A Phase I/II Trial Investigating LOAd703 in Combination with Atezolizumab in Malignant Melanoma

EudraCT: [redacted]
NCT04123470
IND: [redacted]

Sponsor Study ID: LOKON003

Version Nr: 6.1 2023-06-09

Sponsor: Lokon Pharma AB

[redacted] CEO, PhD

Changes to the protocol

Version 6.1 Dated 2023-06-09	Substantial changes • Definition for the End of study has been modified under section Definition and Terms and in the section 3.5 End of Study and section 13.4 Study Report • The expected duration of the study has been updated to reflect change of the End of Study definition (synopsis, 3.4 Duration of Study, 5.1 Treatment overview) • Contact details for the new Site Principal Investigator at Baylor College of Medicine has been updated. Administrative changes • In sections 2.5 and 9.4.5, an update of adverse events associated with atezolizumab was done to align with the latest IB atezolizumab • In section 5.7.5 Administration of Atezolizumab, a reference to section 7.2.6 Vital Signs has been added. • In section 7.5.1 Tumor size; PET assessment has been added. • Contact details in section 1 General information have been updated. • Minor editorial changes were made throughout the document to correct typographical errors and to improve consistency and clarity.
Version 6.0 Dated 2022-04-25	Substantial changes • Number of patients needed to be enrolled to achieve at least 25 evaluable patients at MTD has been changed to up to 50 throughout the document (synopsis, section 3.3 Summary of Trial Design) • The expected duration of the study has been updated (synopsis, section 3.5 End of Study, 5.0 Treatment of Patients). • An additional site has been added (section 1.0 General Information) • New exclusion criteria no. 32: Adenovirus-based vaccines (e.g Vaxzevria, known as COVID-19 vaccine Astra Zeneca, J&J Covid-19 vaccine) are prohibited 3 months prior to initiation of study treatment, during treatment and 6 months after the final dose of LOAd703 (synopsis, section 4.2, concomitant medication section 5.8). • In section 5.8 Approved and Non-approved concomitant treatment it has been added that palliative surgery and local radiotherapy will be allowed. • The time points for vital signs measurements have been updated in section 5.1 Treatment Overview and 7.2.6 Vital signs. • Addition for US only, as already approved for Sweden. In section 5.1 Treatment Overview and 6.2 Screening, 7.2.10 Blood Chemistry and 7.2.11 Hematology it has been clarified

	that "If samples are taken for routine analysis <7 days prior to screening, the results can be used for eligibility evaluation at the discretion of the Investigator, without need of subject the patients for new sampling". • Addition for Sweden only. In section [redacted] addition of "**Valid for Swedish patients:** patients enrolled at Uppsala site, Sweden will be asked to provide additional blood samples for research purposes [redacted] Blood samples will be collected at 2-3 occasions (up to 42 ml in total) during the LOAd703 treatment period [redacted] " have been made. <u>Administrative changes</u> • Unit for serum albumin levels was corrected from ≥ 2.5 mg/dL to ≥ 2.5 g/dL. • Contact details for Biobank in Sweden and Research Analysis Laboratory has been updated. • Information regarding previous studies in section 2.4 has been updated. • In exclusion criteria no. 18, the reference to other exclusion criteria has been corrected. • In section 4.4, criteria for off-treatment, survival follow-up and off-study patients has been clarified and corrected throughout the document. • Clarification has been made in section 5.3.1, that Investigator may also perform intra-tumoral injections of LOAd703 • Clarifications have been made in section 5.3.2 GMO Regulation at Trial Site. • Clarifications have been made in section 6.4, 7.2.7, 7.2.10, 7.2.11 and Appendix I, regarding Modified Follow-Up. In addition a schedule has been added as Appendix III. • Minor corrections in Appendix I. Schedule of events: [redacted] were marked, updated caption 5, adding caption 9 and updated numbering • Update to comply with the patient information and informed consent to allow request for [redacted] and to allow for samples to be analysed outside Sweden (section [redacted] and 7.5.2) • In section 9.2 Evaluating and Documenting Adverse Events (AE) the procedure of AE reporting has been clarified if patients complete the study or are prematurely discontinued from the study. • [redacted] • [redacted]

	• Virus units: 10e10 and 10e11 has been consequently changed to 10^{10} and 10^{11} respectively throughout the document. • The week number for final follow-up visit has been added consequently throughout the document. • Reference to atezolizumab where not relevant, has been removed throughout the document. • Minor editorial changes were made throughout the document to correct typographical errors and to improve consistency and clarity.
Changes made for Sweden only Version 5.1_SWE: Dated 2021-02-15	Substantial change, section 7.2.10: Blood Chemistry and 7.2.11: Hematology: • If samples are taken for routine analysis <7 days prior to screening, the results can be used for eligibility evaluation at the discretion of the investigator, without need of subject the patients for new sampling.
Changes made for Sweden only Version 5.0_SWE: Dated 2020-11-11	Substantial changes: Synopsis and section 4.1 Inclusion criteria: • **Valid for Swedish patients:** Patients not eligible for complete resection with locally advanced melanoma or metastatic melanoma can be included. **Valid for US patients:** Patients with locally advanced melanoma or metastatic melanoma can be included, regardless of patient's eligibility for complete tumor resection. • **Valid for Swedish patients:** Patients with B-Raf mutations must have received appropriate therapy with tyrosine kinase inhibitors(s) or MEK inhibitor (no changes from version 4.0) **Valid for US patients:** Prior treatment with tyrosine kinase inhibitor(s) is optional; patients that have not yet received treatment with tyrosine kinase inhibitor(s) can be included in the study
Version 5.0: Dated 2020-09-21	Substantial changes: Synopsis and section 4.1 Inclusion criteria: • A new criterion was added: A life expectancy of at least 3 months as per the investigator: this is a common inclusion criterion for this type of patients • Patients with locally advanced melanoma or metastatic melanoma can be included, regardless of patient's eligibility for complete tumor resection. • Prior treatment with tyrosine kinase inhibitor(s) is optional; patients that have not yet received treatment with tyrosine kinase inhibitor(s) can be included in the study • Cut-point for serum albumin levels was changed to ≥ 2.5 mg/dL as well as requirement for AST and ALT was changed to ≤ 5 times the ULN if liver metastases are present • Lactate dehydrogenase parameter was removed

	Synopsis and section 4.2 Exclusion criteria: • Exclusion criteria no 1 was modified so that patients with mucosal melanoma will no longer be excluded. • Exclusion of patients with progressive disease within 8 weeks after checkpoint inhibitor therapy and patients who have had more than 3 lines of treatment; were deemed to be to narrow and was replaced by a criterion excluding patients with rapid progression rate as assessed by the investigator • Exclusion criterion describing number and site of metastases was updated: patients with central nervous system involvement (cerebral metastases) will be excluded, but not patients with bone metastases • Washout period between cytotoxic and radiation therapy and protocol therapy (LOAd703/atezolizumab) was shortened to 14 days • Washout period between immunostimulatory therapy and protocol therapy (LOAd703/atezolizumab) was shortened to 21 days • Patients on warfarin continue to be excluded, but clarification was made that low molecular heparin is permitted Administrative changes: • Minor clarifications were done in the exclusion criteria no 6, 7, 8, 12, 14 and 17 (version 4.0). • Synopsis: Extension of study duration: study duration was updated as patient recruitment to LOKON003 study was delayed due to COVID19 pandemic. • Abbreviations: Correction of an abbreviation (DSUR) • Section 1.0: Change in address (e-mail address and name of the mail system at Research Laboratory) • Section 3.2: Correction of sample description in the secondary endpoints: update was made to comply with the rest of the protocol • Section 3.6: Section update with the study timelines: update was made to comply with the synopsis • Section 4.4: Clarification on the description of the Patient Withdrawal: update with relevant hyperlinks to protocol sections and clarification that patient continues with study schedule if withdrawal relates only to one study treatment. • Section 4.4.1: Clarification on the Off-treatment patient section: update that description refers to both study treatment • Section 4.5: Clarification on the description of the Patient Replacement: description refers to safety evaluation for phase I and DLT period, replacement of patients to meet efficacy evaluation is not required • Section 5.1 and 5.2: Repaired hyperlinks referring to Appendix I • Section 5.6.5: Clarification on start time point: LOAd703 is ready to us [redacted] • Section 7.2.10: Clarification on different types of blood clotting test performed at screening as part of the blood chemistry • Section 7.4.1: Clarification on sampling schedule: sampling refers to patients staying overnight • Section 9.2 and 9.2.1: Updated hyperlinks that referred to the NCI CTCAE Version 5.0.

