated antigens (TAAs) to assess antigen cascade • Immunophenotyping of immune cell subsets by flow cytometry • Soluble biomarkers (e.g. cytokines and classical tumor markers) • TCR clonality • PD-1/L1 staining
Primary endpoint	Proportion of subjects with a confirmed OR (CR+PR) as per investigator assessment according to RECIST 1.1.

Secondary endpoints	Safety of the combined treatment as measured by: • Adverse Events (incidence, severity, and seriousness of treatment emergent adverse events [TEAEs]) • Laboratory Measures (summaries and shifts from baseline) • Vital Signs (summaries) OS defined as the time from start of treatment to the time of death from any cause. Duration of response defined as the time from the initial occurrence of documented complete response (CR) or partial response (PR) (whichever occurred first) until documented disease progression or death due to any cause on trial, whichever occurred first. PFS defined as the time from start of treatment to the first event of death or progressive disease (PD) per RECIST 1.1. Percentage of participants with OS and PFS at 6 (PFS only), 9 (PFS only), 12, 18 and 24 months. Immune-related Response Criteria assessment of response rate per iRECIST, delayed responses (pseudo-progressions), duration of response and PFS.
Trial design	Phase 2, Multicenter, Single-Arm, 2 Cohorts, Two-stage
Inclusion criteria – ALL subjects	1. The subject has read, signed and dated the Informed Consent Form (ICF), having been advised of the risks and benefits of the trial in a language understood by the subject. The ICF must be signed prior to any protocol specific assessments. 2. Age ≥ 18 years at date of ICF signature having the ability to comply with protocol. 3. Histologically or cytologically documented locally advanced (T4b, any N M0; or any T, N 1−3 M0) or metastatic (M1, Stage IV; or metastatic recurrence after locoregional treatment) UC (including renal pelvis, ureters, urinary bladder, urethra). Note about the change in the definition of Locally Advanced from TNM v7 to the current v8, while all those cases were Stage IV in v7, with TNM v8 they are reclassified as Stage IIIA (T1-4a N1 M0) and Stage IIIB (T1-4a N2-3 M0). a. Patients with mixed histologies were required to have a dominant transitional cell pattern.

b. Locally advanced bladder cancer that was inoperable on the basis of involvement of the pelvic sidewall or adjacent viscera (clinical stage T4b) or bulky nodal metastasis (N2−N3).

4. Life expectancy ≥ 12 weeks.
5. Measurable disease, as defined by RECIST 1.1. Previously irradiated lesions cannot be counted as target lesions unless there has been demonstrated progression in the lesion since radiotherapy and no other lesions are available for selection as target lesions.
6. Demonstrate adequate organ function as defined in Table 1. All screening labs should be performed within 14 days prior to the first trial product:

Table 1: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1,500 cells/µL
Platelets	≥ 100,000/µL
Hemoglobin	≥ 9.0 g/dL
WBC	> 2,500/µL
Lymphocyte count	≥ 300/µL
Hepatic	
Total bilirubin	≤ 1.5 x Upper Limit of Normal (ULN) **OR** Patients with known Gilbert disease who had serum bilirubin level ≤ 3 x ULN
Aspartate aminotransferase (AST)/ Serum glutamic oxaloacetic transaminase (SGOT) and Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT)	≤ 2.5 x ULN with the following exceptions: ≤ 5 x ULN for subjects with liver metastases **OR** Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5 x ULN
Serum Albumin	≥ 2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

7. For female patients of childbearing potential and male patients with partners of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception (i.e., one that results in a low failure rate [< 1% per year] when used consistently and correctly). Must be on acceptable method for at least 30 days prior to 1st dose of trial product and to continue its use for 5 months after the last dose of atezolizumab.
8. Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (blocks preferred) or at least ten 4µm and one 20µm unstained slides, with an associated pathology report. This specimen will be reviewed by a central reader but results of review will not be required prior to registration and treatment of the subject.
    a. Tumor tissue has to be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable. For core needle biopsy specimens, a result of ten 4µm and one 20µm slides of evaluable quality have to be submitted for evaluation.
    b. Patients who submitted transurethral resection of bladder tumor (TURBT) specimens are required to submit specimens containing muscle invasive component of the bladder tumor as verified by pathology review. If the TURBT specimens do not contain a muscle invasive component (i.e., T2 or greater), then specimens obtained at the time of cystectomy/nephroureterectomy or metastatic spread (i.e., sample from a metastatic lesion) are required. An archival specimen, if available, must also be submitted.
    c. Patients who do not have tissue specimens meeting eligibility requirements must undergo a biopsy sample collection during the screening period. Acceptable samples include core needle biopsies for deep tumor tissue (resulting in ten 4µm and one 20µm slides of evaluable quality) or excisional, incisional, punch, or forceps biopsy samples for cutaneous, subcutaneous, or mucosal lesions.
    d. Patients having additional tissue samples from procedures performed at different times during the course of their urothelial carcinoma are requested (but not required) to also submit these samples for central testing. In situations where multiple specimens are received from different sites or at

different times, the highest score will be used for primary and secondary analyses.

Inclusion for Cohort 1

9. Untreated with chemotherapy for metastatic disease
10. Have at least one of the following:
    a. ECOG (Eastern Cooperative Oncology Group) performance status of 2.
    b. Glomerular filtration rate calculated as creatinine clearance (Cockroft-Gault formula) of ≥20 mL/min and less than 60 mL/min
    c. Hearing loss or neuropathy of any cause Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 2.

Inclusion for Cohort 2

11. Disease progression during or following treatment with at least one platinum-containing regimen (e.g., GC, MVAC, CarboGem, carboplatin-paclitaxel) for inoperable locally advanced or metastatic urothelial carcinoma or disease recurrence, as defined by:
    a. Regimen is defined as patients receiving at least one cycle of a platinum-containing regimen with response assessment. Patients who received one cycle of a platinum-containing regimen but discontinued due to toxicity are also eligible.
    b. Patients who received prior adjuvant/neoadjuvant chemotherapy and progressed within 12 months of treatment with a platinum-containing adjuvant/neoadjuvant regimen are considered as second-line patients.
12. ECOG (Eastern Cooperative Oncology Group) performance status of < 2
13. Calculated creatinine clearance (Cockroft-Gault formula) of ≥20 mL/min

Exclusion criteria for ALL subjects

1. Any approved anti-cancer therapy, including chemotherapy, within 3 weeks prior to initiation of trial product; the following exceptions are allowed:
    a. Palliative radiotherapy for bone metastases or non-target soft tissue lesions completed > 7 days prior to baseline imaging.
    b. Hormone-replacement therapy or oral contraceptives.
2. Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days prior to Day 1 (first dose of trial product) given that all AEs related to prior treatment have resolved to baseline or Grade 1.
3. Active central nervous system (CNS) metastases defined as computed tomography (CT) or magnetic resonance imaging (MRI)

evidence of progression and prior radiographic assessments or Leptomeningeal disease.

Subjects that have had prior diagnosis need to have stable disease by having results or performing CT/MRI with 1 month prior to 1st dose of treatment.

4. Uncontrolled tumor-related pain:
   a. Patients requiring pain medication must be on a stable regimen at trial entry.
   b. Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to trial entry.
   c. Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not currently associated with spinal cord compression) could be considered for loco-regional therapy if appropriate prior to first dose of trial product.
5. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
   a. Patients with indwelling catheters (e.g., PleurX) are allowed.
6. Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or Ca > 12 mg/dL or corrected serum calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab:
   a. Patients who are receiving bisphosphonate therapy or denosumab specifically to prevent skeletal events and who did not have a history of clinically significant hypercalcemia are eligible.
   b. Patients who are receiving denosumab prior to first dose of trial product have to be willing and eligible to receive a bisphosphonate instead while in the trial.
7. Malignancies other than urothelial carcinoma within 3 years prior to Day 1, with the exception of those with a negligible risk of metastasis or death treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent) or localized prostate cancer treated with curative intent and no intent for further treatment or incidental prostate cancer (T1/T2b, Gleason score ≤ 7 undergoing active surveillance and treatment naive).
8. Pregnant and lactating women.

9. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins, or aminoglycoside antibiotics or egg products, poxvirus-based vaccinations, or beef or bovine meat.
10. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation.
11. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, granulomatosis with polyangiitis, Sjogren's syndrome, Guillain-Barre syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.
    a. Patients with a history of autoimmune-related hypothyroidism on a stable, maintenance dose of thyroid replacement hormone with evidence of adequate control or response by TSH (per institution standards) and compliance with prescribed hormone replacement are eligible for this trial.
    b. Patients with controlled Type I diabetes mellitus on a stable dose of insulin and who are compliant with insulin regimen are eligible for this trial.
    c. Patients with history of vitiligo and controlled psoriasis are eligible for the trial.
12. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan
    a. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
13. Positive test for Human Immunodeficiency Virus (HIV).
14. Patients with active hepatitis B virus (HBV; chronic or acute, defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C virus (HCV)
    a. Patients with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HbsAg, negative polymerase chain reaction (PCR) for HBV) are eligible. HBV Deoxyribonucleic Acid (DNA) PCR must be obtained in these patients prior to Day 1.
    b. Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV Ribonucleic Acid (RNA) prior to first dose of trial product.

15. Active tuberculosis.
16. Signs or symptoms clinically significant of infection within 2 weeks prior to Day 1.
17. Received therapeutic oral or intravenous (IV) antibiotics within 1 week prior to Day 1
    a. Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.
18. Significant cardiovascular disease, which includes but is not limited to New York Heart Association (NYHA) Heart Failure Class II or greater, myocardial infarction within the previous 3 months, unstable arrhythmias, unstable angina.
    a. Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction < 50% on a stable medical regimen that was optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate, are eligible.
19. Major surgical procedure other than for diagnosis within 28 days prior to Day 1 or anticipation of need for a major surgical procedure during the course of the trial.
20. Prior allogeneic stem cell or solid organ transplant.
21. Administration of a live, attenuated vaccine within 4 weeks before Day 1 or anticipation that such a live attenuated vaccine would be required during the trial
    a. Influenza vaccination may be given during influenza season only (approximately October to March). Patients cannot receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to Day 1 or at any time during the trial.
22. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicated the use of an investigational drug or that could affect the interpretation of the results or render the patient at high risk from treatment complications.
23. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti−CTLA-4, anti−PD-1, and anti−PD-L1 therapeutic antibodies
24. Treatment with systemic immunostimulatory agents (including but not limited to IFNs, interleukin [IL]-2) within 6 weeks or five half-lives of the drug, whichever was shorter, prior to Day 1.

25. Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, and anti−tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Day 1, or anticipated requirement for systemic immunosuppressive medications during the trial
    a. Patients who receive acute, low-dose, systemic corticosteroid medications (e.g., a one-time dose of dexamethasone for nausea) or for prevention of hypersensitivity reactions to contrast agents may be enrolled in the trial.
    b. The use of inhaled, nasal, ophthalmic, intra-articular, auricular or topical corticosteroids, physiologic replacement doses of glucocorticoids (i.e., for adrenal insufficiency), and mineralocorticoids (e.g. fludrocortisone for adrenal insufficiency) is allowed.

Statistical considerations

Simon's two-stage design (Simon, 1989) will be used within each cohort. Due to the multiple testing involved in having two cohorts, the individual cohort alpha has been set to 0.025 (one-sided) to ensure a trial-wide type I error rate of $\alpha < 0.05$.

The design for the first cohort, platinum ineligible subjects, is based on a prior published ORR of 23% for atezolizumab monotherapy (Balar et al., 2017b). The null hypothesis that the true ORR is 0.23 will be tested against a one-sided alternative. In the first stage, 14 subjects will be accrued. If there are 3 or fewer responses in these 14 subjects, the cohort will be stopped. Otherwise, 19 additional subjects will be accrued for a total of 33. The null hypothesis will be rejected if 13 or more responses are observed in 33 subjects. This design yields an actual 1-sided type I error rate of 0.0244 and power of 0.7027 when the true ORR is 0.43 for the combination.

The design for the second cohort, platinum refractory subjects who are anti-PD-L1 naïve, is based on a prior published ORR of 15% for atezolizumab monotherapy (Rosenberg et al., 2016). The null hypothesis that the true ORR is 0.15 will be tested against a one-sided alternative. In the first stage, 13 subjects will be accrued. If there are 2 or fewer responses in these 13 subjects, the cohort will be stopped. Otherwise, 22 additional subjects will be accrued for a total of 35. The null hypothesis will be rejected if 10 or more responses are observed in 35 subjects. This design yields an actual 1-sided type I error rate of 0.0249 and power of 0.7092 when the true ORR is 0.33 for the combination.

Based on simulations with the two-stage, two-cohort design, the overall type-1 error rate will be approximately 4.7%, and the power for the study, indicating at least one of the two cohorts will be positive given the alternative hypotheses are true, is approximately 91%.

1.5 Trial Procedure Schedule

Trial Procedure	Screening Phase Day -28 to Day 1	Week (3 wk interval +/- 4 days)						Week (6 wk interval +/- 1 wk)		Week (12 wk interval +/- 2 wks)						Long Term FU
		1	4	7	10	13	16	22	28	40	52	64	76	88	100 EOT[12]	3-month interval +/- 2 wks
		Day														
		1	22	43	64	85	106	148	190	274	358	442	526	610	694 EOT	
		Visit														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Trial Procedures																
Informed Consent[1]	X															
Demographics	X															
Medical History	X															
Physical Exam incl. vital signs[2]	X															
Targeted PE incl. vital signs[2]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG[3]	X															
Eligibility Criteria	X															
Concomitant Medications	X	collected at all clinic visits (including atezolizumab dosing visits)														
Adverse Events[4]	X	collected at all clinic visits (including atezolizumab dosing visits)														X[4]
Survival Status and Auto-immune/ IM clinical manifestation																X
Tumor Biopsy	X[5]			X[6]												
Radiology Assessments																
CT scan: Thorax, Abdomen and Pelvis[7]	X				X			X	X	X	X	X	X	X	X	

Trial Procedure	Screening Phase Day -28 to Day 1	Week (3 wk interval +/- 4 days)						Week (6 wk interval +/- 1 wk)		Week (12 wk interval +/- 2 wks)						Long Term FU
		1	4	7	10	13	16	22	28	40	52	64	76	88	100 EOT[12]	3-month interval +/- 2 wks
		Day														
		1	22	43	64	85	106	148	190	274	358	442	526	610	694 EOT	
		Visit														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Laboratory Assessments																
Hematology[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HIV, HbsAg, HCV	X															
INR, PT, aPTT	X															
Thyroid function test	X	X		X		X	every 6 weeks									
Biomarker Analyses[9]	X		X		X			X			X					
Urinalysis	X		X		X		X	X	X	X	X	X	X	X	X	
Pregnancy Test[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dosing																
Prime Vaccine: MVA-BN-CV301[11]		X	X													
Boost Vaccine: FPV-CV301[11]				X	X	X	X	X	X	X	X	X	X	X	X	
Atezolizumab		X	X	X	X	X	X	every 3 weeks[8,10]								

EOT = End of Treatment, PE = Physical Examination, AE = Adverse Event, SAE = Serious Adverse Event, AESI = Adverse Event of Special Interest, WOCBP = Women of Childbearing Potential

[1] ICF can be obtained prior to Screening visit

[2] Blood pressure and pulse rate should be obtained after the subject has been seated in an upright position for at least 5 minutes.

[3] Troponin I will only be measured if clinically indicated.

[4] The reporting period for non-serious AEs and unrelated SAEs/AESIs ends 30 days after last administration of the trial product. The reporting period for related SAEs/AESIs ends 100 days after last administration of the trial product. A phone follow-up will be performed 100 days after the last administration of trial product to collect this information and schedule a follow-up visit, if clinically indicated.

[5] Patients who do not have archived tissue specimens meeting eligibility requirements must undergo a biopsy sample collection during the screening period. Acceptable samples included core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsy samples for cutaneous, subcutaneous, or mucosal lesions.

[6] Optional at any of the following visits: Visit 3-6.

[7] If there is a medical reason, subject may have MRI instead of CT scan upon approval from BN.

[8] Hematology and Serum Chemistry will be performed prior to every atezolizumab infusion. Hematology will include hemoglobin, hematocrit, red blood cell count, total white blood cell count with differential, platelet count, mean cell volume, mean corpuscular hemoglobin, and red blood cell distribution width. Serum chemistry will include: total protein, albumin, alkaline phosphatase, total bilirubin, ALT, AST, lactate dehydrogenase, creatinine, blood urea nitrogen, uric acid, glucose, calcium, phosphorus, bicarbonate, chloride, potassium, sodium, lipase and amylase.

[9] Sample collection (peripheral blood for PBMC, serum) must occur prior to vaccine dosing. Sample collection for Biomarker analyses should be repeated if subject comes off trial due to PD or AE or if the subject has an objective response.

[10] For WOCBP, a pregnancy test is required prior to every atezolizumab infusion. Urine or serum pregnancy test is acceptable at any given visit depending on investigator and/or patient preference.

[11] The trial subject must be kept under close observation at the clinical trial site for at least 30 minutes following vaccinations.

[12] EOT visit should take place within 28 days of withdrawal.

2 Background Information and Scientific Rationale

2.1 Introduction

The estimated incidence of urothelial cancers -including bladder, ureter and renal pelvis- for 2017 in the US is 146,650 cases. The mortality estimated for urinary system cancers is 32,190 deaths (Siegel et al., 2017). Approximately 5% of newly diagnosed bladder cancers present with metastatic disease and 30% with muscle-invasive bladder cancer. Roughly 50% of patients with muscle-invasive bladder cancer will develop distant metastasis (Milowsky et al., 2016). The median age of diagnosis of bladder cancer patients is 73 years, with more than 70% older than 65 years (Miller et al., 2016).

Before the Food and Drug Administration (FDA) approval of programmed death-1 (PD-1)/ programmed death ligand-1 (PD-L1) inhibitory antibodies in 2016 and 2017, chemotherapy was the only treatment available for locally advanced or metastatic urothelial bladder cancer. The most efficacious chemotherapy regimens are those containing cisplatin, which represents a challenge for frail and unfit patients. Low performance status, advanced age, compromised renal function and comorbidities limit the capability of these patients to cope with intensive platinum-based regimens. A first step in selecting the proper treatment for UC patients is to identify to which category they belong, cisplatin eligible or ineligible. The category of cisplatin eligible patients is especially relevant for first-line treatment, since the administration of standard regimens such as DDMVAC [dose-dense methotrexate, vinblastine, doxorubicin and cisplatin] or cisplatin/gemcitabine is associated with a fraction of long-term survivors. However, the prognosis is dismal for patients with disease progression after first-line chemotherapy. The ORR was lower than 10% for all the single agents tested. No chemotherapy agent was ever approved by the FDA for second-line treatment and only vinflunine achieved the approval by the European Medicines Agency (EMA), based on a modest 2-month and non-statistically significant prolongation of OS in a randomized Phase 3 clinical trial (Balar et al., 2017a), (Bellmunt et al., 2009). A prognostic model was derived from the vinflunine pivotal trial database in which the most important prognostic factors were ECOG Performance status higher than 0, hemoglobin level less than 10 g/dL and liver metastasis (Bellmunt et al., 2010). Time from prior chemotherapy was later identified as an additional independent prognostic factor and accordingly it was recommended as a stratifying factor in randomized clinical trials (Sonpavde et al., 2013). In a poster communication to the (ASCO) Annual Meeting 2014 (Sonpavde, 2014), twelve Phase 2 clinical trials studying single agents or combinations included 711 patients and the global median OS was 6.8 months, 95% C.I. 6.2 to 7.3 months, with a range of 3.9 to 10.8 months. The median OS reported in the Phase 3 clinical trial that compared vinflunine versus investigator's chemotherapy choice were 6.9 and 4.6 months respectively (Balar et al., 2017a), (Bellmunt et al., 2009).

As of December 2017, the FDA has approved five PD-1/PD-L1 inhibitory antibodies for locally advanced (LA) or metastatic (M) UC. A summary of these drugs and labels is presented in the following table (Table 2).

Table 2: Summary of Approved Anti- PD-1/PD-L1 Antibodies for Urothelial Cancer

Drug Trade name	Pembrolizumab Keytruda	Atezolizumab Tecentriq	Nivolumab Opdivo	Avelumab Bavencio	Durvalumab Imfinzi
Regular approval	LA/M 2nd -line				
Accelerated approval	LA/M non-eligible for cisplatin	LA/M 2nd -line LA/M non-eligible for cisplatin	LA/M 2nd -line	LA/M 2nd -line	LA/M 2nd -line

LA = locally advanced, M = metastatic

Atezolizumab was the first anti-PD-L1 approved by the FDA for urothelial cancer (UC). The IMvigor210 study is a multicenter, single-arm, two-cohort, Phase 2 trial, with inoperable locally advanced or metastatic UC whose disease had progressed after previous platinum-based chemotherapy. The study included 315 (cohort 1) and 310 (cohort 2) patients that were treated with intravenous atezolizumab 1200 mg, given every 3 weeks (Rosenberg et al., 2016). Co-primary endpoints were the independent review facility-assessed ORR according to RECIST 1.1 and the investigator-assessed ORR according to immune-modified RECIST, analyzed by intention to treat. Compared with a historical control overall response rate of 10%, treatment with atezolizumab resulted in a significantly improved RECIST 1.1 ORR 15% [11–20], p=0.0058. With a median follow-up of 11.7 months (95% CI 11.4–12.2), ongoing responses were recorded in 38 (84%) of 45 responders. Grade 3–4 treatment-related adverse events, of which fatigue was the most common occurred in 50 (16%) of 310 treated patients. Grade 3–4 immune-mediated adverse events occurred in 15 (5%) of 310 treated patients, with pneumonitis, increased AST, increased ALT, rash, and dyspnea being the most common. The median OS was 11.4 months for the 100-patient cohort. The observed correlation between higher PD-L1 expression and longer OS supports the importance of adaptive immunity in driving benefit to immune checkpoint inhibitors. Moreover, the observed association between immune activation genes, immune checkpoint genes and PD-L1 expression in immune cells provides additional support to the concept that PD-L1 expression indicates adaptive immune regulation and a pre-existing but inhibited anticancer immune response.

Patients participating in IMvigor210 could continue atezolizumab beyond progression at the investigator's discretion until the loss of clinical benefit. In total, 137 patients continued atezolizumab out of 220 patients with progression. Five patients (3.6%) continuing atezolizumab after progression had subsequent responses compared with baseline measurements. None of those patients previously experienced a response (Necchi et al., 2017). These observations suggest that atezolizumab treatment beyond progression may result in nonclassical responses and durable tumor burden reductions.

IMvigor211 is a Phase 3 study of atezolizumab in comparison with chemotherapy in people with advanced bladder cancer who were previously treated with a platinum-based chemotherapy. The study evaluated the efficacy and safety of TECENTRIQ compared with physician's choice of chemotherapy (vinflunine, paclitaxel or docetaxel) administered every 3 weeks in 931 people with previously treated mUC, who had progressed during or following a platinum-based regimen. The primary efficacy endpoint was OS and key secondary endpoints include ORR, progression-free survival, and DOR. The primary efficacy endpoint, OS, was to be tested in a successive fashion (hierarchical testing) in study populations defined by PD-L1 expression. Statistical significance needed to be achieved for the study populations in the following order: IC2/3 (≥5%), IC1/2/3 (≥1%), and ITT group. However, because such significance was not achieved for OS in the IC2/3 population, results could not be evaluated for statistical significance in the IC1/2/3 and ITT populations, and these analyses are considered descriptive in nature. The first population tested comprised people with the highest levels of PD-L1 expression (IC2/3), followed by those with any observable level of PD-L1 expression (IC1/2/3), and followed by the overall study population (intention-to-treat: ITT). Per the pre-specified hierarchical testing order, the IC2/3 (≥5%) population was tested first, with an OS HR of 0.87 (95% CI: 0.63, 1.21; median OS (mOS) of 11.1 vs 10.6 months for atezolizumab and chemotherapy respectively); p=0.41. In the overall study population (ITT), people treated with atezolizumab achieved a mOS of 8.6 months (CI: 95%; 7.8, 9.6), compared with 8.0 months (CI: 95%; 7.2, 8.6) with chemotherapy (HR 0.85, 95% CI 0.73–0.99). The OS rate at the 12 months landmark was 39.2% and 32.4% for atezolizumab and chemotherapy respectively. Overall response rates were like those previously reported in the Phase 2 IMvigor210 study and similar between the two study arms, 13.4% for the ITT population and 23% vs 21.6% for atezolizumab and chemotherapy respectively in the IC2/3 population. The median duration of response (mDOR), for those receiving atezolizumab was 21.7 months (95% CI: 13.0, 21.7) in the overall study population, compared with 7.4 months (95% CI: 6.1, 10.3) for those receiving chemotherapy. At the time of data cutoff, 39 out of 62 (63%) of responders to treatment with atezolizumab continued to respond, compared with 13 out of 62 (21%) of responders to chemotherapy (Powles et al., 2017).

Results from a pembrolizumab Phase 3 trial in patients with advanced urothelial carcinoma that progresses after platinum-based chemotherapy have been published (Bellmunt et al., 2017). Pembrolizumab at a dose of 200 mg every 3 weeks was compared with investigator's choice of chemotherapy with paclitaxel, docetaxel, or vinflunine. A total of 542 patients were enrolled and the co-primary endpoints were OS and PFS. The median OS in the total population was 10.3 months (95% CI 8.0 to 11.8) in the pembrolizumab group, as compared with 7.4 months (95% CI, 6.1 to 8.3) in the chemotherapy group (hazard ratio for death, 0.73; 95% CI, 0.59 to 0.91; P = 0.002. The estimated progression-free survival rate at 12 months was 16.8% (95% CI, 12.3 to 22.0) in the pembrolizumab group and 6.2% (95% CI, 3.3 to 10.2) in the chemotherapy group. The ORR was significantly higher (P = 0.001) in the pembrolizumab group (21.1%; 95% CI, 16.4 to 26.5) than in the chemotherapy group (11.4%; 95% CI, 7.9 to 15.8). The estimated percentage of patients with duration of response of at least 12 months was 68% in the pembrolizumab group versus 35% in the chemotherapy group. Fewer treatment-related adverse events of any grade were reported in the pembrolizumab group than in the chemotherapy group (60.9% vs. 90.2%);

there were also fewer events of grade 3, 4, or 5 severity reported in the pembrolizumab group than in the chemotherapy group (15.0% vs. 49.4%).

Locally advanced or metastatic urothelial cancer cisplatin-ineligible patients for first-line treatment is a new approved FDA and EMA indication for both atezolizumab and pembrolizumab. Atezolizumab approval is based on IMvigor201 Phase 2 trial, a single-arm, multicentric study that included 119 patients evaluable (Balar et al., 2017b). The objective response rate was 23%, including 9% CR. Median DOR was not reached by the time of the publication, range 3.7 to 21+ months, with 70% of responses ongoing as of data cutoff. Responses were observed in all categories of cisplatin ineligibility: 25% in patients with impaired renal function, 25% in PS2 patients and 12% and 14% for patients with hearing loss and peripheral neuropathy respectively. The median OS was 15.9 months and 12-month landmark survival was 75%. AEs grade 3-4 were reported in 16% of patients, led to treatment discontinuation in 34% of patients and led to treatment withdrawal in 8%. IMAEs were reported in 12% of patients and grade 5 in 4 patients. Pembrolizumab approval is based on KEYNOTE-052 Phase 2 trial, a single-arm, multicentric study that included 370 patients evaluable (Balar et al., 2017a). The objective response rate was 24%, including 5% CR. Median DOR was not reached by the time of the publication, with 78% of responses ongoing as of data cutoff. Responses were observed in all categories of cisplatin ineligibility: 27% in patients with impaired renal function, 26% in PS2 patients and 31% for patients with other reasons. AEs grade 3-4 were reported in 16% of patients, 5% leading to treatment discontinuation. In both trials, responses were observed across all categories of PD-L1 expression, with the clinically relevant fact that low or absent PD-L1 does not preclude response.

2.2 Trial Rationale

Several studies in mice have shown that poxvirus vector-based vaccines can generate activated T lymphocytes that infiltrate tumors and induce the expression of PD-L1 (Foy et al., 2016). Combinations of poxvirus vectored vaccines with inhibitors of PD-1 have shown synergistic effects in the laboratory (Foy et al., 2016). The available laboratory evidence constitutes the main rational for studying the combination of poxvirus-vectored vaccines with PD-1 and PD-L1 inhibitors in humans. The acknowledgment that PD-1 and PD-L1 inhibitors are particularly active in patients with a pre-existing immune response has led to the hypothesis that tumors without an ongoing immune response (“cold tumors”) may require an immunotherapy capable of inducing tumor-specific T cells activation and trafficking to the tumor site. The use of effective vaccines is a rational solution to initiate a new immune response against those tumors lacking a pre-existing immune response. Cumulative evidence in different human tumors, including bladder cancer, lends support to the concept that the efficacy of PD-1 and PD-L1 inhibitors correlates with the mutational burden of cancer, and the probability of developing a spontaneous anticancer immune response depends on the immunogenicity of the neoantigens. On the other hand, the efficacy of PD-1 and PD-L1 inhibitors have clear clinical limitations, since almost half of the patients showing early benefit will experience progression during treatment, so enhancing the immune response by adding T cell clones capable to recognize cancer shared antigens could be a useful

therapeutic approach to improve the clinical results. In summary, the different mechanisms of action of PD-1 and PD-L1 inhibitors and CV301 are considered potentially complementary and clinical trials exploring the potential of this combination are warranted.

The expression of CEA in bladder cancer has been reported in the range of 41% to 90% (Jautzke and Altenaehr, 1982), (Allard et al., 1995), (Genega et al., 2000). The expression of MUC-1 has been reported in the range of 55% to 91% (Stojnev et al., 2014), (Fina et al., 2016), but in 100% the subgroup of metastatic lesions (Kaur et al., 2014). A summary can be found in Table 3. Since CV301 contains both CEA and MUC-1 human transgenes, it is expected that this active immunotherapy may benefit most patients with UC.

Table 3: Summary of CEA and MUC-1 Expression Levels in Urothelial Bladder Cancer

Expression of CEA and MUC-1 on Urothelial Bladder Cancer					
TAA	% Positive	No. Pts.	Stage	Reference	Comment
CEA	0 to 67	12	Unknown	Hum Prot Atlas	4 Antibodies
	57	150	Primary	Jautzke 1982	Increasing expression with grade and T stage
	90	350	Superficial	Allard 1995	
	41 & 63	46	High grade	Genega 2000	2 Antibodies
MUC-1	64 to 91	12	Unknown	Hum Prot Atlas	5 Antibodies
	62	539	Primary	Stojnev 2014	
	83 & 66	323	Prim. & Met.	Kaur 2014	
	55	31	CTC	Fina 2016	RNA by PCR

2.3 MVA-BN-CV301 & FPV-CV301 Vaccine(s)

2.3.1 Origin and Characteristics of MVA-BN Vector Backbone

Vaccinia virus has been used for over 200 years as a vaccine for smallpox and has a well-established safety profile. The virus actively replicates in human cells, resulting in the presentation of high levels of antigen to the immune system over a period of 1–2 weeks, substantially increasing the potential for immune stimulation. The immune response specific to vaccinia then eliminates the virus. As a result of its safety profile and ability to elicit both humoral and cell-mediated immunity in humans, the vaccinia virus was chosen as one of the vectors to deliver MUC-1, CEA, and Triad of Costimulatory Molecules (TRICOM) in previous National Cancer Institute (NCI)-sponsored trials.

Despite the desirable features of poxviruses, replication-competent viruses like vaccinia should not be administered to severely immunocompromised subjects. To address this problem, an

attenuated vaccinia virus called Modified Vaccinia Ankara (MVA) was developed for high-risk individuals. MVA was generated by over 500 serial passages of a smallpox vaccine from Ankara, Turkey, in chicken embryo fibroblasts, resulting in over 15% loss of the vaccinia virus genome. MVA can infect mammalian cells and express transgenes, but it cannot produce infective viral particles.

Bavarian Nordic (BN) has generated a proprietary isolate of MVA designated MVA-BN®.

MVA-BN has been derived from the licensed MVA used in Europe by additional passages and limiting dilutions in Chicken Embryo Fibroblast cells under serum-free conditions and has been shown not to replicate in human cells and can be safely administered to severely immune compromised animals (Suter et al., 2009). Although MVA exhibits strongly reduced replication in mammalian cells, the block in viral replication resides at the level of virus assembly and egress (Sutter and Moss, 1992), (Carroll and Moss, 1997), resulting in efficient expression of viral as well as recombinant proteins. The ability to stably clone large amounts of foreign DNA into the MVA genome provides a versatile vaccine vector (Sutter and Staib, 2003)) and in addition to developing MVA-BN as a safer smallpox vaccine, BN has used this platform to develop various vaccines against infectious diseases and cancer (Harrer et al., 2005), (Cosma et al., 2003), (Di Nicola et al., 2003),(Di Nicola et al., 2004).

2.3.2 Clinical Experience with MVA-BN and Recombinant MVA-based Vaccines

MVA-BN Vector Platform

MVA-BN is used by itself as a prophylactic vaccine for smallpox, currently approved in Europe and Canada (trade name IMVAMUNE® outside European Union [EU], trade name IMVANEX® in the EU). MVA-BN is also investigated as a vector for immunization against several infectious disease agents and tumor-associated antigens.

To date, 22 clinical trials evaluating the safety and immunogenicity of MVA-BN have been completed and 2 clinical trials are ongoing. As of 12Feb2019, more than 8,800 subjects have been exposed to MVA-BN including risk groups with contraindications to conventional smallpox vaccines. Furthermore, BN has evaluated the safety and immunogenicity of MVA-BN-based recombinant vaccines (including MVA-BN-Filo) in healthy subjects, HIV infected individuals, populations with cancer and children.

In total, for MVA-BN and MVA-BN-based recombinant vaccines, the exposure sums up to more than 13,300 subjects, having received more than 15,000 single doses of vaccine.

For more details, refer to the current CV301 Investigator Brochure (IB).

2.3.3 Safety Overview of MVA-BN and Recombinant MVA-based Vaccines

In all completed and ongoing clinical trials, vaccinations with MVA-BN have shown to be generally safe and well tolerated. No cases of death, assessed as being at least possibly related, have been reported for a subject in a clinical trial using MVA-BN. Results obtained from completed Phase 1 and 2 trials and ongoing trials with several recombinant MVA-BN based vaccines in healthy adults and children, HIV infected subjects and cancer subjects demonstrate a similar safety profile as MVA-BN alone.

Additional information on the safety profile of MVA-BN and recombinant MVA-based vaccines is provided in the CV301 IB.

Adverse Drug Reactions (ADRs)

Looking only at the events that were reported by at least 1% of subjects, the majority of ADRs represented local vaccination site reactions as well as common systemic reactions typical for modern injectable vaccines and were classified as being mild to moderate in intensity and resolved completely without intervention within the first 7 days following vaccination. To date, no trends have been identified suggesting the occurrence of any particular unexpected adverse reactions or classes of adverse reactions following vaccinations with MVA-BN or its recombinants.

Cardiac Signs and Symptoms

Based on observations with replicating smallpox vaccines, particular attention has been placed on monitoring for cardiac signs and symptoms in all clinical trials using MVA-BN. Despite close cardiac monitoring, no confirmed event indicating a case of myo-/pericarditis has been observed in any completed MVA-BN trial.

Serious Suspected Adverse Drug Reactions

As of 12Feb2019, a total of 7 (7 out of 8,888 vaccinated subjects = 0.08%) serious suspected ADRs have been reported for MVA-BN smallpox vaccine in completed and ongoing trials. All of them have been thoroughly reviewed by BN and the trial specific Data and Safety Monitoring Board who concluded that the continued use of MVA-BN in a clinical setting presented no special risks to the subjects. No pattern regarding Serious Adverse Drug Reactions (SADRs) could be detected. For further details, please refer to the CV301 IB, Section 5.3.1.

BN has evaluated the safety and immunogenicity of MVA-BN-based recombinant vaccines for several indications such as cancer, HIV and measles in more than 2,600 subjects including healthy and HIV infected populations. In recombinant MVA-BN vaccine trials, doses up to 5×10^8 $TCID_{50}$ were administered applying varying schedules of repeated vaccinations, e.g. a 3-dose schedule was used for recombinant HIV vaccines and multiple vaccinations have also been performed in subjects receiving a recombinant therapeutic breast cancer vaccine

(MVA-BN-HER2). Results obtained from these Phase 1 and 2 trials demonstrate a similar safety profile and vector immunogenicity as compared to MVA-BN alone.

Two of the recombinant vaccine trials allowed for a direct comparison with MVA-BN as an active control. These trials (HIV-POL-002 and HIV-NEF-004) were performed to evaluate 2 different recombinant MVA-BN-based HIV vaccine candidates in HIV-infected subjects. In both trials, a total of 3 vaccinations with either the recombinant HIV vaccine or MVA-BN were performed according to a 0, 8 and 16-week regimen.

In the ongoing Phase 1 lung trial (CV301-2015-201), during the Phase 1a dose escalation, a dose of 1.6 x 10^9 Inf.U was reached without observing any dose limiting toxicity (DLT). In Phase 1b of the lung trial (CV301-2015-201), a SAE of Pneumonitis with an immune-mediated etiology occurred in a 48-year-old female subject who was receiving a combination of MVA-BN-CV301 and nivolumab for the treatment of NSCLC. The ADR was considered to be possibly related to MVA-BN-CV301 and probably related to nivolumab. Following the onset of Pneumonitis, the subject experienced Vasculitis and Disseminated Intravascular Coagulation (DIC) which culminated in the fatal event of Multi-Organ Failure, all unrelated to treatment with MVA-BN-CV301. A full review took place by BN and the designated trial SMT who concluded that the event met the criteria of a dose-limiting toxicity, but did not warrant changes to the risk-benefit assessment of MVA-BN-CV301 or to the conduct of the CV301-2015-201 clinical trial.