	• Section 12.0: Update in numbering: section Protocol Modifications was moved under section Ethics therefore, numbering of this section was updated • Section 13.3: Clarification on timelines for Record Keeping • Section 13.4: Update on timelines for Study Report submission: to comply with the EU regulations • Section 14.1 Appendix I: Schedule of Events: correction of the footnote numbers in the Table
Version 4.0: Dated 2020-04-20	Substantial changes: • Exclusion criteria 1 was modified so that patients with acral melanoma will not longer be excluded. Administrative change: • A clarification was made in section 2.6.1 [redacted]
Version 3.0: Dated 2020-03-26 *IND and EU*	Substantial changes: • Exclusion criteria 15 was clarified to relate to monotherapy with a single PD-1/PD-L1 antibody. Administrative changes: • Section 1.4: The dept of Oncology in Uppsala has a new address. • Section 5.6.3: [redacted] • Section 5.6.5: the preparation instructions for LOAd703 has been clarified. [redacted] • Section 5.6.6 was clarified in regards to selection of lesion and that subcutaneous lesions, visible to the eye, may be photographed. • Table I: Overview of ongoing clinical trials was updated. • Section 9.4 Immunological AEs and Handling Plan has been updated to refer to the atezolizumab IB. • Table 3 was removed, which affect the numbering of the 2 subsequent tables.
Version 2.0: dated 2020-01-09 (IND) dated 2019-12-02 (EU) *Note: EU version 2.1, dated 2020-01-09, was issued to include administrative changes added to the submitted IND version 2.0 (commented in the list).* *The content in IND version 2.0 is thus identical to the content in EU version 2.1.*	<u>Substantial changes:</u> Secondary objectives and endpoints (sections synopsis, 3.1, 3.2) • The languish is changed to better define what is being evaluated using the objective and endpoints stated. Exclusion criteria (sections synopsis, 4.2: • Criteria 6-12: it is clarified that registration is regarded when the first dose of LOAd703 and atezolizumab is given. • Criteria 18: it is clarified that the contraceptive method must be regarded highly effective, and that abstinence from heterosexual intercourse is a choice of contraceptive method as well depending on the lifestyle of the subject. • Criteria 19: it is clarified that men that has a partner of childbearing potential who refuse highly effective contraceptives are excluded. • Criteria 24: it is added that patients with tested reduced functional respiratory capacity are excluded. Dose limiting toxicity • We added information about the DLT evaluation during dose escalation.

	• 5.6.1, 5.6.5: [redacted]. • 5.6.3, 5.6.5: we changed that [redacted] <u>Administrative change:</u> • Treatment description (synopsis) is clarified with number of study weeks on atezolizumab. • Study duration (synopsis): Total study months are clarified and maximum treatments weeks for each patients considering also the survival follow-up. • Definition of terms are updated for end of study and withdrawal. • General information (section 1.2): the Sponsor has changed address. • Section 1.4: the site in North Carolina was replaced by a site in Los Angeles. *(in IND version 2.0 and in EU version 2.1)* • Section 2.2.2, 2.3.2, 2.4, 2.5: when referred to an IB, the specific section is stated. • Section 2.6.1: we have expanded the risk assessment with information of risks based on [redacted] • Section 2.6.3: we have expanded the risk assessment [redacted] • Section 2.6.4, 2.7: we have expanded the potential benefits and the rationale of combining the two agents used in the study and the rationale for the doses. • Section 3.4, 3.5: we have clarified the total study duration and maximum weeks of participation for each patient considering also the survival follow-up. • Section 4.3: it has been clarified how the investigators and CRO communicates to recruit patients and when slots are available for patient registration in the trial. • Section 4.4.1, 4.4.2, 4.4.3, 9.3.1: off-treatment and off-study patients have been clarified and off-visit patient removed to avoid confusion. • Section 5.1: the survival follow-up has been clarified, and the information that CRO is distributing treatment slots to sites is added. • Section 5.2: study week participation to reflect survival follow-up has been clarified. • Section 5.6.10, 5.7.8: we clarified that study drugs are not available for patients post study. • Section 7.2.12: information of contraceptive methods were added • Section 7.5.3: survival follow-up has been clarified. • Section 9.0, 9.2: it was clarified that both LOAd703 and atezolizumab are considered experimental drugs and that we will record AEs for both. • 9.6: it was clarified that a female partner of child bearing potential to a male trial subject needs to be informed about the study and to inform the investigator if a pregnancy should occur.

	• Table 4 was expanded to include more patients (e.g. columns 21, 24 and 25) and a foot note was added to clarify that if the DLT level reach the elimination limit, this dose level is abandoned from the study independently of DLT events at lower dose levels (Section 10.2.1). *(in IND version 2.0 and in EU version 2.1)* • In section 10.2.1 the DLT period has been adjusted t [redacted] *(in IND version 2.0 and in EU version 2.1)* • Section 11.3: it was clarified that the Sponsor is responsible that the trial is adequately monitored. • Section 14.1: health status was removed from the table since its part of the medical history.

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INVESTIGATOR'S STATEMENT

1. I have carefully read this protocol entitled "A Phase I/II Trial Investigating LOAd703 in Combination with Atezolizumab in Malignant Melanoma" and agree that it contains all the necessary information required to conduct the study. I agree to conduct this study as outlined in the protocol.

2. I understand that this study will not be initiated without approval of the appropriate Institutional Review Committee/Independent Ethics Committee (IRB/IEC), and that all administrative requirements of the governing body of the Institution will be complied with fully.

3. Informed written consent will be obtained from all participating patients in accordance with institutional guidelines, FDA requirements as specified in Title 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidance's, European Union GAP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Section 4.8, and the terms of the Declaration of Helsinki (2013) depending on the country of patient enrollment.

4. I will enroll patients who meet the protocol criteria for entry.

5. I understand that my signature on each completed Case Report Form indicates that I have carefully reviewed each page and accept full responsibility for the contents thereof.

6. I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from the Sponsor unless this requirement is superseded by the Food and Drug Administration, a Competent Authority of the European Union or another Regulatory Authority.

Investigator:

Name: [redacted] Telephone: [redacted]

Institution: [redacted]

Signature: [redacted] Date: [redacted]

SYNOPSIS

Title: A Phase I/II Trial Investigating LOAd703 in Combination with Atezolizumab in Malignant Melanoma

Investigational Product: LOAd703 (delolimogene mupadenorepvec) is an oncolytic adenovirus serotype 5/35 expressing human trimerized CD40L and full-length 4-1BBL under a CMV promoter. Atezolizumab is a humanized IgG1 monoclonal antibody that binds to PD-L1.

Study Design: Single arm, open-label, multicenter trial.

Patients will receive up to 12 LOAd703 intratumoral treatments in combination with intravenous infusions of atezolizumab. LOAd703 will be tested at two dose levels to determine the maximum tolerated dose (MTD) of LOAd703 evaluated in the study using a BOIN design. [redacted]. Atezolizumab will be tested at a fixed dose.

At least 25 response evaluable patients will be enrolled at the MTD for evaluation of their response [redacted]. The total number of patients to be enrolled in the study to achieve at least 25 evaluable patients at MTD, should not exceed 50.

Objectives: The primary objective is to determine the tolerability of LOAd703 administered by intratumoral injection(s) in combination with intravenous atezolizumab.

The secondary objectives are to determine the antitumor activity as well as the pharmacokinetics and biological mechanisms-of-action of LOAd703 in combination with atezolizumab.

Endpoints:

Primary Endpoints

1. The primary endpoint is safety, determined by the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE v5.0).

Secondary Endpoints:

1. Overall response rate evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST), v1.1.
2. Shedding determined as levels of LOAd703 [redacted]
3. LOAd703 leakage to blood [redacted]
4. Anti-adenovirus immunity [redacted]
5. [redacted]

6. [redacted]
7. Immune profile as [redacted]
8. [redacted]

Eligibility:

Inclusion Criteria

1. Pathological confirmation of melanoma.
2. A life expectancy of at least 3 months as per the investigator
3. **Valid for Swedish patients:** Patients has locally advanced melanoma or metastatic melanoma, but not eligible for complete resection of melanoma
   Valid for US patients: Patients has locally advanced melanoma or metastatic melanoma.
4. The patient has measurable disease (e.g., measurable tumor lesions must be present that can accurately be measured in at least one dimension with a minimum size of 10 mm by CT scan and MRI, 10 mm caliper measurement by clinical exam (when superficial), and/or 20 mm by chest X-ray).
5. Patient has at least one injectable tumor lesion that has not been irradiated or has been irradiated but disease progression documented at the site subsequent to radiation therapy.
6. The patient has received appropriate treatment with an anti-PD-1 or anti-PD-L1 antibody with or without an anti-CTLA4.
7. **Valid for Swedish patients:** Patients whose advanced melanoma has a B-Raf mutation must have received appropriate therapy with tyrosine kinase inhibitor(s) and/or MEK inhibitor
   Valid for US patients: Patients whose advanced melanoma has a B-Raf mutation may have received appropriate therapy with tyrosine kinase inhibitor(s) and/or MEK inhibitor as assessed by the investigator.
8. Age $\geq$ 18 years.
9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
10. Serum albumin ≥ 2.5 g/dL.
11. Absolute neutrophil count (ANC) $\geq$ 1.0 x 10e9/L.
12. Platelet count ≥ 100 x 10e9/L.
13. Prothrombin (INR) $\leq$ 1.5 or prothrombin time (PT) $\leq$ 1.5 times ULN; and either partial thromboplastin time or activated partial thromboplastin time (PTT or aPTT) $\leq$ 1.5 times the ULN.
14. Bilirubin < 1.5 times the institutional upper limit of normal (ULN).
15. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq$ 2.5 ($\leq$ 5 if liver metastases are present) times the institutional ULN.
16. The patient must have signed informed consent.