Summary

The safety profile of each of the trials with recombinant MVA-BN-based vaccines is comparable to the safety profile observed with MVA-BN trials as the occurrence of the ADRs is considered to be a reaction to the vector rather than the insert, based on previous experience with recombinant MVA-BN vaccine candidates.

The safety of MVA-BN-CV301 in combination with checkpoint inhibitors is currently under evaluation in the ongoing Phase 1b portion of CV301-2015-201 trial.

The overall frequency of immune mediated events under combination treatment of CV301 plus anti-PD1 appears to be in line with previously published experience for anti-PD1 alone (Brahmer et al., 2018).

During the ongoing Phase 1b of CV301-2015-201, the more frequently occurring reactions such as local injection site reactions and general symptoms were in line with the experience during monotherapy in Phase 1, as well as with the overall backbone vector experience.

2.4 Overview of Fowlpox virus (FPV)

Fowlpox virus is a member of the genus Avipox, which is evolutionarily divergent from vaccinia virus and serologically non-cross-reactive (J. Taylor, 1988), (Beukema et al., 2006). Immune

responses to vaccinia do not block infection and immunization with fowlpox-based vectors. Hence vaccinia-primed or MVA-primed immune responses can be boosted with fowlpox vectors. In addition, fowlpox vectors do not replicate in human cells (only in avian cells) and are therefore much less of a safety risk than replication competent vaccinia-based vectors. Fowlpox vectors mediate a limited infection in human cells, with early viral and transgene expression, but late gene expression is blocked, and no infectious particles are produced. Thus, minimal viral surface antigen is made, and minimal neutralizing antibody immune responses are induced. This enables multiple boosting with the fowlpox-based vectors.

FPV has been investigated and used in vaccine design for at least 2 decades. As with vaccinia virus, it offers the advantages of a large genome but provides an additional safety assurance by not being able to replicate in mammalian cells. Fowlpox virus-based vaccines (HIV, malaria, cancer) have been tested in both animals and humans. No safety concerns have been raised and the adverse events (AE) associated with the use of fowlpox vectors have been limited to mild injection site reactions (Beukema et al., 2006, Essajee and Kaufman, 2004, Webster et al., 2006).

The recombinant FPV-CV301 vaccine is based on a fowlpox vector which is currently being evaluated as part of a prime-boost regimen in the treatment of metastatic castration resistant prostate cancer (PROSTVAC®). Priming with a recombinant vaccinia virus followed by several boosters of the corresponding recombinant fowlpox virus elicited maximum immune response to the expressed tumor antigen Prostate Specific Antigen (PSA), demonstrating the heterologous prime-boost concept using recombinant vaccinia and fowlpox virus based vaccines.

2.4.1 Recombinant Poxvirus-based Vaccines Including Fowlpox-based Vaccines

Fowlpox-based vaccines for the treatment of various cancers have been evaluated in human clinical trials sponsored by the NCI. Over 2,000 cancer subjects, most with metastatic disease, have been treated to date with these poxvirus-based vaccines (Kaufman et al., 2004). No significant safety issues were identified in these trials.

Supportive clinical data were generated in the clinical development program of PROSTVAC in oncologic indications. For details describing the overall experience and safety profile of PROSTVAC, including the complete regimen, consisting of a vaccinia-based prime vaccination and repeated fowlpox-based boost vaccinations, using the same fowlpox vector as being used for FPV-CV301, please refer to the CV301 IB.

2.5 Overview of the Predecessor Product PANVAC

2.5.1 PANVAC-Early “First-Generation” Vaccine

The Vaccinia virus became a first-line choice to develop a cancer immunotherapeutic approach due to its proven safety in different human trials, together with its robust potential to induce strong cell-mediated immune responses. Therefore, early attempts to generate effective oncologic

intervention strategies by NCI involved the PANVAC construct. It comprised a heterologous prime-boost vaccination regimen consisting of a replicating-competent Vaccinia-based delivery vector followed by a Fowlpox vector. Both vectors contained inserts corresponding to 3 genes encoding human immune costimulatory molecules (designated TRIad of COstimulatory Molecules, or TRICOM™) including B7.1, intercellular adhesion molecule-1 [ICAM-1] and leukocyte function-associated antigen-3 [LFA-3]. In addition, these vectors also expressed the carcinoembryonic antigen (CEA) and MUC-1 transgenes.

To date, PANVAC (consisting of PANVAC-V and PANVAC-F administered in a prime-boost regimen) has been administered to approximately 300 subjects in 7 clinical trials.

For details please see the CV301 Investigator's Brochure.

2.5.1.1 Safety Overview of PANVAC

During the initial stages of PANVAC's development program, preclinical studies revealed no dose-limiting toxicity. As well, no major findings concerning biologically significant observations, body weight, hematology, and clinical chemistry were reported. Mainly, the non-clinical treatment-related sequelae included mild, transient swelling and erythema at the subcutaneous injection site with dermal irritation, resolving within 2 to 4 weeks' post-injection. Such profile, together with the data obtained from non-clinical immunogenicity and efficacy studies, provided a solid ground to proceed with the clinical development program towards human studies.

More than 300 subjects have participated across 7 clinical trials, during which both, the vaccinia vector (PANVAC-V, inalimarev) and the fowlpox vector (PANVAC-F, falimarev) were investigated for the treatment of a variety of carcinomas including breast, ovarian, colorectal, pancreatic and bladder.

Overall, the data accumulated so far have shown a reliable safety profile, demonstrating that PANVAC has been well-tolerated in all trials. The most frequent treatment-related AEs were injection site reactions, myalgia, fatigue, vomiting, nausea, and abdominal pain. The majority of vaccine-related AEs were Grade 1 or 2 in severity. Importantly, serious adverse events (SAEs) related to trial treatment, discontinuations due to AE, and deaths related to trial vaccine were rare (one death due to Grade 5 pulmonary infiltrate was assessed as possibly related to trial drug).

Due to the fact that PANVAC constitutes an approach based on a replication-competent Vaccinia-based delivery vector, there are still some potential safety risks that have already been addressed during its development. Traditionally, similar constructs have been used as inoculation candidates against smallpox. Within this context, a series of cardiac AEs of inflammatory nature, such as myo/pericarditis with an incidence ranging from 1 in 175 to 1 in 216 vaccines has been reported (Zitzmann-Roth et al., 2015), (Elizaga et al., 2013),(Engler et al., 2015). As well, a recent prospective surveillance study concerning the use of replicating smallpox vaccines

revealed an increased risk for the development of cardiovascular symptoms such as chest pain (approx. 1 in 12 vaccines) and dyspnea (approx. 1 in 19 vaccines). The risk of myo/pericarditis associated with the replication-competent vaccinia virus has not been observed with MVA-BN or MVA-BN-based construct. Despite close cardiac monitoring throughout the clinical program, no confirmed event of a case of myo-/pericarditis has been observed and there is no evidence suggestive of any cardiac safety signal.

Besides the considerations regarding the viral backbone, it is also relevant to bring into discussion the reliability exhibited by its different components. As previously stated, the PANVAC technological platform expresses inserts for 5 different transgenes, 3 of which constitute human costimulatory molecules (TRICOM) critical for T cell activation that have already shown to enhance T cell responsiveness in mice (Levy et al., 2004). In fact, the therapeutic use of costimulatory molecules has both an acceptable safety profile and immunogenic potential in the clinical and preclinical settings, further contributing in the development of different immunotherapeutic approaches. For instance, dendritic cells-derived exosomes expressing this set of molecules have already been tested in Phase 1 and 2 clinical trials with advanced malignancies (Pitt et al., 2016). Similarly, the use of costimulatory molecules was shown to enhance the immunogenic potential of the allogeneic tumor cell line RCC-26, improving its use as a vaccine in a Phase 1 trial in renal carcinoma subjects (Buchner et al., 2010). Importantly, the results obtained in these trials employing such set of molecules exhibited an acceptable safety profile.

As well, aside from PANVAC, Bavarian Nordic also developed PROSTVAC, a prostate cancer-specific immunotherapeutic candidate using a transgene for the PSA together with the TRICOM strategy. The data accumulated so far across different clinical trials revealed no major safety concerns. Thus, PROSTVAC seems to be well tolerated, with injection site reactions, fatigue and fever being the most frequently reported AEs. In addition, other events reported by > 10% of subjects included nausea, diarrhea, constipation, arthralgia and dizziness. It is important to point out that no signals of inflammatory cardiac reactions have been observed in the more than 1000 subjects studied until now. In fact, the results obtained during a Phase 2 trial show that this immunotherapy had an acceptable safety profile, was well tolerated and associated with a 44% reduction in the death rate of the studied population, thus providing preliminary and stimulating evidence about the potential clinically meaningful benefits obtained after this therapeutic approach (Kantoff et al., 2010b). Such data support an acceptable safety profile compared with the placebo controlled arm that characterizes the TRICOM construct and strongly supports its use in targeted immunotherapies.

2.6 CV301 Next Generation Product Following PANVAC

Given the potential risks associated with the replicating capacity of the vaccinia-based PANVAC-V construct, the next generation cancer immunotherapeutic candidate, MVA-BN-CV301, was generated by Bavarian Nordic. It constitutes a recombinant non-replicating poxvirus-based immunotherapy derived from the MVA-BN construct. The new CV301 strategy

encodes the same 5 transgenes expressed by the previous PANVAC vector: CEA, MUC-1, B7.1, ICAM-1 and LFA-3. However, these inserts encode each of the transgenes with amino acid sequences that are slightly different from the original vectors. In fact, MUC-1 has been modified with additional agonistic epitopes. Consequently, the CV301 construct is expected to promote an antigen-specific targeted immune response for tumors expressing these antigens. In addition, a change in biosafety level also characterizes the new CV301 construct. Thus, whereas vaccinia possesses a BSL-2, MVA has been categorized as BSL1 in Europe. As well, similarly to the earlier PANVAC concept, CV301 also encompasses a heterologous prime-boost regimen employing MVA-BN-CV301 priming doses followed by Fowlpox-based FPV-CV301 boosting doses, thus replacing the former PANVAC-V and PANVAC-F components. Given the similarities between the CV301 and PANVAC vectors, the clinical development program designed for CV301 will rely on the extensive nonclinical and clinical data currently available from PANVAC.

In a first, still ongoing, BN-sponsored Phase 1 Trial of CV301 in Combination with Anti-PD-1 Therapy versus Anti-PD-1 Therapy alone in Subjects with Non-Small Cell Lung Cancer (CV301-2015-201), 12 subjects with various CEA/MUC-1 positive cancers were enrolled in the Phase 1a, 6 male and 6 female subjects, aged between 39 and 77 years. Of these 12 subjects, 3 received MVA-BN-CV301 at the lowest dose level, nominal 4 x 10^8 Inf.U, 3 received the second dose level, nominal 8 x 10^8 Inf.U, and 6 received the highest dose level, nominal 1.6 x 10^9 Inf.U.

Initial safety data from Phase 1 of this trial involving 12 subjects dosed in three different dose levels show that the most frequently occurring treatment-related AEs were temporary and self-limiting, Grade 1 or 2 in severity and included injection site reactions (injection site erythema, pruritus, pain, induration and swelling) and general symptoms including fever/chills, flu-like symptoms, headache, fatigue/weakness, nausea/vomiting, myalgia and arthralgia. There was no occurrence of any of the pre-specified adverse events of special interest (immune-related events and cardiac events). There were no related SAEs. There were no dose limiting toxicities at all three investigated dose levels, so no maximal tolerated dose was identified. Based on this initial safety information, the selected dose level for the further course of the trial was nominal 1.6 x 10^9Inf.U (i.e. 4 injections of 4 x 10^8 Inf.U in 0.5 mL) of MVA-BN-CV301.

2.7 Trial Population

The eligible population is based on the FDA approved indications of atezolizumab and the current standard of care; which includes: male and female subjects ≥18 years of age with locally advanced or metastatic UC, subjects will have mixed histologies that required having a dominant transitional cell pattern and locally advanced bladder cancer that is inoperable on the basis of involvement of the pelvic sidewall or adjacent viscera or bulky nodal metastasis. Metastatic subjects include Stage IV at first diagnosis and metastatic recurrences after locoregional treatments of earlier stages.

Bladder cancer subjects fit for first-line cisplatin are excluded because cisplatin-based combinations remain the standard treatment. The role of immunotherapy in this population is currently under clinical investigation but is not part of this clinical trial.

Two different cohorts of subjects with locally advanced or metastatic urothelial cancer are eligible for this trial: subjects with disease progression after first-line cisplatin-base chemotherapy, or candidates to second-line treatment. Five different antibodies targeting PD-1 or PD-L1 are currently approved in this indication and collectively have shown a better therapeutic index than the historical results achieved with chemotherapy agents. The second cohort is comprised of candidates to first line treatment but cisplatin-ineligible due to some of the following conditions: ECOG PS2, renal function impairment, hearing loss or peripheral neuropathy.

2.8 Risk/Benefit Assessment

2.8.1 Potential Risks

Considering that the novel MVA-BN-CV301 vector derives from the original MVA-BN construct and contains inserts already present in the PANVAC vector, its potential risks are based on the adverse reactions already reported for these two constructs. So far, within the MVA-BN clinical development program, more than 10,500 subjects have received at least one MVA-BN-based construct dose in completed and ongoing clinical trials, giving rise to a substantial database concerning the administration of MVA-based recombinant vaccines in different populations. These include healthy vaccinia-naïve, healthy vaccinia-experienced, HIV-infected subjects, subjects with atopic dermatitis and subjects with previous hematopoietic stem cell transplantation. In addition, the vaccinia-based PANVAC vector has been administered to approximately 450 subjects in different cancer indications. The main adverse reactions associated with both MVA-BN and PANVAC inoculation involve the development of local reactions at the injection site, e.g. erythema, pain, swelling, induration and short-lived flu-like systemic effects, ranging from mild to moderate intensity and resolving completely within the first seven days after vaccination. Additional risks potentially associated with MVA-BN-CV301 include fatigue, abdominal pain, nausea, and vomiting.

Despite the fact that the MVA-BN delivery vector constitutes a non-replicating, highly attenuated vaccinia viral strain, thorough cardiac monitoring protocols have been successfully implemented along the entire MVA-BN clinical development program. Similar safety measures were also carried out during clinical trials employing the replication-competent PANVAC and PROSTVAC-V constructs. No case of myocarditis, confirmed pericarditis, endocarditis or any other type of cardiac inflammatory disease (or related syndromes) has been reported to date for either of these products. However, several ischemic cardiac events and arrhythmias have been reported during PANVAC's clinical development program, particularly in pancreatic cancer subjects. In this regard, it has been shown that pancreatic cancer can induce severe nutritional and metabolic dysfunctions, thus facilitating different types of arrhythmias. Therefore, it seems

neither PANVAC nor MVA-BN-based therapies might induce any inflammatory cardiac events, as opposed to the early generation replicating smallpox vaccines like Dryvax® and ACAM2000®.

Furthermore, an additional series of potential risks associated with the current clinical trial protocol include those derived from blood and tissue sampling procedures. Blood draws may cause discomfort, bruising, light-headedness or fainting and rarely result in infection at the venipuncture site. Biopsy risk may include a small amount of bleeding, pain, swelling, bruising and possibly an infection. As well, similar to other vaccines, there is a risk of an allergic reaction or an anaphylactic event. Consequently, in order to offer appropriate treatment and supervision in case of a severe allergic reaction and/or dyspnea, 30 minutes' observation periods will be implemented by the trial site staff after each vaccination. Additionally, subjects with known severe allergies to eggs, egg products, or aminoglycoside antibiotics (for example ciprofloxacin, gentamicin or tobramycin) should be excluded from receiving MVA-BN-CV301.

The risks associated with atezolizumab are described in the package insert and may be expected during the use of atezolizumab in this clinical trial.

The risk derived from the combination of CV301 with the PD-1 inhibitors nivolumab and pembrolizumab is being studied in 'A Phase 1/2 Trial of CV301 in Combination with Anti-PD-1 Therapy Versus Anti-PD-1 Therapy Alone in Subjects with Non-Small Cell Lung Cancer' (CV301-2015-201, NCT02840994). No safety signal has emerged so far from this ongoing trial. Although the specific combination of CV301 with atezolizumab is being studied for the first time in this clinical trial, the drug classes to which these compounds belong has been previously combined and no safety concern is expected. As an example of a poxvirus-vectored therapeutic cancer vaccine combined with an immune checkpoint inhibitor we refer to the Phase 1 trial that studied PROSTVAC with ipilimumab (Madan et al., 2012).

2.8.2 Benefits

The expected benefit from CV301 used as a single agent is unknown. A randomized Phase 2 clinical trial comparing the use of the therapeutic cancer vaccine PANVAC in combination with docetaxel versus docetaxel alone showed a non-statistically significant trend in PFS in favor of the combination [7.9 months versus 3.9 months, HR=0.65, p=0.09] (Heery et al., 2015). Provenge® (Sipuleucel-T) is the first and only vaccine approved by the FDA and the clinical benefit observed in the pivotal clinical trial showed a unique pattern of OS prolongation without producing ORR nor PFS prolongation (Kantoff et al., 2010a). The recognition of this novel pattern of clinical benefit together with the observation of delayed responses triggered several initiatives to adopt new immunotherapy assessment criteria (Hoos et al., 2010). But results obtained with vaccines used as single agents may differ from results of vaccines used in combination.

The expected clinical benefit from PD-1/PD-L1 inhibitors has a different pattern. A relatively small fraction of subjects achieves durable ORR and this fact translates usually into prolonged

OS. PFS is often reported as negative, statistically nonsignificant and with no advantage observed in medians, but the tails of the Kaplan-Meier curves tend to separate with long-term follow up, which seems consistent with a durable benefit experienced by a relatively small fraction of subjects. The results reported from the pembrolizumab Phase 3 clinical trial in second-line UC (Bellmunt et al., 2017) fit well with this pattern repeatedly reported across various PD-1/PD-L1 inhibitors in multiple indications.

The expected clinical benefit pattern from the combination of CV301 with PD-1/PD-L1 inhibitors is uncertain at this moment. In this trial, ORR is selected as the key endpoint to capture the activity of the combination. Benefit is also expected in other endpoints, but OS and PFS are categorized as secondary endpoints. The safety information available on poxvirus-vectored vaccine justifies the expectation on CV301 contribution to therapeutic benefit without a substantial addition of toxicity.

3 Objectives

Refer to Trial Synopsis (Section 1.4).

4 Trial Design

4.1 Experimental Design

This is a Phase 2, single-arm, multi-institutional clinical trial designed to study the combination of CV301 with atezolizumab in the first-line treatment of UC not eligible for cisplatin-containing chemotherapy (Cohort 1) and in the second-line treatment of UC previously treated with standard first-line cisplatin-based chemotherapy (Cohort 2). The trial will be performed using an optimal two-stage design within each cohort (Simon, 1989). For the purpose of this trial, subjects are considered enrolled once they have received their first dose of trial product.

Stage 1, Cohort 1: Enroll 14 subjects. If objective response is not achieved in at least four subjects, the cohort will be stopped for futility. If objective response is achieved in at least four subjects, the cohort will proceed to Stage 2.

Stage 1, Cohort 2: Enroll 13 subjects. If objective response is not achieved in at least three subjects, the cohort will be stopped for futility. If objective response is achieved in at least three subjects, the cohort will proceed to Stage 2.

Stage 2, Cohort 1: Enroll an additional 19 subjects, such that a total of 33 subjects are available for the primary endpoint analysis.

Stage 2, Cohort 2: Enroll an additional 22 subjects, such that a total of 35 subjects are available for the primary endpoint analysis.

Further details of the two-stage design are in Section 9.

4.2 Description of Trial Procedure

This trial will be conducted according to the schedule found in Section 1.5 for ALL subjects. Visits should be scheduled within the intervals/visit windows given. Protocol waivers or exemptions are not allowed, apart from immediate safety concerns. Therefore, adherence to the design requirements including those specified in the Trial Procedure Schedule are essential and required for trial conduct.

4.2.1 Screening Phase

Patients identified as potential subjects in the trial will be provided with all the necessary information required to make an informed decision about their participation in the trial. At the conclusion of the informed consent process, subjects will be asked to provide written informed consent to participate in the trial by signing an ICF. This must be done before completing any protocol-specified procedures or evaluations (i.e., any procedures or evaluations not considered to be part of the subject's normal care). After signing the ICF, subjects will be evaluated for entry criteria during the Screening period within 28 days before administration of trial drug.

Subjects who fail the initial screening process may be re-screened up to 2 times. In the event of subject re-screening, the unique subject number assigned during the initial screening process should be used.

After written, informed consent, screening assessment will be performed. All screening assessments must be performed within 28 days prior to the first trial product. All screening labs should be performed within 14 days prior to the first trial product.

The following task will be performed at the Screening Visit:

- Demographics
- Medical History
- Physical Exam (PE) including vital signs*
  *Blood pressure and pulse rate should be obtained after the subject has been seated in an upright position for at least 5 minutes
- ECOG
- Electrocardiogram (ECG)
- CT Scans of the thorax, abdomen and pelvis^
  ^If there is a medical reason, subject may have MRI instead of CT scan upon approval from BN.
- Collection of concomitant medications
- Collection of adverse events after signing of informed consent
- Tumor biopsy**

**Subjects who do not have tissue specimens meeting eligibility requirements must undergo a biopsy sample collection during the screening period. Acceptable samples included core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsy samples for cutaneous, subcutaneous, or mucosal lesions).

- Blood samples for: (see Section 8.2.7)
  - Hematology
  - Chemistry
  - Thyroid function test
  - INR, PT, aPTT
  - HIV, HBsAg, HCV
  - Biomarker analysis
- Urine sample for routine urinalysis (see Section 8.2.7)
- Pregnancy test – either serum or urine test (for women of child-bearing potential)

Women and men of reproductive potential must consent to use of highly effective method of contraception at least 30 days prior to first dose of trial product and continue for 5 months after the last dose of atezolizumab (see Appendix 1, Section 17.1) and the method(s) used by each subject must be documented. This list does not apply to subjects with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle.

4.2.2 Active Trial Phase

After successfully passing the screening evaluations, the eligible subjects will enter the active trial phase starting with Visit 1-14.

4.2.2.1 Randomization

Not applicable. This is a single-arm, non-randomized clinical trial.

4.2.2.2 Visit Description

The following tasks will be performed at Visits 1-14.

- Targeted PE including vital signs*
  *Blood pressure and pulse rate should be obtained after the subject has been seated in an upright position for at least 5 minutes
- ECOG
- Pregnancy test – either serum or urine test (for women of child-bearing potential)
- Review of concomitant medications
- Recording of AEs
- Blood samples for: (see Section 8.2.7)

- Hematology
- Chemistry

In addition, at Visit 1:

- Thyroid function test
- First prime vaccination of MVA-BN-CV301** and atezolizumab infusion.

  ** The trial subject must be kept under close observation at the clinical trial site for at least 30 minutes following vaccinations

In addition, at Visits 2, 4, and Visits 6-14:

- Urine sample for routine urinalysis (see Section 8.2.7)

In addition, at Visit 3, 4, 5, or 6:

- Tumor biopsy#

  #Note: Biopsy is optional and can be performed at Visit 3, 4, 5, or 6.

In addition, at Visits 3, 5 and every 6 weeks through to Visit 14:

- Thyroid function test

In addition, at Visits 4 and Visits 7-14:

- CT scan of the thorax, abdomen and pelvis^

  ^If there is a medical reason, subject may have MRI instead of CT scan upon approval from BN.

In addition, at Visits 2, 4, 7 and 10:

- Blood sample for biomarker analysis

In addition, at Visit 2:

- Second prime vaccination of MVA-BN-CV301 and atezolizumab infusion.
  ** The trial subject must be kept under close observation at the clinical trial site for at least 30 minutes following vaccinations

In addition, at Visits 3-14:

- Boost vaccinations of FPV-CV301 and atezolizumab infusion
  ** The trial subject must be kept under close observation at the clinical trial site for at least 30 minutes following vaccinations

Atezolizumab dosing visits: Every 3 weeks after Visit 6 through Visit 14

- Blood samples for: (see Section 8.2.7)
  - Hematology
  - Chemistry
- Pregnancy test – either serum or urine test (for women of child-bearing potential)
- Review of prior/concomitant medications
- Recording of AEs
- Atezolizumab infusion

4.2.3 Long Term Follow-up Period

During the Long-Term follow-up (LTFU) period, subjects will be followed by phone contact at quarterly intervals for survival status assessment and potential autoimmune or immune-mediated clinical manifestations. The FU period may be extended up to 2 years.

4.2.4 Unscheduled Visits

Additional visits to the clinic may be necessary between scheduled visits based on a subject's health status and the investigator's clinical opinion. Unscheduled visits may be performed to repeat laboratory testing, ECG or physical exams due to a new development. Examinations performed at unscheduled visits will be documented in the source documents as well as in the respective Electronic Case Report Form (eCRF) sections for unscheduled visits.

4.2.5 Premature Discontinuation

4.2.5.1 Discontinuation from Treatment

Subjects may discontinue from treatment at any time. The decision to discontinue trial product may be made by the sponsor, investigator or the subject due to, but not limited to, the following:

- Subject's request to discontinue (withdrawal of consent to participate).
- Subject's unwillingness or inability to comply with trial requirements.
- Occurrence of an AE or SAE attributable to a particular agent may result in discontinuation of that agent. The other agent can be continued until other stopping criteria are met.
- Progressive disease (PD) according to RECIST 1.1 (Section 17.4). Note: The only exception to this reason for treatment discontinuation is when the investigator feels the RECIST PD may correspond to a pseudoprogression. In this case the investigator is allowed to continue the treatment and schedule a new tumor evaluation as per iRECIST guidance (Seymour et al., 2017). The clinical conditions suggesting pseudoprogression include symptoms improvement or stabilization, absence of ECOG PS deterioration and absence of unequivocal laboratory parameters or signs of

progression. A 3.6% of ORR have been reported with atezolizumab treatment beyond progression in a post hoc analysis of IMvigor210 Cohort 2 (Necchi et al., 2017).

- Clinical deterioration without radiographic progression.
- Initiation of any other anti-cancer treatment not allowed by the protocol.
- Any reason that, in the opinion of the investigator, precludes the subject from receiving further trial product.
- The trial is stopped or suspended on medical, scientific, or other grounds.

The following procedures must be followed for subjects who discontinue prematurely from trial product:

- If the subject is unable or unwilling to attend all planned visits, every attempt should be made to perform at least a final concluding safety visit, i.e., End of Treatment (EOT) Visit 14/Week 100 within 28 days of withdrawal.
  - If progression is observed on the CT scan scheduled per protocol or decided ahead of protocol-schedule for clinical reasons, CT scan does not have to be repeated.
- Subjects who are discontinued from treatment in the absence of disease progression (e.g., subjects removed for unacceptable toxicity or subject/investigator discretion) should undergo repeat imaging and tumor response assessments until disease progression is documented. Radiological assessment should be continually performed as per schedule. It is recommended that subsequent therapy not be instituted until disease progression is documented.

If the subject is unwilling or unable to come to the clinic for a final EOT assessment, all efforts by the investigator and/or site staff to contact the subject need to be fully documented in the Investigator Site File and the End of Treatment eCRF page, as instructed. Subjects that are withdrawn from treatment will enter the LTFU period.

4.2.5.2 Discontinuation from Long Term Follow-up

All subjects will be followed until death, via telephone contacts at 3 month intervals, to evaluate OS unless the trial is suspended or discontinued. The length of the LTFU is planned to be 2 years, unless all subjects achieve their OS endpoint prior to the end of the 2-year period. If a subject chooses to withdraw from trial survival follow-up, this request must be documented in the source documentation and signed by the investigator. If the subject withdraws from participation in long term telephone follow-up, the trial staff may use a public information source (such as county records) to obtain information about survival status only.

4.3 Trial Duration

- Screening – approximately 4 weeks

- Treatment Phase – approximately 100 weeks
- Long Term Follow-up – Until all subjects achieve the OS endpoint, or a maximum time of up to 2 years

The total duration of the trial for each subject is up to 4 years.

4.4 Safety Monitoring Team

The Safety Monitoring Team (SMT) is a board that oversees the safety of subjects participating in the trial. The members of the SMT consist of Trial Investigators, the medical monitor (BN), and the Director Pharmacovigilance (PV; BN). The primary responsibility of the SMT is to review and evaluate the accumulated trial data per the SMT Charter.

If an event occurs which fulfills the trial halting rules (see Section 4.6 for further details), the SMT will review the event in a timely manner and agree on a recommendation to halt, resume, or terminate the trial participation of the affected subject(s), and/or request advice from the DSMB on continuation, modification, or termination of the trial.

A separate charter describes in detail relevant operational procedures, communication pathways, roles, and responsibilities of the SMT in the trial.

4.5 Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) is an independent board of experts responsible for reviewing clinical trial data on an ongoing basis to ensure the safety of trial subjects and validity and integrity of the trial data. The members of the DSMB are independent, i.e., not involved as investigators on any BN trial and have no direct or indirect financial interests in BN. The primary responsibility of the DSMB is to review periodically and to evaluate the accumulated trial data for participant safety and for the validity and integrity of the data and to make recommendations to BN concerning the continuation, modification, or termination of the trial. The DSMB considers trial specific data, relevant background knowledge about the disease and trial population, and safety data from other trials studying CV301(monotherapy or in combination with immune checkpoint inhibitors) in the reviews.

A separate charter describes in detail relevant operational procedures, communication pathways, roles, and responsibilities of the DSMB in the trial.

4.6 Trial Halting Rules

4.6.1 Safety Halting Rules

A temporary halting or termination for the trial as a whole can be decided by the SMT and/or DSMB following the occurrence of:

- Unexpected (i.e., not listed in the current IB) Grade 3 or higher systemic reaction or lab toxicity (using NCI CTCAE version 5) with an at least reasonable possibility of a causal relationship to the administration of BN-CV301 vaccine (i.e., the relationship to vaccine cannot be ruled out).
- Any unexpected SAE with a consequence of death

Unexpected severity or higher than expected frequency of immune-mediated adverse events described in atezolizumab full prescription information insert and/or other scientifically relevant guidelines such as ASCO Practice Guideline on the management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy (Brahmer et al., 2018). These parameters are not all-inclusive. Other AEs could occur that would trigger a SMT review.

If an event fulfilling the trial halting criteria reaches the investigator's attention, the investigator has the responsibility to alert the PV Department immediately (within 24 hours) and provide a comprehensive documentation of the event.

4.6.2 Efficacy Halting Rules

Individual cohorts may be stopped for futility based on the planned two-stage trial design within each cohort. The two-stage design allows for an interim analysis of the primary efficacy endpoint, which allows the cohort to stop early if the required number of objective responses is not achieved within a cohort. Details of the efficacy endpoints and futility stopping rules are in Section 9.

5 Selection of Subjects

Each investigator will maintain a log of subjects screened for the trial. Included in the log must be documentation of the reason(s) a particular subject failed the screening process.

5.1 Recruitment Procedure

Subjects will be actively recruited. Recruitment strategies, including Institutional Review Board (IRB) approved advertisements, will be evaluated by the Sponsor.

Recruitment will be performed in two stages within each cohort. Once Stage 1 is fully enrolled in a cohort, an interim analysis of the primary efficacy endpoint will be performed to determine whether or not the cohort will continue on to Stage 2. Details of the enrollment of subjects for each stage and sample size are found in the Protocol Summary (Section 1.4).

Patients identified as potential subjects in the trial will be provided with all of the necessary information required to make an informed decision about their participation in the trial.

5.2 Inclusion Criteria

A subject will be eligible for inclusion in this trial only if ALL of the inclusion criteria apply. Refer to Trial Synopsis (Section 1.4).

5.3 Exclusion Criteria

A subject will not be eligible for inclusion in this trial if ANY of the exclusion criteria apply. Refer to Trial Synopsis (Section 1.4).

6 Investigational Medicinal Product

6.1 MVA-BN-CV301

MVA-BN-CV301 vaccine is a frozen suspension for injection, highly attenuated, live recombinant virus based on the viral vector MVA-BN. It is administered as SC application.

One MVA-BN-CV301 vial has a nominal virus titer of 4 x 10^8 Inf.U in 0.5 mL of the drug product.

For further details on MVA-BN-CV301 vaccine, see current version of the CV301 IB.

6.2 FPV-CV301

FPV-CV301 is a frozen suspension for injection, highly attenuated, live recombinant virus. It is administered as SC application.

One FPV-CV301 vial has a nominal virus titer of 1 x 10^9 Inf.U in 0.5 mL of the drug product.

For further details on FPV-CV301 vaccine, see current version of the CV301 IB.

6.3 Atezolizumab (Tecentriq ®)

Tecentriq ® (atezolizumab) is a commercially available fully humanized, engineered monoclonal antibody of IgG1 isotype against the protein PD-L1 approved for the treatment of locally advanced or metastatic urothelial carcinoma that has progressed after platinum-containing chemotherapy.

The recommended dose of atezolizumab is 1200 mg administered as an intravenous infusion over 60 mins every 3 weeks. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Do not administer as an intravenous push or bolus.

For more details, refer to the prescribing information at https://www.gene.com/download/pdf/tecentriq_prescribing.pdf .

A hard copy of the atezolizumab prescribing information will be provided to the site in the trial reference manual.

Also refer to the ASCO Practice Guideline on the management of immune-related adverse events in subjects treated with immune checkpoint inhibitor therapy (Brahmer et al., 2018).

6.4 Production, Packaging and Labeling

Both the MVA-BN-CV301 and FPV-CV301 bulk drug substances are produced at Bavarian Nordic A/S, Denmark.

The final drug product is filled, formulated and labeled at Bavarian Nordic A/S, Denmark.

The packages and vials of MVA-BN-CV301 and FPV-CV301 vaccines are labeled with US investigational new drug (IND) labels.

Atezolizumab is provided by Roche as "naked" vials, then shipped to the contracted US depot for packaging and labeling.

The packages and vials of atezolizumab are labeled with US required label text.

6.5 Shipment, Storage and Handling

Only subjects enrolled in the trial may receive trial product.

Supplies of trial product (MVA-BN-CV301, FPV-CV301, and atezolizumab) will be shipped temperature controlled and monitored, to the clinical trial site from a central US depot. Once arriving at the site, the package should immediately be handed over to personnel in charge of trial product preparation (e.g., the pharmacist). Site personnel are responsible for proper storage of the trial product. Upon receipt, all trial product must be stored in a secure environmentally controlled and monitored area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

Both the MVA-BN-CV301 and the FPV-CV301 vaccines must be shipped to the site and stored at a temperature of -20°C ± 5°C or -80°C ± 10°C avoiding direct light. A vial must not be re-frozen once it has been thawed.

Atezolizumab must be shipped to the site and stored at a temperature of 2°C - 8°C avoiding direct light.

Additional details on the shipment, storage, handling and temperature deviations of the MVA-BN-CV301, FPV-CV301 and atezolizumab can be found in a separate pharmacy manual supplied to each clinical trial site.

6.6 Preparation, Administration and Dosage

Detailed trial-specific instructions on the preparation and administration of MVA-BN-CV301 (prime vaccine), FPV-CV301 (boost vaccine) and atezolizumab are provided in a separate pharmacy manual supplied to each clinical trial site.

6.7 Accountability and Disposal

Used (if allowed by institutional policy) and unused vials of all trial product need to be retained in a place with limited access until appropriate drug accountability has been performed. Drug accountability must be documented whenever the trial product is either prepared or administered.

BN will provide a Drug Accountability Log for recording receipt, dispensation, and destruction of trial product (see Pharmacy Manual). Alternative systems used to track drug accountability are acceptable for use in the trial provided the aforementioned items are adequately captured and records are available for review during scheduled monitoring visits to the site.

After drug accountability has been performed, used and unused vials should either be returned to BN, to the designated drug depot, or discarded according to local regulations.

Destruction or return of trial product must be agreed upon with BN and appropriately documented. Documentation should be reviewed and signed off by the pharmacist and Clinical Research Associate (CRA) assigned to monitor the site.

Sites are responsible for the proper destruction and disposal of used needles and syringes and this should be done according to local regulations. If local disposal is not possible, used clinical supplies may be returned to the Sponsor or to the designated drug depot after prior consultation with BN.

7 Blood and Tissue Collection for Correlative Biomarker Studies for Exploratory Analyses

A total of up to 390 mL of whole blood, archived tumor tissue, and one or two tumor biopsies (optionally) will be collected from each subject during the course of the trial to assess the vaccine's immunogenicity and to allow the identification of predictive or pharmacodynamic biomarkers.

Biomarker testing will be performed at BN and/or selected CRO. Standard Operating Procedures (SOPs) effective at the time of testing will be followed.

The exact procedures for collection, preparation and storage of specimens for exploratory analyses will be described in a separate study-specific instruction provided to investigators and

clinical trial site personnel during trial start-up. Site personnel will receive technical training on all procedures during the investigator meeting and/or the site initiation visit.

7.1 Collection of Blood Samples

PBMC and serum (for biomarker analyses) will be collected from all enrolled subjects as described in the Trial Procedure Schedule (Section 1.5). Sample collection must occur prior to vaccine dosing.

7.2 Collection of Tumor Tissue

Archived or fresh tumor tissue will be collected as described in the trial procedure schedule.

Subjects must have, prior to trial product administration, unstained tissue slides (10 x 4µm and 1 x 20µm sections; or a tissue block from which those slides can be cut) from a prior biopsy or surgical resection for submission for research purposes. Archival tumor biopsies obtained from the invasive primary cancer or metastatic disease performed prior to first dose are acceptable.

If no archived tumor material meeting the specified criteria is available, a fresh biopsy at Screening is mandatory.

Tumor biopsies at Visit 3, 4, 5, or 6 are optional as described in the Trial Procedure Schedule (Section 1.5). A refusal of the biopsy at Visit 3-6 has no impact on the subject's trial participation and treatment. For responders, it is recommended to perform the biopsy at the time of optimal response but before CR is reached. For subjects with progression, it is recommended to perform the biopsy as soon as progression is confirmed and before starting the next treatment.