Exclusion Criteria

1. Malignant melanoma that is uveal.
2. Subjects considered by the investigator to have rapid clinical progression due to melanoma
3. Subjects must not have greater than 3 cerebral melanoma metastases, and/or clinically active cerebral melanoma metastases, and/or a requirement for corticosteroid therapy, and/or carcinomatous meningitis regardless of clinical stability.
4. Any concurrent treatment that would interfere with the effect mechanisms of atezolizumab and LOAd703, including, but not limited to, continuous high-dose corticosteroids (>10 mg per day), lymphodepleting antibodies, or cytotoxic agents.
5. Treatment with inhibitors of immune function, such as lymphotoxic monoclonal antibodies (e.g., alemtuzumab), or rapamycin/rapamycin analogs, or cytotoxic agents within 21 days of the first dose of LOAd703/atezolizumab.
6. Therapeutic treatment with systemic antibiotics within 14 days of the first dose of LOAd703/atezolizumab.
7. Treatment with biologic therapy within 21 days of the first dose of LOAd703/atezolizumab.
8. Treatment with cytotoxic anticancer therapy within 14 days of the first dose of LOAd703/atezolizumab.
9. Treatment with wide-field radiation within 14 days of the first dose of LOAd703/atezolizumab.
10. Prior treatment with an adenovirus-based gene therapy.
11. Use of any investigational agents within 21 days of the first dose of LOAd703/atezolizumab.
12. The use of systemic immunostimulatory agents (including, but not limited to, interferons and IL2) are prohibited within 21 days or 5 half-lives (whichever is longer)

    of the first dose of LOAd703/atezolizumab.
13. Failed resolution/improvement of AEs including those related to anti-PD-1/anti-PD-L1 to grade 0-1 and requirement for treatment with ≥10 mg/day prednisone (or equivalent) for at least two weeks prior to registration.
14. History of CTCAE grade 4 immune-related AEs from monotherapy using an anti-PD-1/anti-PD-L1 antibody.
15. History of CTCAE grade 4 AE that require steroid treatment (>10 mg/day prednisone or equivalent) for >12 weeks.
16. Patients requiring warfarin are not eligible (low molecular weight heparin is permitted).
17. Women who are pregnant (as confirmed by pregnancy test during screening in applicable patients), breastfeeding, or planning to become pregnant during the study period, or women of childbearing potential who are not using acceptable highly effective contraceptive methods. A woman is considered of childbearing potential if she is not surgically sterile or is less than 1 year since her last menstrual period. The following are acceptable as highly effective contraceptive methods: combined (estrogen- and progesterone-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion and vasectomized partner or abstinence of heterosexual intercourse during the entire study period (depending on the preferred and usual life style of the subject).
18. Men who do not consent to the use of condoms during intercourse during study participation or has a partner of childbearing potential, who will not use any of the highly effective contraceptive methods exemplified in exclusion criteria no 17.

19. Known active hepatitis B or C infection, or HIV infection.
20. Patients with active, severe autoimmune disease or immune deficiency or previous Guillain-Barré syndrome. Patients with eczema, psoriasis, lichen simplex chronicus or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
    a. Rash must cover <10% of body surface area.
    b. Disease is well-controlled at baseline and requires only low-potency topical corticosteroids.
    c. Occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.
21. History of leptomeningeal disease.
22. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently).
23. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan or tested reduced functional respiration capacity. However, history of radiation pneumonitis in the radiation field (fibrosis) is permitted.
24. Unstable angina, uncontrolled cardiac arrhythmia, recent (within 3 months) history of myocardial infarction or stroke, or New York Class III/IV congestive heart failure.
25. Major surgical procedure other than for the malignant melanoma diagnosis, within 4 weeks prior to initiation of the study treatment, or anticipation of the need for a major surgical procedure during the study.
26. Prior allogeneic stem cell or solid organ transplantation.
27. History of severe allergic anaphylactic reactions to chimeric human or humanized antibodies, or fusion proteins.
28. Known hypersensitivity to CHO cell products or any component of the atezolizumab formulation.
29. Uncontrolled intercurrent illness including, but not limited to, psychiatric illness/social situations that in the opinion of the Investigator would compromise compliance to study requirements or put the patient at unacceptable risk.
30. Other malignancy within the past 2 years (not including basal cell or squamous cell carcinoma of the skin, prostate cancer without the need of other treatment than hormones or *in situ* cervix, breast or melanoma).
31. Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment, and for 5 months after the final dose of atezolizumab and/or LOAd703.
32. Adenovirus-based vaccines (e.g., Vaxzevria, known as COVID-19 vaccine Astra Zeneca, J&J Covid-19 vaccine) are prohibited 3 months prior to initiation of study treatment, during treatment and 6 months after the final dose of LOAd703.

Treatment Description: Two dose levels of LOAd703 (total viral load: $1x10^{11}$ and $5x10^{11}$ VP) will be tested in combination with a fixed dose of atezolizumab (1200 mg). Treatments of LOAd703 (up to 12) will be delivered by image-guided intratumoral injection concurrent with intravenous atezolizumab treatment (1200 mg), where both treatments will be given

every 3 weeks. [redacted]. Patients will continue atezolizumab treatment up to study [redacted] unless tumor progression or unacceptable toxicity is observed. Radiological imaging as well as blood [redacted] sampling will be performed to monitor safety, mechanisms-of-action and disease status. [redacted]

Accrual Objective: Up to 50 patients

Study Duration: The trial encompasses a treatment phase ending with last patient last visit (LPLV) (FPI: Q3 2020; LPLV:Q1 2024; study end: Q1 2024). For each patient, active participation with study visits is maximum 60 weeks where after they are followed for survival as long as the trial remains open. Hence, maximum trial duration for a patient is 48 months.

ABBREVIATIONS

aCTLA4	Anti-cytotoxic T lymphocyte antigen 4
ACS	American Cancer Society
Ad	Adenovirus
ADA	Anti-drug antibodies
AE	Adverse event
AICD	Activation-induced cell death
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATMP	Advanced therapy medicinal product
AUC	Area under curve
BOIN	Bayesian Optimal Interval
[redacted]	[redacted]
CBR	Clinical benefit rate
CD	Cluster of differentiation
CDC	Center for Disease Control
CD40L	CD40 ligand, CD154
CEA	Carcinoembryonic antigen
CHO	Chinese hamster ovary cells
CI	Confidence interval
CFR	Code of Federal Regulation
CMV	Cytomegalovirus
CR	Complete response
CRO	Contract research organization
CRP	C reactive protein
CRS	Cytokine release syndrome

CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocyte
CV	Curriculum vitae
DC	Dendritic cell
DCF	Data clarification form
DLT	Dose limiting toxicity
DMP	Data management plan
DSUR	Development safety update report
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
eCRF/CRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
FASS	Swedish online reference of approved drug products
FDA	Food and Drug Administration
FPI	First patient in
FU	Follow-up
GCP	Good clinical practice
GDPR	General data protection regulation
GM-CSF	Granulocyte macrophage-colony stimulating factor
GMO	Genetically modified organism
HUVEC	Human umbilical vein endothelial cell
IA	Immunology assessment
IB	Investigator's Brochure
IEC	International ethics committee
IFNg	Interferon gamma
IL	Interleukin
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional review board
IRR	Immune-related reaction
i.t.	Intratumoral
IU	Infectious units
IV	Intravenous
LFF/LÖF	Swedish patient insurance
LOAd	Lokon oncolytic adenovirus
LPLV	Last patient last visit
LOAd703	LOAd virus containing transgenes CD40L and 4-1BBL
MedDRA	Medical Dictionary for Drug Regulatory Activities
MDSC	Myeloid-derived suppressor cell

MHC	Major histocompatibility complex
mLOAd703	LOAd703 virus containing murine transgenes (CD40L and 4-1BBL)
MPA	Medical products agency
MR	Mixed response
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MTD	Maximum tolerated dose
[redacted]	[redacted]
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NK	Natural killer
NSAID	Nonsteroidal anti-inflammatory drug
ORR	Overall response rate
OS	Overall survival
OV	Oncolytic virus
[redacted]	[redacted]
PD	Progressive disease
PDAC	Pancreatic ductal adenocarcinoma
PD-1	Programmed death receptor 1
PD-L1	Programmed death receptor ligand 1
PET	Positron emission tomography
PFS	Progression-free survival
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
q3w or q4w	Every third week or every fourth week
Rb	Retinoblastoma
RCA	Replication-competent adenovirus
RECIST	Response evaluation criteria in solid tumors
RSI	Reference safety information
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Suspected adverse reaction
SD	Stable disease
SmPC	Summary of Product Characteristics
SoC	Standard of care
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reactions
TCR	T cell receptor
TGFb	Transforming growth factor beta
Th	T helper
TLR	Toll-like receptor
TMZ-CD40L	Trimerized membrane-bound CD40L
TNFa	Tumor necrosis factor alpha
Treg	T regulatory cell

TTP	Time-to-tumor progression
[redacted]	[redacted]
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VP	Virus particles
WBC	White blood cells
4-1BBL	4-1BB ligand, CD137 ligand

DEFINITION OF TERMS

Baseline	Assessment/value before the 1st dose of LOAd703/atezolizumab.
DLT period	DLT evaluation for each patient is done whe [redacted]
End of treatment	Last Patient's Last Visit (LPLV)
End of study	Last Patient's Last Visit (LPLV)
Enrolled patient	A patient who has signed informed consent and the screening visit can be initiated.
Evaluable patient	A patient that has [redacted] A patient that has [redacted]
Registered patient	An enrolled patient who has fulfilled the eligibility criteria after the screening visit has been performed and given a treatment slot in the study.
Study month	One study month = 4 weeks
Screen failure	Patient withdrawn before first LOAd703 dose.
Off-treatment	A patient that is discontinued from treatment, but will return for the clinical follow-up visits (modified schedule) and survival follow-up.
Survival follow up	A patient that is followed for survival.
Off-study	A patient that withdraws consent, is lost to follow up or study is terminated. No more information is collected for the patient i.e. the date for last data capture for the patient.

1.0 GENERAL INFORMATION

1.1 Protocol Number and Title of the Study

Sponsor Protocol Number: LOKON003

Title: A Phase I/II Trial Investigating LOAd703 in Combination with Atezolizumab in Malignant Melanoma

1.2 Sponsor

Lokon Pharma AB
[redacted]

Chief Executive Officer
[redacted]

Sponsor Medical Advisor
[redacted]

Clinical Trial Manager
[redacted]

1.3 CRO

[redacted]

1.4 Investigators and Institutions

The dose escalation part of the study is planned to be conducted at 2 sites in US and 1 site in Sweden. For the dose expansion part of the study, additional clinics may be added in the US and Sweden. An updated contact list will always be available in the Investigator Study File.