For biopsies, the subjects will consent at the time of the procedure. Subjects imaging and clinical status will be reviewed with interventional radiology. Only if the subject is determined to be at low risk for significant complications from biopsy by interventional radiology will the subject be given the option to proceed with biopsy. The subject will be informed that there is no individual benefit from the biopsy and no results will be communicated to the subject. If the subject refuses the biopsy at that time, the refusal will be documented in the medical record and in the research record.

7.3 Exploratory Analyses

Exploratory analyses will be performed as outlined in the trial synopsis (Section 1.4) and will comprise e.g. Immunogenicity testing of PBMC and tumor tissue (e.g. T cell receptor clonality, TILs or antigen specific immune responses to CEA and MUC-1 as well as to other TAAs).

Serum will be analyzed for soluble biomarkers (e.g. cytokines and classical tumor markers).

Tumor cells will be evaluated for gene or protein expression (e.g. PD-L1 or classical tumor markers).

Tumor DNA may be analyzed for mutational burden; DNA damage response gene mutations, MSI status, MMR deficiency status

7.4 Future Use of Lab Specimen

Specimens remaining after completion of all immunogenicity testing for the trial will be stored for future analysis supporting the licensure path of CV301. Subjects will be asked to consent to storage/future use of their samples and will be informed about data protection measures. Specimens will be stored in Bavarian Nordic's secured laboratory area or at an external storage facility in a coded, pseudonymized manner to ensure data protection.

8 Safety

For the purposes of this trial, "trial vaccine" is defined as CV301 and "trial medication" is defined as atezolizumab. "Trial product" refers to both, CV301 and atezolizumab collectively.

Safety will be monitored by performing physical examinations including vital signs, routine laboratory measurements, as well as by evaluating AEs.

Investigators are responsible for monitoring the safety of subjects who have entered this trial and for assuring appropriate medical care is provided. In addition, investigators are responsible for alerting BN or designee to any event that seems unusual, even if the event may be considered an unanticipated benefit to the subject, and for reporting the event on the appropriate AE eCRF or safety report form.

Investigators are responsible for providing subjects who experience AEs, especially SAEs that cause subjects to discontinue participation in the trial, with appropriate medical care. Frequency of FU of any particular AE is left to the discretion of the investigator. Duration of FU and requirement for immediate SAE reporting (within 24 hours of becoming aware of the event) are described in Section 8.2.5 and Section 8.3.1.

8.1 Definitions

8.1.1 Medical History

Diseases, treatments and surgical interventions present before and up to signing of ICF will be considered medical history. Medical history will be collected and documented in the Medical History eCRF at the screening visit. Special attention should be given to any history of prior allergic reactions, especially to vaccines.

8.1.2 Adverse Events

AEs are defined as any untoward (undesirable) occurrence of a medical event in a clinical trial subject temporally associated with the administration of an IMP or a medical product (MP) which does not necessarily have a causal relationship with this IMP/MP. The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE.

Collection of non-serious AEs begins at the time the subject signs informed consent and continues for 30 days following administration of the last dose of trial product.

Abnormal laboratory values assessed as being clinically significant by the investigator are to be documented as AEs. In addition, abnormal laboratory values fulfilling the Grade 3 or Grade 4 criterion according to the toxicity scale (Appendix 2; Section 17.2) are to be documented as AE in the CRF, regardless of whether they are considered clinically relevant or not. Toxicity grade and seriousness of an AE will be assessed separately, i.e., a Grade 3 or Grade 4 AE will not automatically be regarded as serious.

Clinically significant findings from the treatment period physical examinations will be recorded as AE.

8.1.3 Adverse Event of Special Interest (AESI)

Immune Mediated Adverse Events (IMAE) and Cardiac events are considered AESIs in the context of this trial.

Immune-Mediated Adverse Events of Special Interest

Autoimmune diseases and immune-mediated clinical syndromes, emerging since the initiation of trial product, will be reported as potential IMAEs.

So far, no signal has emerged from the diverse poxvirus constructs studied in the clinic, but the theoretical possibility exists that breaking the immune tolerance to self-antigens may induce autoimmune phenomena. This possibility deserves close vigilance.

The use of PD-1/L1 inhibitors in cancer treatment has expanded rapidly in the last few years. It is imperative that clinicians are knowledgeable about the toxicities associated with these agents, their recommended management and how best to monitor for them. In order to increase awareness, outline strategies and offer guidance on the recommended management of IMAEs in subjects treated with check-point inhibitors, ASCO in collaboration with the National Comprehensive Cancer Network (NCCN) developed clinical practice guidelines (Brahmer et al., 2018) which should be referenced in addition to the mandatory atezolizumab United States Prescribing Information (USPI).

Cardiac Adverse Events of Special Interest

A Cardiac AESI is defined in this trial as:

- Any cardiac sign or symptom (i.e., attributed by the investigator to be cardiac related), developed since the first vaccination
- ECG abnormalities determined to be clinically significant, developed since the first vaccination

AESIs should be reported to BN within 24 hours of the site's awareness. The collection period for AESIs begins once trial product is first initiated. An additional eCRF dedicated to potential IMAEs is linked to the (S)AE/AESI eCRF and must also be completed.

8.1.4 Serious Adverse Events

SAE is any untoward medical occurrence or reaction that at any dose:

- Results in death
- Is life-threatening
  The term "life-threatening" in the definition of "serious" refers to an event in which the subject 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.
- Requires in-subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- *or is an otherwise an important medical event

For purposes of this trial, an AE meeting the following criteria will also be considered Serious:

- Suspicion of transmission of an infectious agent via trial product
- Overdose of the trial product
- **Potential drug-induced liver injury (DILI)

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

- Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

**Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:

- Treatment-emergent ALT or AST > 3 × baseline value in combination with total bilirubin > 2 × ULN (of which ≥ 35% is direct bilirubin)
- Treatment-emergent ALT or AST > 3 × baseline value in combination with clinical jaundice

The following will NOT be considered SAEs:

- Hospitalizations < 24 hours, or for planned surgeries or procedures.
- Progression of underlying.
- Death due to progression of underlying malignancy
- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Elective surgery, planned prior to signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy).
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the trial. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g. lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

8.2 Assessment

8.2.1 Relevant Medical History

Relevant medical history, to include symptoms resulting from bladder cancer at the time of screening (not the bladder cancer diagnosis itself), will be collected and documented at the Screening Visit on the Medical History eCRF.

Date and stage of the first diagnosis of bladder cancer must be recorded in the Cancer History eCRF ONLY. Histology and supportive immunohistochemistry markers as well as relevant molecular markers, should be obtained when available and also documented on the Cancer History eCRF.

Detailed description of all bladder cancer treatments (including drug and non-drug therapies, surgeries, radiation therapies) with their corresponding start and stop dates should be recorded on the applicable eCRF (either the Prior Cancer Medication eCRF or the Non-Drug therapies eCRF), with special attention to first-line treatment for locally advanced or metastatic UC.

8.2.2 Prior and Concomitant Medication

All medication for concomitant diseases, except homeopathic substances and dietary supplements, must be recorded in the Prior and Concomitant Medications eCRF and the subject's medical record and should include information about the indication, dosage regimen, and onset and end of treatment.

The following medication, taken within 90 days of the screening visit, will also be recorded in the Prior and Concomitant Medications eCRF and the subject's medical record: vaccines, corticosteroids (via any route of administration), other immune-modulating drugs, immunoglobulin and/or any blood products, investigational drugs and depot preparations.

8.2.2.1 Permitted Medications

Any medications prescribed for concomitant disease or symptomatic relief of current disease are permitted with the exception of the ones listed in Section 8.2.2.2.

For clarification purposes, the following medications and therapies are also allowed:

Palliative radiotherapy for bone metastases or non-target soft tissue lesions completed > 7days prior to Screening imagining.

Hormone-replacement therapy or oral contraceptives.

Prophylactic antibiotics e.g., for prevention of urinary tract infection (UTI) or to prevent chronic obstructive pulmonary disease (COPD) exacerbation.

Influenza vaccination may be given during influenza season only (October – March) except live, attenuated vaccine (see Section 8.2.2.2)

Prior non-experimental cancer vaccines and cellular immunotherapy indicated for superficial UC (for example Bacillus Calmette-Guérin [BCG]) or postsurgical adjuvant treatment of operable infiltrating UC.

The use of inhaled, nasal, ophthalmic and topical corticosteroids, physiologic replacement doses of glucocorticoids (i.e., for adrenal insufficiency) and mineralocorticoids (e.g., fludrocortisone for adrenal insufficiency).

The use of acute, low-dose, systemic corticosteroid medications (e.g., a one-time dose of dexamethasone for nausea or for prevention of hypersensitivity reactions to contrast agents).

8.2.2.2 Prohibited Medications

The following medications are prohibited during the trial, as well as prior to Day 1 based on the relative type of medication. Additional medications may be deemed prohibited based on review during screening, if there is the risk to the subject or the ability to capture the trial outcome for the subject.

- Any approved or experimental anti-cancer therapy including chemotherapy within 3 weeks prior to Day 1, and throughout the trial.
- Treatment with any other investigational agent within 28 days prior to Day 1.
- Therapeutic oral or IV antibiotics within 1 week prior to Day 1.
- Live, attenuated vaccine including influenza vaccine (FluMist), within 4 weeks of Day 1 and throughout the trial.
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD-1 and anti-PD-L1 therapeutic antibodies and throughout the trial.
- Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, and anti-TNF agents) within 2 weeks prior to Day 1 and throughout the trial, or anticipated requirements for systemic immunosuppressive medications during the trial.

8.2.3 Physical Examination

Complete physical examination

A complete physical examination will be performed at Screening. The examination includes a review of major organ systems as well as height and weight. The examination should be directed at finding evidence of any infections, tumors and lymphadenopathy. In addition, auscultation of

the heart and lungs to check specifically for signs of any heart condition will be performed. Complete physical exams may be performed at visits other than those indicated based on investigator's discretion.

Any clinically significant findings at the baseline physical examination will be recorded as medical history events, and any new or worsening clinically significant findings post-treatment will be captured as adverse events. The only data captured in the eCRF for the physical examination itself will be the date it was performed.

Targeted physical examination

A targeted physical examination, guided by any signs or symptoms previously identified or any new symptoms that the subject has experienced since the last visit, is conducted at visits according to the Trial Procedure Schedule (Section 1.5) during the Treatment Phase. Clinically significant findings from the treatment period physical examinations will be recorded as AE.

8.2.4 Vital Signs

Vital signs will be measured at visits according to the Trial Procedure Schedule (Section 1.5). Blood pressure and pulse rate should be obtained after the subject has been seated in an upright position for at least 5 minutes. Vital signs may be assessed at times other than those listed, based on investigator discretion.

8.2.5 AEs

AEs (e.g., feeling of ill-health, subjective symptoms and objective signs, intercurrent diseases, accidents, etc.) observed by the investigator and/or reported by the subject, regardless of relationship to trial product, must be assessed and recorded in the AE eCRF. Only clinically significant findings from the treatment period physical examinations will be recorded as AE.

AEs will be collected and documented at all visits of the active trial phase (including atezolizumab dosing visits) and if ongoing after the active trial phase followed until resolution or until the remote FU visit at the latest.

SAEs and AESIs will be assessed and documented at all trial visits, including the remote FU Visit. Ongoing AESIs and SAEs will be followed up until resolution or achievement of stable clinical conditions.

8.2.5.1 Progression of Underlying Malignancy

For the purpose of this trial, progression of underlying malignancy is not considered an (S)AE. Hospitalization, prolonged hospitalization, or death due solely to the progression of underlying malignancy will be captured on the AE-section of the eCRF, but may NOT be reported as an

SAE. However, clinical symptoms of progression should be reported as (S)AEs if they cannot be determined to be exclusively due to the progression.

Symptomatic deterioration may occur in the absence of radiographic evidence of tumor progression in some subjects. Alternatively, the disease progression may be so evident that the investigator may elect not to perform further assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. In these cases, efforts should be made to quantitatively document the progression of the underlying malignancy to the extent possible.

8.2.6 Cardiac Assessment

A standard 12-lead ECG will be performed at Screening. ECGs will be evaluated by the investigator for clinical significance. Troponin I will only be measured if clinically indicated.

8.2.7 Safety Laboratory Measurements

Safety laboratory (hematology and serum chemistry) is determined at the Screening Visit and at Visits 1-14 while urinalysis is determined at the Screening Visit and Visits 2, 4, 6-14 for all subjects. Thyroid function test (TSH, free T3 and free T4) will be performed at Screening and every 6 weeks through to Visit 14. If clinically indicated, Safety laboratory tests can be performed at any other visit(s). The safety laboratory measurements are performed at the site specific local laboratory. Laboratory normal ranges are provided by the local laboratory and filed in the Regulatory File.

Safety laboratory parameters to be evaluated are in Table 4.

Table 4: Protocol Required Safety Laboratory Assessments

Hematology	Biochemistry	Urinalysis
Red blood cell (RBC) count Hemoglobin White blood cell (WBC) count; total and differential Platelet count Hematocrit Mean cell volume (MCV) Mean corpuscular hemoglobin (MCH) Red blood cell distribution width (RDW)	Total protein Albumin Alkaline phosphatase Total bilirubin AST ALT Lactate dehydrogenase (LDH) Creatinine Blood urea nitrogen (BUN) Uric acid Glucose Phosphorous Bicarbonate Chloride Sodium	Specific gravity Protein Glucose Blood Microscopic exam, if abnormal results are noted.

Hematology	Biochemistry	Urinalysis
	Potassium Calcium Amylase Lipase Thyroid Function Test Panel: • TSH • Free T3 • Free T4	

The intensity of laboratory/systemic quantitatively measured toxicities will be graded according to the NCI-CTCAE version 5 toxicity scale in Appendix 2, Section 17.2. In case of other laboratory values not included in the NCI-CTCAE scale the general grading scale below will be used.

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

The following parameters will only be evaluated during the Screening Visit for assessment of inclusion/exclusion criteria:

- INR
- PT
- aPTT
- HIV
- HBsAg
- HCV

8.2.8 Pregnancy

Women of childbearing potential (WOCBP) and partners of participating males must be using acceptable method of contraceptive measures as outline in Appendix 1, Section 17.1 for 30 days prior to the first vaccination on Day 1, throughout the entire trial and for 5 months after the last dose of atezolizumab. WOCBP subjects will have a pregnancy test (serum or urine) at every visit including atezolizumab infusion only visits which occurs every 3 weeks.

Any pregnancy (participating females and female partners of participating males) that occurs during trial participation must be reported using a clinical trial pregnancy form. To ensure subject

safety, each pregnancy must be reported to BN or designee within 24 hours of learning of its occurrence and should follow the procedures outlined in Section 8.3.3.

8.3 Reporting

8.3.1 Reporting of SAE

All SAEs (initial and FU information) will be reported electronically through the Electronic Data Capture (EDC) platform within 24 hours of the discovery of the event. Manual SAE report forms are available in the Trial Reference Manual, however manual SAE report forms should be forwarded only in the event that electronic capturing is not functioning and must be entered on the AE eCRF when it again becomes available. BN or designee may request FU and other additional information from the Investigator (e.g., hospital admission/discharge notes, laboratory results, etc.).

The investigator should not delay reporting because of missing information. Nonetheless, the report should be as complete as possible. This initial notification should include, at a minimum, sufficient information to permit identification of the following:

- The reporter (investigator's name and contact information)
- The subject
- Involved trial product
- AE(s)
- Seriousness criterion and/or criterion for AESI
- Date of onset
- Investigator assessment of causality

The collection of SAE/AESI begins at the time the subject signs informed consent and continues for 30 days following administration of the last dose of trial product for unrelated SAEs/AESIs, and 100 days for related SAEs/AESIs after the last dose of trial product, due to the possibility of a delayed immune effect of anti-PD-1/L1 agent (atezolizumab).

All SAEs, irrespective of the treatment received by the subject, must be reported to BN's PV department within 24 hours of the investigator learning of the event.

All deaths should be reported with the primary cause of death as the SAE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to BN's PV department as outlined above.

If trial product is discontinued because of an SAE, this information must be included in the SAE report.

Investigators must report SAEs to their governing IRBs in writing as soon as possible and in accordance with national and local laws and regulations.

8.3.2 Reporting of AESIs

As noted in Section 8.1.3, IMAEs and cardiac events are considered AESIs as well as the AESI requirements from the manufacturer of Tecentriq®. AESIs occurring throughout the reporting period are to be recorded on the AE eCRF by marking the appropriate tick box as well as the (S)AE/AESI eCRF, regardless of seriousness or attribution. AESIs have to be reported immediately after detection. An automatic email notification will be sent to the relevant project members as soon as an AESI has been reported in the EDC. In addition to the above mentioned eCRFs, an IMAE eCRF is also linked to the (S)AE / AESI eCRF in the EDC and must be completed by the investigator when reporting an IMAE AESI.

Appendix , Section 17.3 outlines the reporting process and timelines for AESIs.

8.3.3 Reporting of Pregnancies

Trial product exposed pregnancies cannot be excluded with certainty. Subjects who are discovered to be pregnant prior to the first vaccination will be excluded from the trial and regarded as screen failures. Subjects who are discovered to be pregnant during the active trial period must not receive additional doses of CV301 or atezolizumab, but may continue other trial procedures at the discretion of the investigator. All reports where the embryo or fetus may have been exposed to the trial product (either through maternal exposure or transmission of trial product via semen following paternal exposure) should be followed-up until delivery in order to collect information on the outcome of the pregnancy.

Subjects should be instructed to notify the investigator if it is determined – also after completion of the trial – that they became pregnant either during the trial or within 30 days after receiving the last dose of CV301 dose or 5 months after the last dose of atezolizumab.

If a subject becomes pregnant during the active trial period this must be reported to BN on a manual Pregnancy Notification Report Form (available in the Site Reference Manual) within 24 hours of the investigator's becoming aware of the event.

Female subjects or female partners of male subjects will be counseled as to any possible known risks to either the partner or the child. At the current time, no pregnancies have been reported for subjects treated with CV301 and therefore no data exist that would identify risks to partner or child. It is the responsibility of the investigator to counsel the subject on the identified risks of atezolizumab according to the USPI as well as disclose any known risks prior to the subject consenting to receive treatment with atezolizumab.

A pregnancy should be followed till outcome, and the health status of the mother and child including date of delivery and the child's gender and weight should be reported to BN as soon as

possible after delivery on a Pregnancy Outcome Report Form (available in the Site Reference Manual). The female partner should sign the Pregnant Partner Informed Consent Form for follow up.

Any event during pregnancy fulfilling the criteria for an SAE will be reported as SAE to BN PV department. However, hospitalization for delivery is a prospectively planned hospitalization and is not considered a SAE per se. Pregnancies resulting in an abnormal outcome (i.e., congenital abnormality, birth defect, or infant death) should be reported as SAEs within 24 hours of the investigator becoming aware of the event.