Baylor College of Medicine
[redacted]

Site Principal Investigator: [redacted]
Email: [redacted]

Cedars-Sinai Medical Center,
[redacted]

Site Principal Investigator: [redacted]
Email: [redacted]

Uppsala University Hospital
[redacted]

Site Principal Investigator: [redacted]
Email: [redacted]

Huntsman Cancer Institute
(Site has been closed, WCG-IRB approval on 03May2023)
[redacted]

Site Principal Investigator: [redacted]
Email: [redacted]

1.5 Manufacturers

LOAd703 Manufacturer
[redacted]

Atezolizumab Manufacturer
F. Hoffmann-La Roche Ltd
[redacted]

1.6 Biobank

Uppsala Biobank [redacted]

1.7 Laboratories

Clinical Analyses
All study sites will use their local laboratory for clinical chemistry and hematology analyses.

Research Analysis Laboratory

[redacted]

2.0 BACKGROUND

2.1 Tumor Immunology and Cancer Immunotherapy

The immune system can recognize and kill tumor cells using the same mechanisms as it recognizes and kills virally infected cells to save the host against lethal infections. Like virally infected cells, tumor cells are self-cells, and viral- or tumor-associated epitopes are presented to CD8+ cytotoxic T lymphocytes (CTLs) via major histocompatibility complex I (MHC-I) on the cells. Both virally infected cells and tumor cells may prevent CTL recognition by downregulating MHC molecules, making the cells targets for natural killer (NK) cells. While viruses initially activate an anti-viral immune response by alerting antigen-presenting cells such as dendritic cells (DCs) to activate lymphocytes, tumor cells and its stroma tend to produce substances that inhibit immune activation and tumor immunity. In order to evade the immune system, tumors inhibit DC maturation and promote the differentiation and attraction of immunosuppressive (type 2) cells to the tumor milieu such as myeloid-derived suppressor cells (MDSCs) and T regulatory cells (Tregs). These immune regulating cells produce suppressive cytokines and growth factors that suppress activated CTLs in the tumor mileu and lead to T cell anergy (unresponsiveness) or even death.[1,2]

The principal goal of cancer immunotherapy is to break tumor tolerance (e.g., break anergy) and revert the ongoing type 2 immune responses to type 1. Type 1 is characterized by activation of T helper 1 (Th1) lymphocytes, CTLs, NK cells and M1 macrophages as well as by a cytokine pool that includes IFNγ, IL12, IL21 and TNFa.[3]

The implementation of checkpoint blockade antibodies targeting CTLA4 and PD-1/PD-L1 for various solid malignancies, as well as chimeric antigen receptor (CAR) T cells for B cell malignancies, has made immunotherapy a cornerstone in cancer management.[4,5] Nevertheless, most patients with solid malignancies do not respond to checkpoint blockade therapy or become resistant. Novel concepts to treat cancer by stimulating the immune system are currently being investigated that may be used alone, or in combination with checkpoint antibodies, such as immunostimulatory gene therapy utilizing oncolytic viruses as gene delivery vehicles.[6]

2.2 Oncolytic Virus (OV) Therapy

2.2.1 Oncolytic Viruses

The ability of certain viruses to infect cells, propagate and kill them by lysis during the release of new virions means that they can be utilized as cancer therapeutics. To limit oncolysis to tumor cells, the expression of viral replication genes is restricted by adding promoters that are preferentially active in the tumor.[6,7,8] For maximum potency, the OVs should infect all tumor cells. However, this is challenging if the tumor has metastasized, since systemic spreading of the virus to distal tumor may be limited by the immune system. Nevertheless, by arming the OVs with immunostimulatory genes (transgenes), it is possible to inject one or a few lesions to induce a systemic anti-tumor response whereby activated tumor-specific T cells can circulate and reach all tumor lesions. There are many different OVs being evaluated both preclinically and clinically. Most of the clinically advanced OVs encode GM-CSF such as the FDA- and EMA-approved OV Imylgic®.[9] Other options such as LOAd703 described herein encodes one or more immune stimulators. Imylgic® and other OVs are currently being combined with checkpoint blockade antibodies in clinical trials.

2.2.2 The Investigational Product LOAd703

LOAd703 is a novel immunotherapy for cancer. It is an oncolytic adenovirus serotype 5 with a fiber (shaft and knob) from serotype 35 (Ad5/35) to increase cell binding and infectivity of cells expressing human CD46. Virus replication and oncolysis is restricted to cells with a dysfunctional retinoblastoma (Rb) pathway due to an E1AΔ24 and multiple E2F-binding domains upstream of

E1A.[8] Rb in normal cells is bound to the transcription factor E2F which blocks its intrinsic capacity to induce transcription of genes that promote transition from G1 into S phase of the cell cycle. When Rb is phosphorylated, E2F is released and stimulates cell proliferation.[10] Human tumors have a wide spectrum of mutations that alter the Rb protein and/or factors that lead to hyper-phosphorylation of Rb. Hence, in cancer cells E2F is free to drive transcription of the virus. The virus infects and kills tumor cells via oncolysis due to excessive virus replication while healthy non-malignant cells can be infected but new virus particles are normally not produced. Therefore, LOAd703 does not kill, and is therefore not toxic to healthy cells. LOAd703 has a transgene cassette with two immunostimulatory genes (TMZ-CD40L and 4-1BBL) driven by a CMV promoter. The CMV promoter is not tissue-restricted and the immunostimulatory genes can be expressed in all cells that are infected by LOAd703, independent of virus replication. Thus, LOAd703 targets both the tumor and its stroma to induce transgene expression but virus-mediated oncolysis will only occur in tumor cells. Since the virus is administered by intratumoral (i.t.) injection, the expression of the transgenes is localized to the tumor area.

CD40L is a potent stimulator of myeloid cells and an inducer of Th1 type immune responses.[11] The TMZ-CD40L transgene is a specially designed human CD40 ligand (CD40L; CD154) that lacks the intracellular signaling domain and instead fuses the extracellular and transmembrane domains to an isoleucine zipper domain.[12] This creates a membrane-bound trimerized CD40L molecule that lacks intracellular signaling in the TMZ-CD40L-expressing cell but still binds and transmits signals to other cells that express its receptor, CD40. TMZ-CD40L can mature DCs to become potent stimulators of T- and NK cells and can enhance the expression of adhesion receptors on endothelial cells which promotes lymphocyte attachment and migration into inflamed areas.[12,13] On the other hand, CD40L can also play a role in tumor cell death due to a dysregulated signaling cascade whereby CD40 ligation in CD40+ cancer cells can lead to tumor growth inhibition and apoptosis.[11]

The 4-1BB ligand (4-1BBL; CD137L) transgene is the full-length human 4-1BBL gene. It binds to its receptor 4-1BB (CD137) expressed on activated T cells and NK cells. 4-1BBL stimulation of T cells and NK cells protects the cells from activation-induced cell death (AICD) via upregulation of apoptosis inhibitors such as BCL-xL. 4-1BBL stimulation also promotes efficient lymphocyte proliferation and memory T cell formation.[14,15]

The LOAd703 virus is not functional in animal models since it requires human CD46 for infection and cannot replicate even when animal cells are modified to express human CD46. Further, human TMZ-CD40L and 4-1BBL do not cross react with their murine receptor counterparts. Hence, toxicity studies cannot be performed in *in vivo* models. Oncolytic effect can be demonstrated in immuno-deficient xenograft mice implanted with human tumors and treated with LOAd703. This leads to tumor growth control and tumor regression, but in this model, the effect of the transgenes cannot be evaluated since the mice lack adaptive immunity.[13] Effect of the immunostimulatory transgenes can be evaluated in immunocompetent mice implanted with a murine tumor expressing human CD46 and treated with a LOAd703 virus containing murine TMZ-CD40L and 4-1BBL. This leads to the robust stimulation of DCs, T cells and NK cells. Further, LOAd703 can potentiate the effect of anti-PD-L1 antibodies in an animal cancer model.

The major effector mechanisms of LOAd703 are: 1) induction of cell death via either oncolysis or CD40-mediated apoptosis, and 2) activation of the immune system via CD40L, 4-1BBL and the adenoviral backbone. The major effector arm is likely immune activation, but the induction of cell death by oncolysis further strengthens anti-tumor responses due to the release of tumor antigens resulting in tumor antigen-specific immune stimulation.

Detailed preclinical information can be found in the LOAd703 Investigator's Brochure (IB) Section 6.0 NONCLINICAL EVALUATION OF LOAd703 which is an integral part of this protocol.

2.3 Immune Checkpoint Blockade Therapy

2.3.1 Checkpoint Blockade

Immune checkpoints are inhibitory signals that diminish T cell activation and lead to T cell exhaustion. To overcome these inhibitory signals and sustain T cell activation during the anti-tumor response, checkpoint blockade antibodies have been developed to block inhibitory immune checkpoints such as CTLA4 or PD-L1/PD-1.