9 Statistical Considerations

This is a single-arm, multi-center, two-cohort Phase 2 clinical trial to assess the safety and preliminary efficacy of CV301 in combination with PD-1/L1 blockade in subjects with locally advanced or metastatic urothelial cancer including the bladder, ureter, or renal pelvis. The trial will be performed as a two-stage design (Simon, 1989) within the following two cohorts:

Cohort 1: Ineligible for cisplatin-containing chemotherapy

Cohort 2: Previously treated with standard first-line cisplatin-based chemotherapy, PD-1/L1 naïve

The goal is to demonstrate that CV301 plus atezolizumab can induce objective responses in subjects with locally advanced or metastatic urothelial cancer in at least one of the two cohorts.

Presentation of results will occur by cohort for efficacy and exploratory endpoints, and by cohort and overall for safety, disposition, demographic, and baseline characteristic endpoints. In general, continuous endpoints will be analyzed using mean, standard deviation, median, minimum, and maximums. Categorical endpoints will be analyzed using frequencies and percentages.

9.1 Endpoints

See Protocol Synopsis (Section 1.4).

9.2 Sample Size Calculation

Refer to Protocol Synopsis (Section 1.4).

9.3 Analysis Populations

For the purpose of statistical analysis, there will be 2 analysis populations: Full Analysis Set (FAS) and the Efficacy Evaluable Set (EE).

The FAS consists of all subjects taking any amount of trial vaccine, whether MVA-BN-CV301 or FPV-CV301. The FAS will be the primary population for all analyses.

The EE Set consists of all subjects from the FAS who received 2 prime doses of MVA-BN-CV301 (Weeks 1 and 4).

The EE population will be used in sensitivity analyses for efficacy.

Subjects who failed to meet the EE Set criteria will be replaced unless 4 or more responses in Cohort 1 (or 3 or more responses in Cohort 2) have been observed for the FAS population, or the number of responders will still be less than 4 in Cohort 1 (or 3 in Cohort 2) even if all replacement subjects would be responders. If there are more than 14 evaluable subjects in Cohort 1 (or 13 in Cohort 2) at the end of Stage 1 analysis, or more than 33 in Cohort 1 (or 35 in Cohort 2) evaluable subjects at the end of Stage 2 analysis, primary evaluation will be based on the first 14 (or 13) accrued or first 33 (or 35) accrued FAS subjects.

9.4 Subject Disposition

The number and percent of subjects who meet all protocol inclusion and exclusion eligibility criteria, who discontinue trial product, and reason for trial product discontinuation will be presented using the FAS. Subject participation by site will also be presented.

9.5 Subject Characteristics

Subject characteristics including demographics, disease characteristics, prior cancer therapies, and relevant medical history will be summarized for the purpose of describing the subject population using the FAS.

9.6 Prior/Concomitant Medications

All concomitant medications (including Long Term FU anti-cancer treatments) and prior medications will be coded to Anatomic-Therapeutic-Chemical (ATC) drug classes and preferred drug names using the WHO Drug Dictionary. The incidence of prior and concomitant medication usage will be summarized by ATC class and preferred drug names for the FAS.

9.7 Efficacy Analysis

9.7.1 Primary Efficacy Analysis

The ORR is defined as the proportion of subjects with an objective tumor response (CR or PR) based on RECIST 1.1 evaluations as performed by the investigator. Based on prior published results with atezolizumab, the null ORR for Cohort 1 is 0.23, and for Cohort 2 is 0.15.

Cohort 1: In the first stage, 14 subjects will be accrued. If there are 3 or fewer responses in these 14 subjects, the cohort will be stopped. Otherwise, 19 additional subjects will be accrued for a total of 33. The null hypothesis will be rejected if 13 or more responses are observed in 33 subjects. This design yields an actual type I error rate of 0.0244 and power of 0.7027 when the true ORR is 0.43 for the combination.

Cohort 2: In the first stage, 13 subjects will be accrued. If there are 2 or fewer responses in these 13 subjects, the cohort will be stopped. Otherwise, 22 additional subjects will be accrued for a total of 35. The null hypothesis will be rejected if 10 or more responses are observed in 35 subjects. This design yields an actual type I error rate of 0.0249 and power of 0.7092 when the true ORR is 0.33 for the combination.

In the case that the number of responses required to move to Stage 2, individually per cohort, is met in the FAS population, the study will move to Stage 2 without enrolling the full EE Set. If Stage 1 results are not clear after enrolling the prescribed number of Stage 1 subjects in the FAS, enrollment will continue until the EE Set meets the prescribed number of Stage 1 subjects for the interim futility analysis. In the event continuing enrollment of the EE Set would still not produce a positive outcome for Stage 1, the cohort will be discontinued without meeting the full Stage 1 sample size for the EE set.

For the final primary efficacy analysis, the number and percent of subjects with OR, and in each category of objective tumor response, will be summarized based on the FAS. The two-sided 90% exact binomial confidence interval for the ORR will be calculated using the Clopper-Pearson method.

Sensitivity analyses will be performed based on a repeated analysis using the EE Set, as well as any potential immune-related responses observed. In case these immune-related responses are observed, ORR analyses using iRECIST criteria will also be provided. For iRECIST, complete or partial responses are still able to be achieved after an initial unconfirmed progression, whereas with RECIST 1.1 once any evidence of progression is recorded, no further responses are able to be evaluated. For subjects who are not evaluated by iRECIST criteria, their tumor response based on RECIST 1.1 response guidelines will be used.

9.7.2 Secondary Efficacy Analyses

9.7.2.1 Progression-Free Survival

PFS is defined as the time interval from first treatment to objective tumor progression or death. Accordingly, the precise definition of progression and the timing of CT scans to document progression are very important. Every effort must be made to assure that timeframes for FU CT scans are achieved. Assessments must be adequate to evaluate target lesions, non-target lesions, and to search for new lesions.

The secondary endpoint of PFS will be based on the investigator's assessment using RECIST 1.1 response guidelines. PFS will be defined as the time from the day of first treatment with trial product to the start of disease progression or death (any cause), whichever occurs first. Subjects who do not have disease progression or have not died will be censored at the date when the last tumor assessment determines a lack of progression. If a subject begins a new anti-cancer therapy or has radiotherapy or surgery at a lesion site prior to documented progression (or death), the subject will be censored at the last assessment where the subject was documented as progression free prior to the intervention.

The Kaplan-Meier curve for PFS and the median PFS will be presented for the FAS Set.

Additionally, an investigator assessed PFS analysis that includes both investigator-judged PD according to RECIST 1.1 and symptomatic deterioration will be provided.

A binary endpoint for PFS will also be analyzed at milestone time points. The number and percentage of subjects who are progression free based on the above definition at 6, 9, 12, 18, and 24 months will be summarized within the FAS. The two-sided 90% exact binomial confidence interval for the PFS at each time point will be calculated using the Clopper-Pearson method.

A recently published meta-analysis concluded that in checkpoint inhibitor trials 6-month PFS rate is recommended as an endpoint because it is the best predictor of 12-month OS rate (Ritchie et al., 2018). In the absence of prospective validation, the decision adopted is to retain 6-month PFS rate as a secondary endpoint with the aim of complement the primary endpoint ORR in the interpretation of trial results as a whole.

In case some additional immune-related responders are observed, PFS analysis using iRECIST criteria will be performed. The iRECIST modification requires a confirmation of PD at least 4 weeks later with imaging; once confirmed, the date of progression is defined as the first date that the total tumor burden was shown to have increased by at least 20% compared with the nadir. For subjects who are not evaluated by iRECIST criteria, their disease progression based on RECIST 1.1 response guidelines will be used.

9.7.2.2 Overall Survival

OS is defined as the time interval from first treatment to death of any cause. Subjects who are alive will be censored at the last known date subject is alive. The 12-month OS rate and the product-limit estimate of median survival, as well as their 90% confidence intervals will be summarized. A Kaplan-Meier curve will summarize OS graphically. The 18-month and 24-month survival rates will also be provided along with their 90% CIs.

9.7.2.3 Duration of Response

Duration of response is defined as the time from response (CR or PR, whichever occurs first) to investigator assessed progression using RECIST 1.1 or death, and will be summarized based on

the number of subjects with response in the FAS. Subjects who do not have disease progression or have not died will be censored at the date when the last radiographic tumor assessment determines a lack of progression.

Duration of response will be summarized using the product-limit estimate of median survival along with its 90% confidence interval. The Kaplan-Meier curve will summarize duration of response graphically.

In case some additional immune-related responders are observed, duration of response analyses using iRECIST criteria will be provided. For subjects who are not evaluated by iRECIST criteria, their tumor response based on RECIST 1.1 response guidelines will be used.

9.7.3 Subgroup Analyses

Each cohort will be analyzed individually for the efficacy endpoints as the background response rates are known to be different in each group. In addition, small sample size prevents further subgroup analyses from being possible.

9.8 Exploratory Analyses

Analyses of exploratory endpoints will be based on the FAS, where both baseline and at least one post-baseline assessment are available. Missing data will not be imputed. Analyses will focus on comparing the post-baseline values with the baseline values. Correlation between tumor response and immune responses will be explored.

Continuous data will be summarized via mean (and 95% CI), standard deviation, median, minimum, and maximum by visit where samples are collected per trial schedule. In case of log-normal data, log transformations may be performed and summarized with the geometric means in place of the arithmetic means and 95% CIs.

9.9 Safety Analysis

Safety will be monitored by performing physical examinations including vital signs, routine laboratory measurements, as well as by evaluating AEs. AEs will be followed as described in Section 8 of this protocol.

Safety will be evaluated by the incidence of Treatment-Emergent Adverse Events (TEAEs) and SAEs, physical examination, laboratory abnormalities and percentage of subjects experiencing dose modifications, interruptions, and/or discontinuation, based on the FAS.

9.9.1 Adverse Events

Adverse events will be recorded on the case report forms by the Investigator using verbatim terms that best describe the event. A TEAE is an adverse event with an onset on or after initiation of

trial product, or an adverse event present at initiation of trial product that worsens (*i.e.*, increase in severity: On-Study Grade > Baseline Grade; or relationship to trial product is reported as a possible, probable, or definite). Verbatim descriptions of TEAEs will be mapped to Medical Dictionary for Regulatory Affairs (MedDRA) Version 20 or newer and graded according to NCI-CTCAE, Version 5. All TEAEs (to include SAEs and AESIs) occurring from the first dose through 30 days of last dose of trial product, if unrelated to trial product or non-serious, and all trial product related SAEs and AESIs through 100 days of last dose of trial product, will be summarized by system organ class, and preferred term and further by NCI-CTCAE grade. On subject-based AE tables, for each specific TEAE, a subject will be counted only once under the maximum severity experienced. Similar summaries will be provided for all Grade 3 or higher TEAEs, SAEs, and AEs that lead to discontinuation of trial product. All AEs will be included in the subject listings. Separate listings of subjects that discontinue trial product due to an AE, and listings of subjects with SAEs and deaths will also be presented.

9.9.2 Laboratory Data

Laboratory toxicities will be defined based on universal normal ranges and NCI-CTCAE, Version 5.0. The number and percentage of subjects will be summarized by grade using the most severe grade by cycle. Clinically significant changes in laboratory values will be summarized. Laboratory values will be listed, with Grade 3 or 4 values flagged.

9.9.3 Treatment Exposure

Treatment exposure to CV301 in combination with atezolizumab will be provided. Number of CV301 injections and atezolizumab infusions administered, duration of exposure, and number of subjects with dose interruptions will be summarized based on the FAS.

Missing Data

For duration of OS, PFS, or duration of response, subjects who are lost to FU will be analyzed as censored observations on the date of last known alive for OS, or last radiographic assessment for PFS and duration of response. Missing or partial dates will be imputed for prior/concomitant medications, adverse events, and cancer history. Details will be provided in the statistical analysis plan.

9.10 Multiplicity

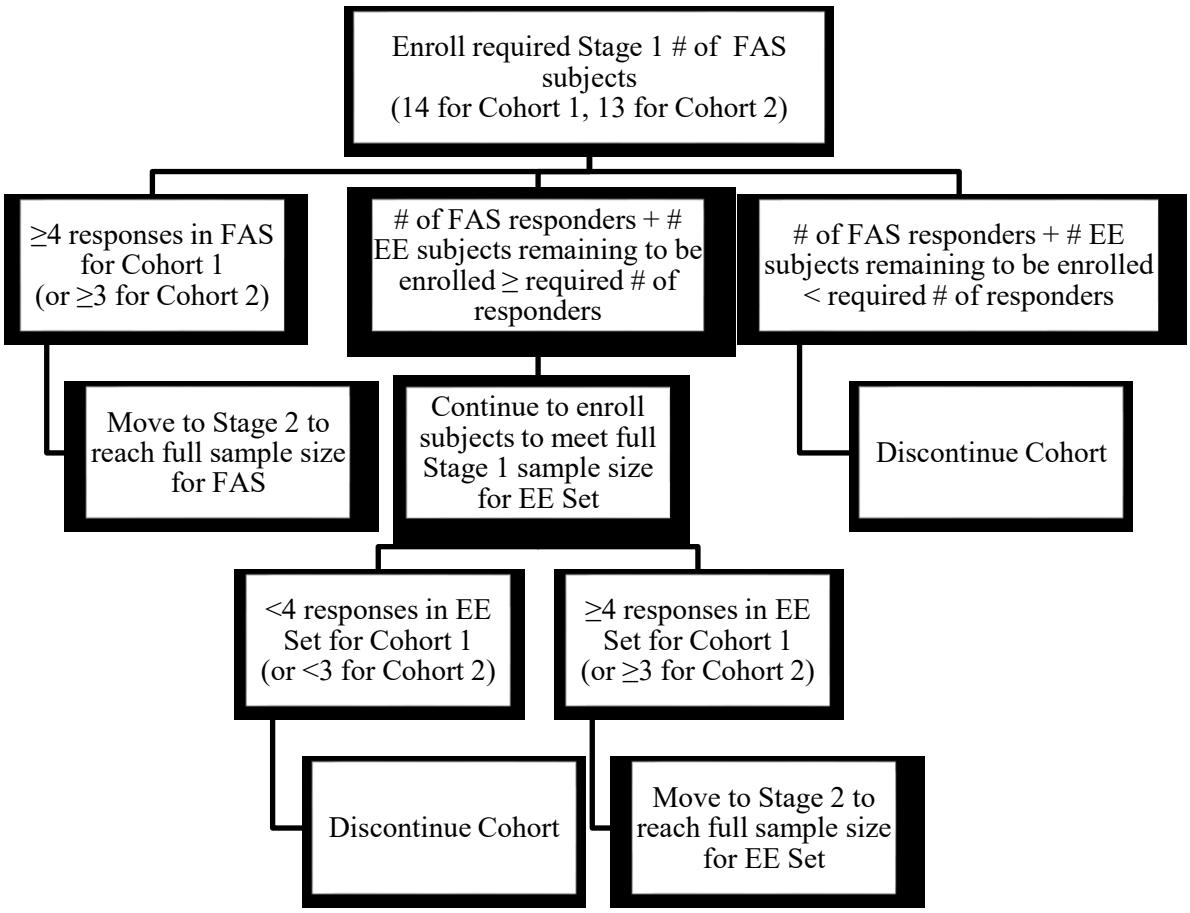
Due to the two-cohort, two-stage design of this Phase 2 trial, the primary endpoint of objective response rate will be tested multiple times. To account for this, the sample size for each cohort was based on a one-sided nominal alpha of 0.025 and 70% power. As each cohort represents an independent test, the overall trial-wide type I error rate would remain at or below 0.05 (one-sided). Based on simulations with the two-stage, two-cohort design, the overall type-1 error rate will be approximately 4.7%, and the power for the trial indicating at least one of the two cohorts will be positive given the alternative hypotheses are true, is approximately 91%.

9.11 Interim Analysis

Due to the two-stage design, an interim analysis with pre-specified stopping rules will be performed within each cohort. The ORR will be calculated after the first stage subject accrual is complete, separately for each cohort. Although the primary efficacy analysis will be performed on the FAS, if it is unclear within the first 14 FAS subjects in Cohort 1 (or 13 in Cohort 2) that the criteria are met for futility for Stage 1, enrollment will continue in the cohort until the full Stage 1 sample size is reached for the EE Set. If, even with enrolling additional subjects for the EE Set and those subjects all being responders, the cohort would not be able to reach the required number of responders to move to Stage 2, the cohort will be discontinued without reaching the full size of the EE Set.

The decision rules are as follows:

Figure 1: Interim Analysis Decision Tree



The decision to stop an individual cohort will be independent for each cohort.

9.12 Timing of Analyses

The first post-treatment objective radiographic response assessment by the investigator will occur approximately 10 weeks after first treatment, with the second occurring 12 weeks later at the Week 22 visit. For subjects who have completed multiple scans, the best objective response will be used.

If at least 4 objective responses in Cohort 1 (or 3 objective responses in Cohort 2) are observed in the FAS prior to the end of Stage 1, enrollment of Stage 2 subjects will continue regardless of the full enrollment of the EE Set. If the results of Stage 1 are unclear based on full enrollment of Stage 1 in the FAS, enrollment will continue until the full Stage 1 sample size is reached for the EE Set. If success is not possible in Stage 1, even with continuing enrollment until the full EE set was reached and all additional subjects were responders, the cohort will be discontinued without meeting full enrollment of the EE Set. In addition, the timing of the initiation of Stage 2 in a cohort need not depend on the completion of Stage 1 in the opposite cohort.

The end of Stage 2 analyses will again be based on best objective response outcomes. If the required number of responses are observed for a positive outcome in Stage 2 for the FAS, enrollment will be stopped and the trial will be declared a success. If it is unclear if the study is successful based on the FAS subjects, additional subjects will be enrolled until the full sample size for Stage 2 is reached in the EE Set. Because objective radiographic response rates may increase with further follow up, the data may be analyzed with updates if subsequent follow up demonstrates additional objective responses.

Final analyses will occur when all subjects have either completed the 2-year treatment period, or have progressed.

9.13 Changes in Statistical Methods

All changes in statistical methods from that described in the Statistical Analysis Plan will be documented in the Clinical Study Report.

10 Ethical Aspects

10.1 Ethical and Legal Regulations

This trial will be conducted in a manner consistent with the principles that have their origin in the Declaration of Helsinki and in accordance with FDA regulations (21 CFR § 11, 50, 54, 56, and 312), with the ICH GCP guidelines (ICH E6), as well as with any and all applicable federal, state and/or local laws and regulations.

10.2 Approved by IRB

Before enrollment of subjects into the clinical trial, as required by federal regulations (21 CFR § 56), ICH GCP and local regulations, the current protocol and ICF will be reviewed and approved by an appropriate IRB. A letter documenting the IRB or IEC approval must be received by the sponsor before the initiation of the trial at a clinical site. Amendments to the protocol will be subject to the same requirements as the original protocol.

The Investigator will submit a progress report at least once yearly to the IRB. However, the frequency of these reports will depend on IRB requirements. As soon as possible after completion or termination of the trial, the Investigator will submit a final report to the IRB per the IRB requirements, and in compliance with FDA regulations and ICH GCPs.

The Investigator, the sponsor, or designee shall promptly notify the IRB or IEC of any SAEs, or any other information that may affect the safe use of the trial drug during the course of the trial, per the IRB local requirements, and in compliance with FDA regulations and ICH GCPs.