Recently, checkpoint blockade therapy has shown impressive results in cancer patients, in particular in malignant melanoma. However, most patients are refractory to treatment or become resistant after an initial response. Resistance is likely due to the patient's immune status, e.g., having an immunosuppressive tumor microenvironment with very few activated anti-tumor reactive T cells, which may not depend on PD-L1/PD-1 interactions. Studies combining oncolytic virus with checkpoint blockade inhibition have demonstrated enhanced effect in preliminary reports. The use of Imylgic® with pembrolizumab increased response rates from approximately 30% to 60%.[16]

2.3.2 Atezolizumab

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1, a ligand expressed on a variety of cell types as well as malignant cells. Overexpression of PD-L1 on tumor cells may be a mechanism of tumor evasion and has been demonstrated to inhibit anti-tumor responses.[17] Atezolizumab inhibits the interaction between PD-L1 and its receptors PD-1 and B7.1 (CD80), which would otherwise inhibit T cell proliferation, cytokine production and cytolytic activity.[18,19] In addition, atezolizumab demonstrates minimal binding to Fc receptors, eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to improve anti-tumor activity by enhancing tumor-specific T cell responses.[20,21] Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is approved for the treatment of urothelial carcinoma and non–small cell lung cancer and is currently being studied as a single agent in advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Detailed preclinical information can be found in the atezolizumab Investigator's Brochure Section 4 Nonclinical Studies which is an integral part of this protocol.

2.4 LOAd703 Previous Clinical Studies

Currently, LOAd703 is being evaluated in combination with standard-of-care (SoC) chemotherapy treatment in two ongoing phase I/II clinical trials. In one of the trials, atezolizumab is added to the combination treatment in a second study arm. Briefly, the trials are open label studies to evaluate dose, safety and efficacy. In both trials, three dose levels are evaluated followed by expansion of the maximum tolerated tested dose. An overview of the trials is shown in Table 1.

Table 1. Overview of ongoing LOAd703 clinical trials

	LOKON001 (NCT02705196)	**LOKON002 ([redacted])**
Site	US; Baylor College of Medicine; Principal Investigator: [redacted]	Sweden, Uppsala University Hospital; Coordinating Principal Investigator: [redacted] Sweden, Karolinska University Hospital; Principal investigator [redacted]
Indication	Pancreatic ductal adenocarcinoma (PDAC)	PDAC, ovarian cancer, colorectal cancer, and biliary cancer
Phase	Phase I/II: LOAd703 dose escalation in 3 cohorts ($5x10^{10}$, $1x10^{11}$ or $5x10^{11}$ VP/injection) and expansion of cohort at MTD	Phase I (dose escalation in 3 cohorts; $5x10^{10}$, $1x10^{11}$ or $5x10^{11}$ VP/injection) and Phase II (expansion of MTD cohort)
No. of patients	Maximum 55 evaluable patients	Maximum 53 evaluable patients
Treatment	Arm 1: LOAd703 + gemcitabine/nab-paclitaxel Arm 2: LOAd703 + gemcitabine/nab-paclitaxel + atezolizumab • LOAd703 i.t. injections given every other week (6-12 LOAd703 treatments total). • Gemcitabine IV infusion 1000 mg/m^2 + nab-paclitaxel 125 mg/m^2 (d1, 8, 15 of a 28-day cycle) until progression or toxicity. • Atezolizumab IV infusion 1680 mg every fourth week.	LOAd703 + SoC treatment • LOAd703 i.t. injections given every other week (8 LOAd703 treatments total). • SoC chemotherapy tailored to the indication, or gemcitabine if SoC is not an available option (1000 mg/m2; d1, 8, 15 of a 28-day cycle).
Study duration	37-47 weeks; then survival follow-up every 3 months. FPI 2016, LPLV estimated 2023.	40 weeks; then survival follow-up every 3 months. FPI 2018, LPLV estimated 2024.

In the LOKON001 study, the safety and efficacy of LOAd703 therapy in combination with chemotherapy is being investigated in maximum 55 evaluable patients with PDAC. The patients receive 6 injections of LOAd703 combined with gemcitabine plus nab-paclitaxel (28-day cycles with treatment on day 1, 8 and 15). Responding patients have the option of 6 additional LOAd703 treatments.

In LOKON002, patients with PDAC, ovarian cancer, colorectal cancer or biliary cancer are treated with 8 injections of LOAd703 in combination with SoC chemotherapy tailored to the indication, or gemcitabine if no SoC option is available (28-day cycle with treatment on day 1, 8 and 15).

See latest version of Investigator Brochure (IB) for updated information regarding number of patients treated with LOAd703.

[redacted]

[redacted]

Reference safety information (RSI) is detailed in the LOAd703 IB Section 7 EFFECT IN HUMANS, which is an integral part of this protocol.

2.5 Atezolizumab – Previous Clinical Studies

Atezolizumab monotherapy is approved in many countries for the treatment of patients with advanced urothelial carcinoma and advanced non–small cell lung cancer. Atezolizumab in combination with nab-paclitaxel was recently approved for treating patients with advanced triple negative breast cancer. It is also currently being studied as a single agent in many other clinical settings, including treatment of patients with advanced- and early (adjuvant)-stage disease. Atezolizumab is being evaluated as both a monotherapy and in combination with chemotherapy, targeted therapy, and cancer immunotherapy. Clinical data are available from more than 20 studies. [redacted] the fixed dose of 1200 mg that will be administered every three weeks (q3w) in this study.

[redacted]

Detailed clinical information can be found in the atezolizumab IB Section 5 Effects in Humans, which is an integral part of this protocol.

2.6 Potential Risks and Benefits

2.6.1 LOAd703 - Potential Risks and Action Plan

LOAd703 is an advanced therapy medicinal product (ATMP) that is classified as a gene therapy, but it is also an immunotherapy. The risks that are potentially incurred in this study can be viewed as those potential risks associated with LOAd703 as a gene therapy, including the immunostimulatory transgenes, as well as the potentially increased risk of combining two immunotherapeutics.

Error! Reference source not found. summarizes the risk factors for LOAd703 which is followed by a discussion of the known risks of atezolizumab and the potential risks of combination treatment.

Table 2. LOAd703 risks and risk factors

[redacted]

[redacted]

2.6.2 Atezolizumab - Potential Risks and Action Plan

[redacted]

[redacted]

2.6.3 Combination of LOAd703 and Atezolizumab - Potential Risks and Action Plan

2.6.4 Potential Benefits – Rationale for Combining LOAd703 and Atezolizumab

2.7 Rationale for the Phase I/II Doses

This study will begin at the LOAd703 dose level $1x10^{11}$ VP per treatment (cohort 1), and if safe, the dose will be escalated to $5x10^{11}$ VP per treatment every 3 weeks (q3w) (cohort 2). These dose levels have been demonstrated to be safe in the ongoing LOKON001 (NCT02705196) and LOKON002 ([redacted]) trials where patients were treated i.t. every other week (q2w) with 6-12 and 8 LOAd703 treatments, respectively. No intra-patient dose escalation is allowed. Dose reductions may be applicable due to toxicity (see 5.5 *Dose Limiting Toxicity (DLT*), and 5.6.8 *LOAd703 Dose Modifications*).

Atezolizumab will be given as a fixed dose (1200 mg, q3w) which is the approved dose level and schedule for the treatment of urothelial carcinoma and non–small cell lung cancer. Atezolizumab may be subject to dose adjustments due to toxicity (see 5.7.7 *Atezolizumab Dose Modifications*).

[redacted]

2.8 Patient Population

Melanoma is a cancer that develops from melanocytes in the epidermal layer of the skin. Melanoma is the fifth most common cancer among men and women.[32] It is often diagnosed in older patients but is also one of the most common cancers in young adults, especially young women.[33] Risk factors include sun/UV exposure, skin type (white/fair skin, moles, etc.), genetic disposition, and sex; the risk is higher for women before the age of 50, and higher for men after 50 years of age.[34] More than 90% of melanoma cancers are due to skin cell damage from ultraviolet radiation exposure.[35]

The incidence of melanoma has doubled in the last three decades in the US from an incidence of 11.2 to 22.7 per 100,000.[36] In 2019, it is projected that 96,480 adults in the US (57,220 men and 39,260 women) will be diagnosed with melanoma.[32] Although it accounts for only 1% of all skin cancers, melanoma is the deadliest type of skin cancer, accounting for >90% of skin cancer deaths.[37] In 2019, it is estimated that over 7000 people in the US will die from melanoma.[32]

While localized melanoma is typically curable with surgery, metastasized melanoma in regional and distant areas have a 5-year survival rate of 63% and 20%, respectively.[37] Metastatic melanoma is known to be refractory to traditional therapies like chemotherapy and radiation, and until 2010, there was no evidence-based therapy available that could demonstrate significantly improved overall survival (OS) for patients with unresectable advanced melanoma. In patients with stage IV metastatic melanoma, less than half survived >1 year and only 20% were alive after 3 years. Since 2010, new systemic therapies such as checkpoint inhibitors have improved treatment options for patients with unresectable advanced melanoma.[38] In addition to immunotherapy, targeted therapies (BRAF- and MEK-inhibitors) can be utilized in patients with BRAF mutations, which may account for over half of all melanomas.[34] In 2015, the first oncolytic virotherapy, T-VEC (Imlygic®; talimogen lahparepvec), was approved for the treatment of melanoma (FDA and EMA). T-VEC as well as several other oncolytic viruses, such as CAVATAK, are being actively developed, as monotherapies or as combination therapies together with checkpoint inhibitors.

In this study, patients with melanoma that have received at least one prior line of checkpoint blockade antibody therapy (mono or combination) can be enrolled in the study. Both men and women of all races and ethnic groups are eligible to participate in this trial. However, children are not eligible for participation since safety and tolerability have not yet been determined in adults.

All patients enrolled will receive LOAd703 combined with the checkpoint inhibitor atezolizumab. LOAd703 treatment stimulates DCs, NK and T cells while atezolizumab blocks the inhibitory signaling via PD-L1/PD-1 which may prolong T cell activation and the anti-tumor response.

3.0 TRIAL DESIGN

3.1 Objectives

The primary objective is to determine the tolerability of LOAd703 given by i.t. injection(s) in combination with atezolizumab administered by IV.

The secondary objectives are to determine the antitumor activity as well as the pharmacokinetics and biological mechanisms-of-action of LOAd703 in combination with atezolizumab.

3.2 Endpoints

Primary Endpoints

1) The primary endpoint is safety, determined by the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) v5.0.

Secondary Endpoints

- Overall response rate evaluated by RECIST v1.1.
- Shedding determined as level of LOAd703 [redacted]
- LOAd703 leakage to blood [redacted]
- Anti-adenovirus immunity [redacted]
- [redacted]
- [redacted]
- Immune profile as [redacted]
- [redacted]

3.3 Summary of Trial Design

This trial is a multicenter, open label, single arm, dose-escalation Phase I/II trial. The study will have a Bayesian Optimal Interval (BOIN) design (target DLT rate=0.3) to determine the MTD of LOAd703 against a fixed dose of atezolizumab. This design has algorithmic escalation/de-escalation rules like a traditional 3+3 design, but it also allows for specification of the target DLT rate and expanded accrual beyond N=6 with continued and consistent toxicity monitoring. This means that the assessment of DLT rate continues throughout the study, giving a well-defined safety evaluation of the entire study. Refer also to sections *10.0 STATISTICS, 5.5 Dose Limiting Toxicity (DLT) and 5.6.9 LOAd703 Maximum Tolerated Dose (MTD)*.

[redacted] The total number of patients to be enrolled in the study to achieve at least 25 evaluable patients at MTD, should not exceed 50.

3.4 Duration of Study

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Timeline:	First patient in	Q3 2020
	Last patient's last visit	Q1 2024
	Study end	Q12024

After a screening period [redacted], each patient will receive a maximum of 12 LOAd703 injections (q3w) in combination with atezolizumab (q3w) after which supportive therapy with atezolizumab alone is continued until the final clinical visits (i.e. maximum 7 additional infusions). The patients will be scheduled for study visits until final clinical follow-up in study [redacted]

If both treatments are prematurely discontinued the final clinical follow-up visit could be scheduled earlier, [redacted]

In total, patients will visit the clinic regularly for a maximum 60-weeks ([redacted]). Thereafter only OS will be recorded every [redacted] whereby information will be collected via e.g. telephone calls (US) or medical records (SWE, US) until death or study end.

3.5 End of Study

The End of the treatment stage is defined as the date of the LPLV and the End of study is defined as LPLV.

4.0 SELECTION AND WITHDRAWAL OF PATIENTS

Study patients will be recruited among patients taken care of at the study center but may also include patients referred from other hospitals. Once a patient is enrolled in the trial, the Site Investigator is responsible for the care of the patient.

Patients must meet all the following inclusion criteria and none of the exclusion criteria to be registered in the study:

4.1 Inclusion Criteria

1. Pathological confirmation of melanoma.
2. A life expectancy of at least 3 months as per the investigator.
3. **Valid for Swedish patients:** Patients has locally advanced melanoma or metastatic melanoma, but not eligible for complete resection of melanoma.
   Valid for US patients: Patients has locally advanced melanoma or metastatic melanoma.
4. The patient has measurable disease (e.g., measurable tumor lesions must be present that can accurately be measured in at least one dimension with a minimum size of 10 mm by CT scan and MRI, 10 mm caliper measurement by clinical exam (when superficial), and/or 20 mm by chest X-ray).

5. Patient has at least one injectable tumor lesion that has not been irradiated or has been irradiated but disease progression documented at the site subsequent to radiation therapy.
6. The patient has received appropriate treatment with an anti-PD-1 or anti-PD-L1 antibody with or without an anti-CTLA4.
7. **Valid for Swedish patients:** Patients whose advanced melanoma has a B-Raf mutation must have received appropriate therapy with tyrosine kinase inhibitor(s) and/or MEK inhibitor **Valid for US patients:** Patients whose advanced melanoma has a B-Raf mutation may have received appropriate therapy with tyrosine kinase inhibitor(s) and/or MEK inhibitor as assessed by the investigator.
8. Age ≥ 18 years.
9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
10. Serum albumin ≥ 2.5 g/dL.
11. Absolute neutrophil count (ANC) ≥ 1.0 x 10e9/L.
12. Platelet count ≥ 100 x 10e9/L.
13. Prothrombin (INR) ≤ 1.5 or prothrombin time (PT) ≤ 1.5 times ULN; and either partial thromboplastin time or activated partial thromboplastin time (PTT or aPTT) ≤ 1.5 times the ULN.
14. Bilirubin < 1.5 times the institutional upper limit of normal (ULN).
15. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 (≤ 5 if liver metastases are present) times the institutional ULN.
16. The patient must have signed informed consent.

4.2 Exclusion Criteria

1. Malignant melanoma that is uveal.
2. Subjects considered by the investigator to have rapid clinical progression due to melanoma.
3. Subjects must not have greater than 3 cerebral melanoma metastases, and/or clinically active cerebral melanoma metastases, and/or a requirement for corticosteroid therapy, and/or carcinomatous meningitis regardless of clinical stability.
4. Any concurrent treatment that would interfere with the effect mechanisms of atezolizumab and LOAd703, including, but not limited to, continuous high-dose corticosteroids (>10 mg per day), lymphodepleting antibodies, or cytotoxic agents.
5. Treatment with inhibitors of immune function, such as lymphotoxic monoclonal antibodies (e.g., alemtuzumab), or rapamycin/rapamycin analogs, or cytotoxic agents within 21 days of the first dose of LOAd703/atezolizumab.
6. Therapeutic treatment with systemic antibiotics within 14 days of the first dose of LOAd703/atezolizumab.
7. Treatment with biologic therapy within 21 days of the first dose of LOAd703/atezolizumab.
8. Treatment with cytotoxic anticancer therapy within 14 days of the first dose of LOAd703/atezolizumab.
9. Treatment with wide-field radiation within 14 days of the first dose of LOAd703/atezolizumab.
10. Prior treatment with an adenovirus-based gene therapy.
11. Use of any investigational agents within 21 days of the first dose of LOAd703/atezolizumab.
12. The use of systemic immunostimulatory agents (including, but not limited to, interferons and IL2) are prohibited within 21 days or 5 half-lives (whichever is longer) of the first dose of LOAd703/atezolizumab.

13. Failed resolution/improvement of AEs including those related to anti-PD-1/anti-PD-L1 to grade 0-1 and requirement for treatment with ≥10 mg/day prednisone (or equivalent) for at least two weeks prior to registration.
14. History of CTCAE grade 4 immune-related AEs from monotherapy using an anti-PD-1/anti-PD-L1 antibody.
15. History of CTCAE grade 4 AE that require steroid treatment (>10 mg/day prednisone or equivalent) for >12 weeks.
16. Patients requiring warfarin are not eligible (low molecular weight heparin is permitted).
17. Women who are pregnant (as confirmed by pregnancy test during screening in applicable patients), breastfeeding, or planning to become pregnant during the study period, or women of childbearing potential who are not using acceptable highly effective contraceptive methods. A woman is considered of childbearing potential if she is not surgically sterile or is less than 1 year since her last menstrual period. The following are acceptable as highly effective contraceptive methods: combined (estrogen- and progesterone-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion and vasectomized partner or abstinence of heterosexual intercourse during the entire study period (depending on the preferred and usual life style of the subject).
18. Men who do not consent to the use of condoms during intercourse during study participation or has a partner of childbearing potential, who will not use any of the highly effective contraceptive methods exemplified in exclusion criteria no 17.
19. Known active hepatitis B or C infection, or HIV infection.
20. Patients with active, severe autoimmune disease or immune deficiency or previous Guillain-Barré syndrome. Patients with eczema, psoriasis, lichen simplex chronicus or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
    a. Rash must cover <10% of body surface area.
    b. Disease is well-controlled at baseline and requires only low-potency topical corticosteroids.
    c. Occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.
21. History of leptomeningeal disease.
22. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently).
23. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan or tested reduced functional respiration capacity. However, history of radiation pneumonitis in the radiation field (fibrosis) is permitted.
24. Unstable angina, uncontrolled cardiac arrhythmia, recent (within 3 months) history of myocardial infarction or stroke, or New York Class III/IV congestive heart failure.
25. Major surgical procedure other than for the malignant melanoma diagnosis, within 4 weeks prior to initiation of the study treatment, or anticipation of the need for a major surgical procedure during the study.
26. Prior allogeneic stem cell or solid organ transplantation.

27. History of severe allergic anaphylactic reactions to chimeric human or humanized antibodies, or fusion proteins.
28. Known hypersensitivity to CHO cell products or any component of the atezolizumab formulation.
29. Uncontrolled intercurrent illness including, but not limited to, psychiatric illness/social situations that in the opinion of the Investigator would compromise compliance to study requirements or put the patient at unacceptable risk.
30. Other malignancy within the past 2 years (not including basal cell or squamous cell carcinoma of the skin, prostate cancer without the need of other treatment than hormones or *in situ* cervix, breast or melanoma).
31. Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment, and for 5 months after the final dose of atezolizumab and/or LOAd703.
32. Adenovirus-based vaccines (e.g., Vaxzevria, known as COVID-19 vaccine Astra Zeneca, J&J Covid-19 vaccine) are prohibited 3 months prior to initiation of study treatment, during treatment and 6 months after the final dose of LOAd703.