Copies of all correspondence between the investigator and the IRB must be forwarded immediately to the Sponsor or designee. In case of withdrawal of IRB approval of the trial, the Sponsor or designee has to be contacted immediately by facsimile, e-mail or telephone.

10.3 Confidentiality and Data Protection

Information on maintaining subject confidentiality in accordance with individual local and national subject privacy regulations must be provided to each subject as part of the informed consent process either as part of the ICF or as a separate signed document (for example, in the US, a site-specific Health Insurance Portability and Accountability Act [HIPAA] consent may be used).

The Investigator or designee must explain to each subject that for the evaluation of trial results, the subject's protected health information (PHI) obtained during the trial may be shared with BN and its designees, regulatory agencies, and IRBs. As the trial Sponsor, BN will not use the subject's PHI or disclose it to a third party without applicable subject authorization. It is the Investigator's or designee's responsibility to obtain written permission to use PHI from each subject. If a subject withdraws permission to use PHI, it is the Investigator's responsibility to obtain the withdrawal request in writing from the subject and to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of trial results.

During the review of source documents by the monitors or auditors, the confidentiality of the subject will be respected with strict adherence to professional standards and regulations.

11 Informed Consent

The investigator is responsible for ensuring that the subject understands the potential risks and benefits of participating in the trial, including answering any questions the subject may have throughout the trial and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the trial.

No subject can participate in the trial without first having given informed consent in writing. The investigator or his delegate will inform the subject clearly and completely, verbally and in writing, about the purpose, procedures and the potential benefits and risks of participation in the trial prior to the initiation of any trial specific procedure. The subject will also be informed of the potential future use of biological samples collected during the trial.

The ICF will be used to explain to the subject in simple terms the potential risks and benefits of trial participation and to document that the subject is satisfied with his or her understanding of the risks and benefits of participating in the trial.

The investigator is responsible for ensuring that informed consent to participate in the trial is given by each subject (or their legal representative). This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of trial drug.

One signed copy of the ICF (including HIPAA) must be given to each subject and one signed copy must remain in the Investigator Site File and be available for verification by the monitor, Sponsor/CRO auditor or competent regulatory authorities at any time.

Subjects must be informed unequivocally that they may refuse participation in the trial and that they may withdraw from the trial at any time and for whatever reason and that withdrawal of consent will not affect their subsequent medical treatment or relationship with the treating physician.

Subjects also consent to authorize the monitor, quality assurance personnel and regulatory authorities to inspect source documents for data verification and quality assurance purposes. Such verifications will always be conducted at the clinical trial site and under the ethical supervision of the investigator. To the degree possible, confidentiality of the subject's PHI will be maintained.

The Informed Consent will be prepared in accordance with ICH GCP guidelines and must be approved by the appropriate IRB.

12 eCRF and Retention of Records

12.1 eCRF

eCRFs will be used to collect the clinical trial data and must be completed for each screened subject. All data must be accurately recorded such that the information matches the data contained in subject's medical records (e.g., physicians' notes, nurses' notes, clinic charts, and other trial-specific source documents). Authorized trial site personnel (i.e., listed on the Delegation of Authority form) will complete training based on the electronic data capture (EDC) system for the trial, as well as complete the trial-specific eCRFs according to the eCRF Completion Guidelines (provided as a separate document). The Investigator will ensure that the eCRFs are accurate and completed within 5 days of each subject's visit. At all times, the Investigator has final responsibility for the accuracy and authenticity of all clinical data.

The eCRFs exists within an EDC system with controlled access managed by BN or its authorized representative for this trial. Trial staff will be appropriately trained in the use of trial-specific eCRFs and application of electronic signatures before the start of the trial, and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trial per CRF. Note, only changes entered into the eCRF fields, themselves, can be used for reporting of trial results. Information entered into the change logs (for example, query responses) will be for documenting reasons for changes only.

The Investigator attests that the information contained in the eCRFs is true by providing electronic signature within the EDC system. After database lock, the Investigator will receive a copy of the subject data (e.g., paper, CD-ROM or other appropriate media) for archiving at the clinical trial site.

12.2 Retention of Records

The Investigator/trial staff must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. All essential documents, as listed in ICH GCP guidelines, will be retained by the Investigator for at least 2 years after the date the last marketing application is approved for the drug in the indication being investigated and until there are no pending or contemplated marketing applications; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after formal discontinuation of clinical development of the drug.

The Investigator must notify and obtain written approval from BN before destroying any clinical trial documents or images (e.g., scan, radiograph, ECG tracing) at any time. The Sponsor will inform the Investigator of the date that the trial records may be destroyed or returned to BN.

Should an Investigator wish to assign trial records to another party, advance written notice will be given to the Sponsor. BN must also be notified in advance and provide express written approval of any change in the maintenance of clinical trial documents, should the Investigator choose to move trial records to another location.

If the Investigator cannot guarantee the aforementioned archiving requirements at the clinical trial site for all such documents, special arrangements must be made between the Investigator and BN to store these documents in secure sealed containers away from the clinical trial site. These documents must be able to be returned in their secure sealed containers to the clinical trial site for auditing purposes.

13 Monitoring of the Trial

Representatives of BN or its designee (e.g., CRO) will monitor this trial until completion. Monitoring will be conducted according to the monitoring plan which must be approved by BN. The monitoring plan will specify in detail the items for source data verification and other tasks, to be performed by the CRA during the clinical trial site visit.

Monitoring will be conducted through personal visits with the Investigator and site staff, remote monitoring, as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the trial is conducted in compliance with the protocol, SOPs, and other written instructions and regulatory guidelines, and to ensure the quality and integrity of the data. This trial is also subject to reviews or audits.

To assure the accuracy of data collected in the eCRFs, it is mandatory that the monitor have access to all original source documents, including all electronic medical records (EMR) at reasonable times and upon reasonable notice. During the review of source documents, every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical trial.

14 Audits and Inspections

Site audits may be carried out at any time during or after completion of this trial by the Quality Assurance Department at Bavarian Nordic or designee. All trial-related documentation must be made available to the designated auditor. The Investigator agrees to allow the IRB, representatives of BN, its designated agents and authorized employees from local, state, or Regulatory Authority (e.g., FDA) to inspect the facilities used in this clinical trial at any time before, during, or after completion of the clinical trial and, for purposes of verification, allow direct access to the hospital or clinic records of all enrolled subjects. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information. In the event of such an inspection, BN will be available to assist in the preparation. All pertinent trial data should be made available as requested for verification, audit, or inspection purposes.

15 Responsibility of the Investigators

The Principal Investigator (PI) agrees to carry out the trial in accordance with the guidelines and procedures outlined in this clinical trial protocol. The PI especially consents to strictly adhere to the ethical principles mentioned in Section 10.1 of this protocol.

Changes to the protocol require a written Protocol Amendment to be submitted and approved by the local IRB, the Coordinating Investigator and the PI of the respective clinical trial site. Changes are allowed only if the trial value is not reduced and if they are ethically justifiable. The amendment must be passed on to all participating investigators with the obligation to adhere to its provisions. If warranted, the subject information has to be changed accordingly.

It is within the responsibility of the investigator that the CRF has to be completed in a timely manner after each subject visit and signed after the subject has finished the trial for each subject participating in the trial.

At the conclusion of the trial, the investigator will return all partly used, unused and empty vaccine containers to the Sponsor or the vaccine containers will be destroyed at the clinical trial site according to local legal requirements.

The investigator may ask to terminate the trial due to administrative or other reasons. If this should be the case, appropriate measures which safeguard the interests of the participating subjects must be taken after verification and consultation with the PI.

Each investigator will maintain appropriate medical and research records for this trial, in compliance with ICH GCP (E6), Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of subjects. He/she will permit authorized representatives of the Sponsor and regulatory agencies to review (and, when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the trial safety and progress.

The PI agrees to follow the detailed publication policy included in the clinical trial agreement.

By signing this protocol, the PI confirms that he/she has read the entire clinical trial protocol, agrees to its procedures, and will comply strictly with the formulated guidelines.

16 References

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17 Appendices

17.1 Appendix 1: Contraception Eligibility Criteria for Female and Male Subjects

A woman is considered of childbearing potential unless post-menopausal (defined as ≥12 months without a menstrual period) or surgically sterilized. A female subject is eligible to participate if she is not pregnant (as confirmed by a negative βhCG test), not lactating, and at least one of the following conditions applies:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in this trial may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug

Nonhormonal IUDs, such as ParaGard®

Tubal ligation

Vasectomy

Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

LESS EFFECTIVE METHODS OF CONTRACEPTION

Diaphragm with spermicide
Cervical cap with spermicide
Vaginal sponge
Male condoms with spermicide
Male Condom without spermicide
Progestin only pills by WOCBP subject or male subject's WOCBP partner
Female Condom**

** A male and female condom must not be used together

17.2 Appendix 2: NCI Common Terminology Criteria For Adverse Events (NCI CTCAE version 5).

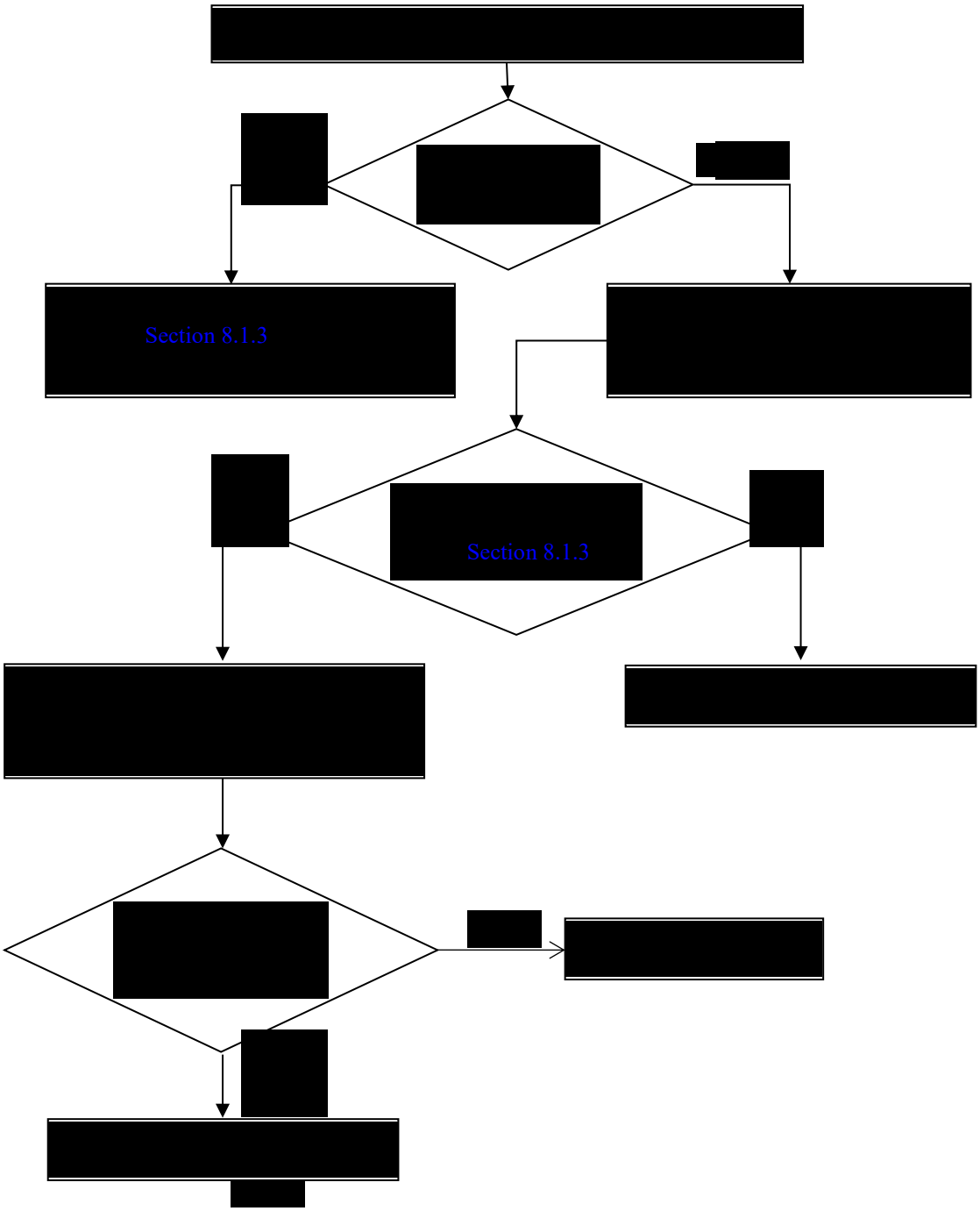
A copy of the CTCAE version 5 can be downloaded from the NCI website at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Should a subject experience any AE not listed in the CTCAE version 5, the following grading system should be used to assess severity:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

17.3 Appendix 3: Algorithm for Reporting of AESIs



17.4 Appendix 4: RECIST 1.1 Criteria

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence, taking as reference for progressive disease the smallest measurements recorded since treatment started. The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-target Lesions	New Lesions*	Overall Response	Best Overall Response when confirmation is required
CR	CR	No	CR	> 4 week confirmation**
CR	Non-CR/non-PD	No	PR	> 4 week confirmation**
CR	Not evaluated	No	PR	> 4 week confirmation**
PR	Non-CR/non-PD/not evaluated	No	PR	> 4 week confirmation**
SD	Non-CR/non-PD/not evaluated	No	SD	Documented at least once 4 weeks from baseline**
PD	Any	Yes or no	PD	No prior SD, PR, or CR
Any	PD***	Yes or no	PD	No prior SD, PR, or CR
Any	Any	Yes	PD	No prior SD, PR, or CR

*See RECIST 1.1 Manuscript for further details on what is evidence of new lesions.

**Only for non-randomized trials with response as primary endpoint

***In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Confirmation: To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed at least 4 weeks after the criteria for response are first met.

17.5 Appendix 5: Protocol Changes

Protocol Edition 2

Minor administrative and grammatical updates.

Throughout the protocol, changed IMP and trial treatment to trial product.

List of abbreviations was updated

Section 1.4, Synopsis, Number of Sites

Updated to **12**

Rationale

Increased for enrollment purposes.

Section 1.4, Synopsis, Exploratory Objectives, bullet #5

Added **Analysis of tumor DNA for** Tumor mutational burden; DNA damage response gene mutations, MSI status, MMR deficiency status; deleted ~~ctDNA~~

Rationale

Corrected to what may be analyzed.

Section 1.4, Synopsis, Secondary endpoints, Safety

Added description of safety measurements.

Rationale

To show what safety measurements will be evaluated.

Section 1.4, Synopsis, Inclusion for All Subjects, #1

Added: **The ICF must be signed prior to any protocol specific assessments.**

Rationale

Added for further clarification.

Section 1.4, Synopsis, Inclusion for All Subjects, #3

Added: Histologically or cytologically documented locally advanced (T4b, any N **M0**; or any T, N **1**−3 **M0**) or metastatic (M1, Stage IV; or metastatic recurrence after locoregional treatment) UC (including renal pelvis, ureters, urinary bladder, urethra).

Note about the change in the definition of Locally Advanced from TNM v7 to the current v8, while all those cases were Stage IV in v7, with TNM v8 they are reclassified as Stage IIIA (T1-4a N1 M0) and Stage IIIB (T1-4a N2-3 M0).

Rationale

Added for further clarification.

Section 1.4, Synopsis, Inclusion for All Subjects, #7

Added: **Must be on acceptable method for at least 30 days prior to 1st dose of trial product** and to continue its use for 5 months after the last dose of atezolizumab.

Rationale

Added for further clarification.

Section 1.4, Synopsis, Inclusion for All Subjects, #8

Reworded: Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (blocks preferred) or ~~10-15~~ **at least ten 4µm and one 20µ**m unstained slides, with an associated pathology report. This specimen will be reviewed by a central reader but results of review will not be required prior to registration and treatment of the subject.

Rationale

To ensure the correct number and types of slides are provided.

Section 1.4, Synopsis, Inclusion for All Subjects, #8a

Reworded: Tumor tissue has to be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable. For core needle biopsy specimens, ~~at least three cores~~ **a result of ten 4µm and one 20µm slides of evaluable quality** have to be submitted for evaluation.

Rationale

To ensure the correct number and types of slides are provided.

Section 1.4, Synopsis, Inclusion for All Subjects, #8c

Reworded: Patients who do not have tissue specimens meeting eligibility requirements must undergo a biopsy sample collection during the screening period. Acceptable samples include core needle biopsies for deep tumor tissue **(**~~minimum three cores~~ **resulting in ten 4µm and one 20µm slides of evaluable quality)** or excisional, incisional, punch, or forceps biopsy samples for cutaneous, subcutaneous, or mucosal lesions.

Rationale

To ensure the correct number and types of slides are provided.

Section 1.4, Synopsis, Inclusion for Cohort 1, #9

Added: Untreated with chemotherapy for **metastatic disease.**

Rationale

Added for further clarification.

Section 1.4, Synopsis, Inclusion for Cohort 2, #12

Changed ECOG value from ~~≤2~~ to **<2.**

Rationale

Corrected to guidelines.

Section 1.4, Synopsis, Exclusion Criteria for ALL subjects, #2 and Section 8.2.2.2 Prohibited Medications

Correction of number of days to **28** days prior to **Day 1 (first dose of trial product)** for treatment with any other investigational agent or participation in another clinical trial with therapeutic intent.

Rationale

More appropriate timing.

Section 1.4, Synopsis, Exclusion Criteria for ALL subjects, #3

Reworded: Active central nervous system (CNS) metastases defined as computed tomography (CT) or magnetic resonance imaging (MRI) ~~evaluation during screening~~ **evidence of progression** and prior radiographic assessments or Leptomeningeal disease.

Added: **Subjects that have had prior diagnosis need to have stable disease by having results or performing CT/MRI with 1 month prior to first dose of treatment.**

Rationale

To ensure exclusionary subjects are not enrolled in the trial.

Section 1.4, Synopsis, Exclusion Criteria for ALL subjects, #4c

Reworded: Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not currently associated

with spinal cord compression) could be considered for loco-regional therapy if appropriate prior to ~~enrollment~~ **first dose of trial product.**

Rationale

For clarity.

Section 1.4, Synopsis, Exclusion Criteria for ALL subjects, #6b

Reworded: Patients who are receiving denosumab prior to ~~enrollment~~ **first dose of trial product** have to be willing and eligible to receive a bisphosphonate instead while in the trial.

Rationale

For clarity.

Section 1.4, Synopsis, Exclusion Criteria for ALL subjects, #11 a and b

Clarified which subjects are allowed who have hypothyroidism and controlled Type I diabetes mellitus

Rationale

To ensure exclusionary subjects are not enrolled in the trial.

Section 1.4, Synopsis, Exclusion Criteria for ALL subjects, #14b

Reworded: Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV Ribonucleic Acid (RNA) prior to ~~enrollment~~ **first dose of trial product**.

Rationale

For clarity.

Section 1.5, Trial Procedure Schedule, Adverse Events

Added collection at Screening.

Rationale

AEs will be collected once subject signs the informed consent.

Section 1.5, Trial Procedure Schedule, Footnotes

Changed numbering due to additional footnotes added.

Section 1.5, Trial Procedure Schedule, Footnote #1

Added footnote: **ICF can be obtained prior to Screening visit**.

Rationale

To ensure ICF is signed prior to any protocol specific procedures are performed including having female subjects of child bearing potential go on adequate birth control.

Section 1.5, Trial Procedure Schedule, Footnote #4

Added that a **follow-up visit should be scheduled if clinically indicated** for follow-up on related SAEs/AESIs reported up to 100 days after last administration of trial product.

Rationale

To clarify that a follow-up visit should be scheduled if necessary, regarding the assessment of the SAE/AESI.

Section 1.5, Trial Procedure Schedule, Footnote #7

Added footnote: **If there is a medical reason, subject may have MRI instead of CT scan upon approval from BN.**

Rationale

To clarify that if there is a medical reason why a subject cannot have a CT scan, a MRI is acceptable upon approval from BN.

Section 1.5, Trial Procedure Schedule, Footnote #9

Added footnote: **Sample collection (peripheral blood for PBMC, serum) must occur prior to vaccine dosing. Sample collection for Biomarker analyses should be repeated if subject comes off trial due to PD or AE or if the subject has an objective response.**

Rationale

To clarify when Biomarker samples should be drawn.

Section 1.5, Trial Procedure Schedule, Footnote #10

Added footnote: **For WOCBP, a pregnancy test is required prior to every atezolizumab infusion. Urine or serum pregnancy test is acceptable at any given visit depending on investigator and/or subject preference**.

Rationale

To clarify that a pregnancy test is required prior to atezolizumab infusion at atezolizumab infusion only visits.

Section 1.5, Trial Procedure Schedule, Footnote #11

Added footnote: **The trial subject must be kept under close observation at the clinical trial site for at least 30 minutes following vaccinations.**

Rationale

To ensure subjects are monitored after vaccine injections for safety.

Section 1.5, Trial Procedure Schedule, Footnote #12

Added footnote: **EOT visit should take place within 28 days of withdrawal.**

Rationale

To clarify timing of EOT visit.

Section 2.3.2 Clinical Experience with MVA-BN and Recombinant MVA-based Vaccines

Updated safety information.

Rationale

Additional information obtained since original protocol was written.

Section 2.3.3 Safety Overview of MVA-BN and Recombinant MVA-based Vaccines, Serious Suspected Adverse Drug Reactions

Updated safety information.

Rationale

Additional information obtained since original protocol was written.

Section 4.1 Experimental Design

Addition of statement regarding when a subject is considered enrolled.

Rationale

Since enrolled is defined differently by each Sponsor and trials, this statement was added to clarified what is considered enrolled in this trial.

Section 4.1 Experimental Design and Section 9.13 Timing of Analysis

Correction of number of subjects needed in each cohort to continue enrollment of the trial to Stage 2.

Rationale

To match statistical considerations in the Synopsis and Section 9.7.1 Primary Efficacy Analysis. These sections were written incorrectly in the original protocol.

Section 4.1 Experimental Design and Section 9.13 Timing of Analysis

Update to analysis population used to determine success for Stage 1, as well as how determination of Stage 1 success will be determined.

Rationale

To be conservative, the goal is to include all treated subjects in the determination of success in Stage 1 of the trial. In the event that success or failure is unclear, the efficacy evaluable population will continue to be enrolled such that a complete determination of the success or failure of Stage 1 may be achieved. Timing wording updated to correspond to the possibility of stopping at enrollment of the FAS, or continuing the enrollment of the EE Set in the event additional subjects are needed to determine Stage 1 success.

Section 4.2.1 Screening Phase, Paragraph 3

Addition of when the 28 day screening should be performed within, within 28 days **prior to the first trial product**.

Rationale

To clarify timeframe when screening assessments need to be performed.

Section 4.2.1 Screening Phase, Paragraph 4, Bullet 6 and Section 4.2.2.2 Visit Description, Visits 4 and Visits 7-14

Added: CT Scans of the thorax, abdomen and pelvis

> **If there is a medical reason, subject may have MRI instead of CT scan upon approval from BN.**

Rationale

To clarify that if there is a medical reason why a subject cannot have a CT scan, a MRI is acceptable upon approval from BN.

Section 4.2.1 Screening Phase, Bullet List

Added bullet: **Collection of adverse events after signing of informed consent**

Rationale

To clarify AEs are being collected after subject signs informed consent.

Section 4.2.1 Screening Phase, Last Paragraph

Reworded: Women and men of reproductive potential must consent to use of highly effective method of contraception ~~for the duration of the trial~~ **at least 30 days prior to first dose of trial product and continue** for 5 months after the last dose of atezolizumab (see Appendix 1, Section 17.1) and the method(s) used by each subject must be documented. This list does not apply to subjects with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle.

Rationale

To clarify timeframe when method of contraception should start.

Section 4.2.2.2 Visit Description, Visit 1, Visit 2 and Visit 3-14

Addition of the following: **** The trial subject must be kept under close observation at the clinical trial site for at least 30 minutes following vaccination**

Rationale

To ensure subjects are monitored after vaccine injections for safety.

Section 4.2.5.1 Discontinuation from Treatment, Bullet #9

The addition of: If the subject is unable or unwilling to attend all planned visits, every attempt should be made to perform at least a final concluding safety visit, i.e., End of Treatment (EOT) Visit 14/Week 100 **within 28 days of withdrawal**.

> **If progression is observed on the CT scan scheduled per protocol or decided ahead of protocol-schedule for clinical reasons, CT scan does not have to be repeated**.

Rationale

To clarify when the EOT visit should occur and information on CT scans.

Section 4.2.5.1 Discontinuation from Treatment, Last Paragraph

Addition of documenting **the End of Treatment** to eCRF page where subject's unwillingness or unable to attend final visit needs to be documented.

Rationale

To specify which eCRF page to record the data.

Section 4.2.5.2 Discontinuation from Long Term Follow-up

Added the following sentence: **The length of the LTFU is planned to be 2 years, unless all subjects achieve their OS endpoint prior to the end of the 2-year period.**

Rationale

To define length of time for long term follow-up period.

Section 4.3 Trial Duration, Bullet 3

Added the following: Long Term Follow-up – **Until all subjects achieve the OS endpoint, or a maximum time** of up to 2 years.

Rationale

To define length of time for long term follow-up period.

Section 4.4 Safety Monitoring Team, Paragraph 1

Changed SMT members from ~~Principal Investigator, the Senior Investigator~~, the medical monitor (BN) and the Director Pharmacovigilance (PV:BN) to **consist of Trial Investigators**, the medical monitor (BN) and the Director Pharmacovigilance (PV:BN).

Rationale

To define SMT membership.

Section 4.5, Data and Safety Monitoring Board

Addition of this Section.

Rationale

The DSMB was added at the request of IRBs.

Renumbering of Sections 4.6 onwards due to the addition of new Section 4.5.

Section 4.6.1 Safety Halting Rules; 8.2.7 Safety Laboratory Measurements; 9.9.1 Adverse Events; 9.9.2 Laboratory Data and Appendix 2

Changed NCI CTCAE from version 4.03 or newer to version **5**

Rationale

Updated to most current version.

Section 6.1, MVA-BN-CV301 and 6.2, FPV-CV301

Removed the following sentence: ~~The specific dose will be determined upon release testing of the drug product.~~

Rationale

The specified dose is the nominal virus titer.

Section 6.4, Production, Packaging and Labeling

Added information regarding atezolizumab.

Rationale

Since atezolizumab is being provided by the Sponsor the information needs to be included in the protocol.

Section 6.5, Shipment, Storage and Handling

Removed the following sentence: ~~Usage of the investigational medicinal product (IMP) is only allowed upon final approval of all shipment relevant paperwork by BN or its authorized designee~~.

Rationale

Deleted based on BNs updated SOP.

Section 6.5, Shipment, Storage and Handling

Added information regarding atezolizumab.

Rationale

Since atezolizumab is being provided by the Sponsor the information needs to be included in the protocol.

Section 7.1, Collection of Blood Samples

Added the following sentence: **Sample collection must occur prior to vaccine dosing**.

Rationale

To clarify when Biomarker samples should be drawn.

Section 7.2 Collection of Tumor Tissue

Corrected the number of unstained tissue slides from 10 x 4µm and ~~2x~~ 20µm sections to 10 x 4µm and **1** x 20µm sections.

Rationale

Corrected to what is needed and match the Study Specific Instructions for clinical site tumor and biopsy samples.

Section 7.3 Exploratory Analyses

Added the following sentence: **Tumor DNA may be analyzed for mutational burden; DNA damage response gene mutations, MSI status, MMR deficiency status**

Rationale

To add additional analyses which might be performed.

Section 8 Safety

Added the following sentence: **For the purposes of this trial, "trial vaccine" is defined as CV301 and "trial medication" is defined as atezolizumab. "Trial product" refers to both, CV301 and atezolizumab collectively.**

Rationale

To define IMP for the purpose of the trial.

Section 8.1.2 Adverse Events

Added the following sentence: **Clinically significant findings from the treatment period physical examinations will be recorded as AE.**

Rationale

To explain what findings are reported in the eCRF.

Section 8.1.3 Adverse Events of Special Interest (AESI), Paragraph 1

Reworded: Autoimmune diseases and immune-mediated clinical syndromes, ~~occurring~~ emerging ~~after signing of informed consent~~ since the initiation of trial product, will be reported as potential IMAEs.

Rationale

To correct when AESIs will be collected.

Section 8.1.3 Adverse Events of Special Interest (AESI), Paragraph 4

~~Appropriate management of AEs associated with immune-oncology agents, such as PD-1/L1 blocking agents, may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs: Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin and Neurological. For details on guidelines for the management of immune related events please see the approved atezolizumab United States Prescribing Information (USPI) and other scientifically qualified guidelines (Haanen et al., 2017).~~

Reworded: The use of PD-1/L1 inhibitors in cancer treatment has expanded rapidly in the last few years. It is imperative that clinicians are knowledgeable about the toxicities associated with these agents, their recommended management and how best to monitor for them. In order to increase awareness, outline strategies and offer guidance on the recommended management of IMAEs in subjects treated with check-point inhibitors, ASCO in collaboration with the National Comprehensive Cancer Network (NCCN) developed clinical practice guidelines (Brahmer et al., 2018) which should be referenced in addition to the mandatory atezolizumab United States Prescribing Information (USPI).

Rationale

To update guidance on AESI reporting.

Section 8.1.3 Adverse Events of Special Interest (AESI)

Reworded paragraph 6: AESIs should be reported ~~on both the AE and SAE/AESI eCRF~~ to BN within 24 hours of the site's awareness. ~~The same timelines and reporting processes as for SAEs are applicable~~. The collection period for AESIs begins once trial product is first initiated. An additional eCRF dedicated to potential IMAEs is linked to the (S)AE/AESI eCRF and must also be completed.

Rationale

To update guidance on AESI reporting.

Section 8.1.4 Serious Adverse Events

Added this section and moved SAE information from Section 17.3 Appendix 3 to this section.

Rationale

To be in line with the rest of the safety section.

Section 8.2.2.2 Prohibited Medications

The following paragraph was added: **The following medications are prohibited during the trial, as well as prior to Day 1 based on the relative type of medication. Additional**

medications may be deemed prohibited based on review during screening, if there is the risk to the subject or the ability to capture the trial outcome for the subject.

Rationale

To provide clarification.

Section 8.2.3 Physical Examination, Complete physical examination

The following paragraph was added: **Any clinically significant findings at the baseline physical examination will be recorded as medical history events, and any clinically significant findings post-treatment will be captured as adverse events. The only data captured in the eCRF for the physical examination itself will be the date it was performed.**

Rationale

To explain what findings are reported in the eCRF.

Section 8.2.3 Physical Examination, Targeted physician examination

The following paragraph sentence was added: **Clinically significant findings from the treatment period physical examinations will be recorded as AE.**

Rationale

To explain what findings are reported in the eCRF.

Section 8.2.5 AEs, Paragraph 1

The following changes were made: ~~All~~ AEs (e.g., feeling of ill-health, subjective symptoms and objective signs, intercurrent diseases, accidents, etc.) observed by the investigator and/or reported by the subject, regardless of relationship to trial product, must be assessed and recorded in the AE eCRF. **Only clinically significant findings from the treatment period physical examinations will be recorded as AE.**

Rationale

To explain what findings are reported as AEs.

Section 8.2.7 Safety Laboratory Measurements and Appendix 2

Added the following table:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated.

Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Rationale

Additional grading scale to be used.

Section 8.3.1 Reporting of SAE

Corrected who SAE reports are to be provided to and where they are reported

Rationale

Align with BN SOPs.

Section 8.3.2 Reporting of AESIs

The addition of adding AESIs per manufacturer of Tecentriq®.

Rationale

The need to capture AESIs per manufacturer of Tecentriq®.

Section 8.3.3 Reporting of Pregnancies, Paragraph 1

Deletion of the following information: Trial product exposed pregnancies cannot be excluded with certainty. Subjects who are discovered to be pregnant prior to the first vaccination will be excluded from the trial and regarded as screen failures. Subjects who are discovered to be pregnant during the active trial period ~~(up to and including 30 days after receiving a dose of vaccine and 5 months after receiving a dose of atezolizumab)~~ must not receive additional doses of CV301 or atezolizumab, but may continue other trial procedures at the discretion of the investigator. All reports where the embryo or fetus may have been exposed to the trial product (either through maternal exposure or transmission of a investigational product via semen following paternal exposure) should be followed-up until delivery in order to collect information on the outcome of the pregnancy.

Rationale

Error in original protocol as this information is in regards to the reporting period for capturing pregnancies after completion of the trial which is stated in the next paragraph (Section 8.3.3 Reporting of Pregnancies, Paragraph 2)

Section 8.3.3 Reporting of Pregnancies, Paragraph 4

Added the following information: Female subjects or female partners of male subjects will be counseled as to any possible known risks to either the partner or the child. **At the current time, no pregnancies have been reported for subjects treated with CV301 and therefore no data exist that would identify risks to partner or child. It is the responsibility of the**

investigator to counsel the subject on the identified risks of atezolizumab according to the USPI as well as disclose any known risks prior to the subject consenting to receive treatment with atezolizumab.

Rationale

Explaining reporting procedures.

Section 8.3.3 Reporting of Pregnancies, Paragraph 5

Reworded: A pregnancy should be followed ~~to term~~ **till outcome**, ~~any premature terminations reported~~, and the health status of the mother and child including date of delivery and the child's gender and weight should be reported to BN as soon as possible after delivery **on a Pregnancy Outcome Report Form (available in the Site Reference Manual)**. The female partner should sign the Pregnant Partner Informed Consent Form for follow up.

Rationale

Explaining reporting procedures.

Section 9.3 Analysis Populations

This section has been changed to make the FAS the primary analysis population for all analyses, and the EE Set a sensitivity population for efficacy analyses. In addition, the requirements for the EE Set have been relaxed to require only both priming doses of MVA-BN-CV301.

Rationale

To be conservative, and to include all treated subjects for the final analysis, the FAS is now used as the primary population for all analyses, including efficacy. The EE population has been modified to be more inclusive such that a larger proportion of the population may be used for the sensitivity analyses, as well as determination of Stage 1 success.

Section 9.4 Subject Disposition; Section 9.5 Subject Characteristics; Section 9.6 Prior/Concomitant Medications

Addition of FAS population.

Rationale

To clarify which analysis population will be presented.

Section 9.7.1 Primary Efficacy Analysis, Paragraph 1

Addition of the following sentence: The ORR is defined as the proportion of subjects with an objective tumor response (CR or PR) based on RECIST 1.1 evaluations as performed by the

investigator. **Based on prior published results with atezolizumab, the null ORR for Cohort 1 is 0.23, and for Cohort 2 is 0.15.**

Rationale

At the request of site to include the null hypothesis in this section.

Section 9.7.1 Primary Efficacy Analysis

Analysis set for primary efficacy analysis changed to FAS, with EE Set now the population for sensitivity analyses. Clarification added as to how the FAS and EE Set will be used to determine success of Stage 1.

Rationale

The inclusion of all treated subjects allows for a more conservative and inclusive final analysis. The clarification of how to determine Stage 1 success allows the FAS population to be used as the primary analysis population, with allowing additional subjects to be recruited in the event Stage 1 success cannot be determined within the FAS set.

Section 9.7.2.1 Progression-Free Survival

Deletion of: Accordingly, the precise definition of progression and the timing of CT scans to document progression are very important. Every effort must be made to assure that timeframes for FU CT scans are achieved ~~so that both treatment groups can be usefully compared~~.

Rationale

There will be no comparison between treatment groups.

Section 9.7.2.1 Progression-Free Survival

Addition of recently published meta-analysis on checkpoint inhibitor 6-month PFS rate as an endpoint.

Rationale

It complements the primary endpoint ORR in the interpretation of the trial results.

Section 9.7.2.1 Progression-Free Survival, 9.7.2.3 Duration of Response and 9.8 Exploratory Analysis

Replacement EE Set with FAS

Rationale

FAS is the population that will be analyzed.

Section 9.9.1 Adverse Events

Removal of**:** Similar summaries will be provided for all Grade 3 or higher TEAEs, SAEs, and AEs that lead to ~~dose reduction or~~ discontinuation of trial product.

Rationale

Dose reduction is not allowed.

Section 9.10 Missing Data

Addition of the following information: For duration of OS, PFS, or duration of response, subjects who are lost to FU will be analyzed as censored observations on the date of last known alive **for OS or last radiographic assessment for PFS and duration of response. Missing or partial dates will be imputed for prior/concomitant medications, adverse events, and cancer history. Details will be provided in the statistical analysis plan.**

Rationale

To clarify how missing data will be handled.

Section 9.12 Interim Analysis

Updates to explain determination of Stage 1 success based on the update to FAS as the primary efficacy analysis population. Decision tree updated to match.

Rationale

The primary efficacy analysis population was updated to be the FAS to be more conservative and inclusive. As the determination of Stage 1 success may be unclear based on the FAS alone, additional enrollment of EE subjects has been explained in the event this will support the determination of Stage 1 success.

Section 12.1 eCRF, Paragraph 1

Addition of the following information: Authorized trial site personnel (i.e., listed on the Delegation of Authority form) will **complete training based on the electronic data capture (EDC) system for the trial, as well as** complete **the trial-specific** eCRFs according to the eCRF Completion Guidelines (provided as a separate document).

Rationale

Describes what training is needed for entering data into the eCRF.

Section 12.1 eCRF, Paragraph 2

Addition of the following information: The eCRFs exists within an EDC system with controlled access managed by BN or its authorized representative for this trial. Trial staff will

be appropriately trained in the use of trial-**specific** eCRFs and application of electronic signatures before the start of the trial, and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trial **per CRF. Note, only changes entered into the eCRF fields, themselves, can be used for reporting of trial results. Information entered into the change logs (for example, query responses) will be for documenting reasons for changes only.**

Rationale

Describes what data are used for reporting trial results.

Appendix 4, 5, and 6

These were renumbered to **3**, **4**, and **5.**

Rationale

Due to the deletion of Appendix 3.