4.3 Screening, Enrollment and Registration Log, Identification List and Numbering of Subjects

It is the responsibility of the Investigator that all patients considered candidates for the study be listed in the *"Screening, Enrollment and Registration log"*. The reason for rejecting a patient before informed consent is obtained should be specified in the comments field of the log. Patients will receive a consecutive patient number when signing the informed consent and are thereafter considered enrolled as study patients so they can initiate the screening visit. The patient number will have the following format: [redacted]. The trial site will keep an "*Identification list*" of all enrolled patients that connects the subject's identity to their study number.

Study patients who have been screened and excluded before the week 0 visit are considered screening failures and will be noted as such in the *"Screening, Enrollment and Registration log"*. The reason for excluding the patient from the study should be specified in the comments field of the *"Screening, Enrollment and Registration log"*.

When the inclusion criteria and none of the exclusion criteria have been fulfilled, the site can request a study slot by the CRO. When the study slot is confirmed by the CRO, the patient is considered registered in the study and the registration date is documented in the *"Screening, Enrollment and Registration log*. The study investigators participate in regular phone conferences with the CRO and Sponsor to follow the recruitment process and study development.

NOTE: During dose escalation, the slots are limited to 3 per cohort, of which the first patient must receive [redacted] before patient 2 and 3 can start. During dose escalation it is therefore important to have close communication with the CRO before screening, in order to confirm the timing and avoid having eligible patients ready for treatment when there is no slot available. During dose escalation, the first dose will not be given to two or more patients on the same day (within 24 hours of dosing).

Instructions on communication and the registration procedures are found in the Investigator Site File.

4.4 Withdrawal of Patients

A patient has the right to withdraw his or her consent for participating in the study, at any time, and without giving any specific reason.

The *study treatment* can be discontinued (i.e. from either LOAd703 or atezolizumab or from both treatments) at any time if it is medically necessary, as judged by the Investigator or the Sponsor, based on the development of toxicity as specified in sections *5.5 Dose Limiting Toxicity (DLT), 5.6.8 LOAd703 Dose Modifications, 5.6.9 LOAd703 Maximum Tolerated Dose (MTD)* and *5.7.7 Atezolizumab Dose Modifications.*

If only one of the study treatments is discontinued, the patient still continues with the other study treatment and follows the study schedule according to the protocol.

4.4.1 Off-treatment patient

The patient is discontinued from both LOAd703 and atezolizumab ([redacted]) or from Atezolizumab ([redacted]) if the following criteria are met:

1. The development of toxicity, which precludes further treatment with both study treatments, in the Investigator's judgment, and as specified in sections *5.5 Dose Limiting Toxicity (DLT), 5.6.8 LOAd703 Dose Modifications, 5.6.9 LOAd703 Maximum Tolerated Dose (MTD)* and *5.7.7 Atezolizumab Dose Modifications.*
2. A response that is sufficient to downstage the patient to resectable or borderline resectable disease, in which case the Investigator may decide to pursue chemoradiation and/or surgical resection.
3. Patient has confirmed progressive disease
4. Patient requests to discontinue treatment.
5. Female patient becomes pregnant.

Off-treatment patients: should continue to be followed according to a modified clinical follow-up schedule (see section 6.4 *Evaluation, Modified Follow-Up and Final Follow-Up Visit* and *14.3 Appendix III: Modified Follow-Up Schedule*). This means that patients will continue his/her participation in the study and return to visits for AE assessment, sampling, and radiology (according to protocol) but not receive treatment.

The visits should continue at least [redacted] meaning that the final clinical follow-up visit ([redacted]) may be scheduled earlier. [redacted]

4.4.2 Survival follow-up patient

If another treatment is initiated due to progressive disease or other reasons, the patient will be followed for survival until death or End of Study (see section *7.5.3 Survival Follow-Up*). The final clinical follow-up visit ( ) should then be scheduled to collect endpoint data ( ) as close to the start of new treatment as possible.

4.4.3 Off-study patient

The patient will be withdrawn from participation in this trial at any time if any of the following criteria are met:

1. The patient requests to be removed from the trial and withdraws consent.
2. Lost to follow-up/serious noncompliance to protocol.
3. The trial is terminated.

No further data, except for survival, will be collected for these patients (see section *7.5.3 Survival Follow-Up*).

4.5 Replacement of Patients

If a patient does not complete of LOAd703 and atezolizumab (for a reason other than LOAd703- or atezolizumab-attributed toxicity), this patient will be replaced by another subject in order to meet the minimum criteria for safety (see section 10.2 *Sample Size*).

4.6 Noncompliance

All instances of noncompliance and all protocol deviations will be recorded.

5.0 TREATMENT OF PATIENTS

5.1 Treatment Overview

The patients will be informed about the study and sign informed consent whereby they are enrolled in the screening phase of the protocol to determine their eligibility, including assessment of health status and radiological evaluation. Imaging obtained within 3 weeks prior to registration may be used for baseline evaluation at the discretion of the Investigator.

Also, if samples have been taken for routine analysis <7 days prior to screening, the results can be used for eligibility evaluation at the discretion of the Investigator.

Within 7 days after registration, the patients will initiate treatment. The patients will be given up to 12 percutaneous LOAd703 i.t. injections combined with atezolizumab, both administered every 3 weeks. Two cohorts consisting of at least 3 patients per cohort will be evaluated. The LOAd703 dose will be escalated, one dose per cohort, to evaluate the following dose levels: $1x10^{11}$ VP/injection (cohort 1) and $5x10^{11}$ VP/injection (cohort 2). The treatment will be administered by percutaneous i.t. injection which may be image-guided depending on the tumor location. Atezolizumab will be administrated IV using a fixed dose (1200 mg/infusion).

On the day of the treatment, . LOAd703 dose, dose modifications and omissions will be

carried out as per instructions in sections 5.6.8 *LOAd703 Dose Modifications* and 7.2.5 *Continuation Criteria*. Atezolizumab dose, dose modifications, and omissions will be instituted per standard guidelines (US: TECENTRIQ® Full Prescribing Information, [redacted], Sweden: SmPC/FASS for atezolizumab/TECENTRIQ®) and 7.2.5 *Continuation Criteria*.

Missed LOAd703 or atezolizumab doses will not be made up in order to maintain adherence to the protocol schedule. For details regarding LOAd703 injection and atezolizumab infusion, see sections 5.6.5 *Preparation of LOAd703 Prior to Treatment* 5.6.6 *Administration of LOAd703, 5.7.4 Preparation of Atezolizumab Prior to Treatment,* and 5.7.5 *Administration of Atezolizumab*, respectively.

For the first 2 LOAd703 treatments of any trial patient, the patients are monitored overnight. Vital signs will be noted [redacted]

Prior to each LOAd703 and/or atezolizumab treatment (within -2 days), the Investigator must meet the patient to perform a complete AE evaluation (including laboratory values) and assess the toxicity screening to assure that the patient is able to receive next treatment (see sections 7.2.5 *Continuation Criteria* and 4.4 *Withdrawal of Patients*).

[redacted] Radiological assessment will be performed at enrollment and thereafter every two months. [redacted], the patients will undergo the final follow-up visit and thereafter enter the survival follow-up. The informed consent form includes a specific question about whether the patient consents to the study team following up their condition every 4 months after the final follow-up visit at the clinic.

OS will be recorded for the patients until death or until End of Study. The survival data may be collected via medical records (SWE, US) or by telephone/email from the Investigator or research nurse/coordinator (US) (see *7.5.3 Survival Follow-Up*). OS will be reported as a descriptive addendum to the study report.

When the first patient in a cohort has received [redacted] the next two patients in the cohort can begin treatment but must start treatment at least one day apart (24 hours). Note that enrollment and screening is allowed if slots are available in a cohort at any time. Slots are distributed upon request by the CRO (see section 4.3 for more information).

If a patient does not complete [redacted] (for a reason other than LOAd703 attributed DLT), this patient will be replaced by another subject and not regarded as a DLT evaluable. The BOIN design to evaluate safety allows for continuous DLT assessments and cohort sizes larger than 3 and will thus continue throughout the study.

The decision to escalate dose is taken by the Sponsor after a safety meeting including the Sponsor, CRO, Clinical Project Manager (for taking notes only), Medical Advisor and at least 2 of the site Principal Investigators as a minimum. The maximum tolerated dose (MTD) level will be expanded for continued safety and efficacy evaluation and at least 25 efficacy evaluable patients will be

enrolled at MTD. By using the BOIN design, the actual MTD is therefore determined at the end of the study (see section *5.6.9 LOAd703 Maximum Tolerated Dose (MTD)*). The justification of cohort sizes and the sample size calculation are described in section *10.0 STATISTICS*.

5.2 Treatment Schedule for Study Visits

The LOAd703 treatment schedule and study visits over time are described in *Figure 1: Study timeline* and *14.1 Appendix I: Schedule of Events*. LOAd703 treatment is given up to 12 times. Atezolizumab will be administered continuously during study participation if judged beneficial and safe for the patient by the Investigator. In total, the patient can participate in study visits for 60 weeks ([redacted]). If patients are not on-treatment, the blue-labeled study visits for sampling are canceled. On-treatment patients refers to patients continuing LOAd703 and/or atezolizumab treatment. Patients discontinuing treatment (i.e., off-treatment) can have the final follow-up visit scheduled earlier. The final follow-up visit should be at least [redacted] so that the final endpoint data are collected. After the final follow-up visit at the clinic, patient health status and the overall survival will be recorded until death or End of Study, (see *7.5.3 Survival Follow-Up*).

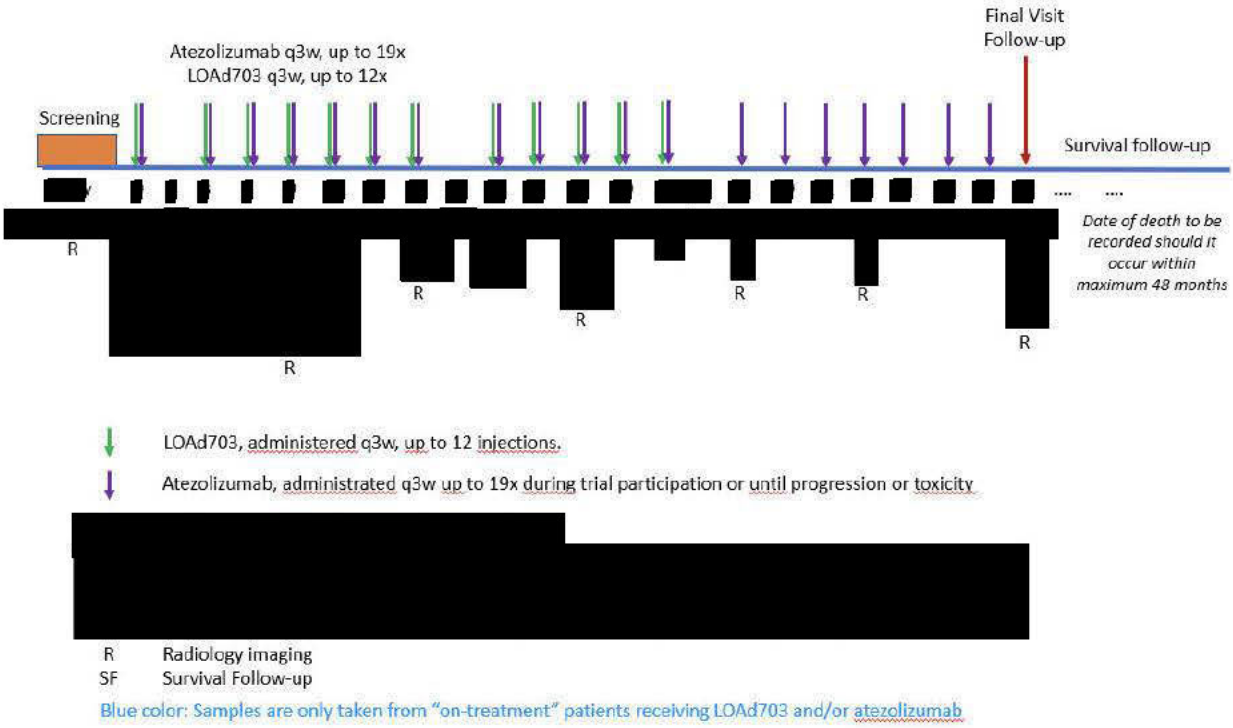


Figure 1. Study timeline. Schedule for study treatments, sampling, and follow-up visits. The planned study participation with visits to the clinic for an individual patient spans a maximum of 60 weeks [redacted]) provided that either LOAd703 or atezolizumab is continued. Note that shedding samples will be collected [redacted] Further, atezolizumab PK sampling at [redacted] Following the final follow-up clinical visit, patient health status and overall survival will be recorded until death or End of Study (see *7.5.3 Survival Follow-Up*).

5.3 Study Sites

5.3.1 General Description

The patients recruited in this trial will participate in the trial activities at the study sites under the guidance of the site Principal Investigator. As soon as a patient is enrolled in the trial, the Investigator is responsible for the patient.

LOAd703 is administered by i.t. injection. The selection of injectable lesions is decided by the Investigator after consultation with the interventional radiologist. The injections are performed by the radiologist or Investigator following the same procedures as when a biopsy is taken, see "*Instructions for tumor lesion selection for LOAd703 injections and effect evaluation*" in the Investigator Site File.

The hospital personnel involved in this trial have experience and/or training using immunostimulatory adenovirus-based treatments. Study patients are treated in a hospital with a fully equipped emergency care unit. The study nurse/coordinator brings the patient and the LOAd703 virus to the injection suite and stays during the injection, whereupon the patient is transferred to the appropriate hospital unit for monitoring and atezolizumab administration. Trial visits such as sampling and meetings with the study team will also take place at the hospital unit.

5.3.2 GMO Regulation at Trial Site

The LOAd703 virus will be handled only by genetically modified microorganism (GMO)-trained staff. The Sponsor is responsible for GMO training. Trained staff are receiving a GMO certificate, and a copy is archived in the Investigator Site File as proof that they have received appropriate training. Beside information in section *5.6 LOAd703 Drug Product, a* GMO booklet with training material, instructions for GMO handling and accidents (see instruction: *LOKON003 Handling, preparation and treatment with LOAd703*), and a list of certified staff will be available at each trial site.

5.4 Referrals from Other Hospitals

If a patient is referred to a study site by another hospital to participate in this trial, all study activities will be carried out only at the study site including treatments, sampling and assessments. The site Principal Investigator is responsible for all trial patients during their participation in the trial.

5.5 Dose Limiting Toxicity (DLT)

As LOAd703 will be dose escalated, the patients will be monitored for dose limiting toxicity (DLT). DLT is defined as any grade 3 or higher toxicity (CTCAE Version 5.0) that is attributed (definitely, possibly or probably) to LOAd703. A DLT attributed to LOAd703 will lead to dose reduction (see *5.6.8 LOAd703 Dose Modifications*).

Phase I: The first patient on each dose level must have been evaluated for DLT [redacted] before patient 2 and 3 in the same cohort can start treatment. Patient 2 and 3 should start treatment at least 24 hours apart.

All 3 patients in the cohort must have been evaluated for DLT before decision on dose escalation is taken for the next cohort.

Phase II: Patient enrollment continues and evaluation for DLTs [redacted] (see *10.2 Sample Size*).

Toxicity attributed to atezolizumab will not be assessed as DLTs in the study but can still lead to dose modifications (see *5.7.7 Atezolizumab Dose Modifications*).

If a patient experiences an AE grade 3 or higher that can be attributed to the LOAd703 injection procedure (i.e., a bacterial infection, injection site pain, etc.), to disease, or another unrelated cause, it is not a DLT. SAEs due to injection procedure can lead to change of injection procedure (such as change of lesion) instead of treatment discontinuation, depending on the type of AE and the risk of recurrence of the AE.

[redacted]

5.6 LOAd703 Drug Product

5.6.1 LOAd703 Brief Description

[redacted]

[redacted]

5.6.2 LOAd703 Packaging and Labeling

[redacted]

5.6.3 LOAd703 Storage and Handling

[redacted]

5.6.4 LOAd703 Accidents

[redacted]

[redacted]

5.6.5 Preparation of LOAd703 Prior to Treatment

[redacted]

5.6.6 Administration of LOAd703

Detailed instructions are provided by the Sponsor, see "*Instructions for tumor lesion selection for LOAd703 injections and effect evaluation*" in the Investigator Site File.

Selection of Tumor Lesion

The Investigator and the radiologist assess together which lesion(s) are suitable for direct or image guided injection. [redacted]

[redacted]

Administration

[redacted]

5.6.7 LOAd703 Unused Clinical Trial Supplies

All unused trial supplies of frozen LOAd703 will be returned to the Sponsor unless the Sponsor decides otherwise. [redacted]

5.6.8 LOAd703 Dose Modifications

[redacted]

5.6.9 LOAd703 Maximum Tolerated Dose (MTD)

The maximum tested and tolerated dose (MTD) for LOAd703 is defined as the highest safe dose tested in the study based on the BOIN assessment (see 10.0 STATISTICS).

5.6.10 LOAd703 Continuation of Treatment Post Study

The study drugs are not available for patients post study without approval by the Sponsor, the ethics committee (IEC/IRB), and by the relevant regulatory authorities. The patients will discuss with the physician the next steps for their cancer treatment.

5.7 Checkpoint Blockade Therapy with TECENTRIQ®/Atezolizumab

5.7.1 Atezolizumab Brief Description

[redacted]

[redacted]

5.7.2 Atezolizumab Packaging and Labeling

[redacted]

5.7.3 Atezolizumab Storage and Handling

[redacted]

5.7.4 Preparation of Atezolizumab Prior to Treatment

[redacted]

[redacted]

5.7.5 Administration of Atezolizumab

[redacted]

5.7.6 Atezolizumab Unused Clinical Trial Supplies

All unused trial supplies of atezolizumab will be returned to the Sponsor, unless the Sponsor decides otherwise. [redacted]

5.7.7 Atezolizumab Dose Modifications

Atezolizumab dose, dose modifications, and omissions will be instituted per standard practice (US: TECENTRIQ® Full Prescribing Information, [redacted], Sweden: SmPC/FASS for atezolizumab/TECENTRIQ®) and according to the continuation criteria (see 7.2.5 *Continuation Criteria*). Missed doses will not be made up in order to maintain adherence to the protocol schedule.

5.7.8 Continuation of Atezolizumab Treatment Post Study

The study drugs are not available for patients post study from Sponsor without approval from the Sponsor, the ethics committee (IEC/IRB), and by the relevant regulatory authorities. The patients will discuss with the physician the next steps for their cancer treatment.

5.8 Approved and Non-Approved Concomitant Treatment

Patients can receive full supportive care while on this study. [redacted]

Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment, and for 5 months after the final dose of atezolizumab and/or LOAd703.

Adenovirus-based vaccines (e.g., Vaxzevria, known as COVID-19 vaccine Astra Zeneca, J&J Covid-19 vaccine) are prohibited 3 months prior to initiation of study treatment, during treatment and 6 months after the final dose of LOAd703.

Need for palliative surgery as well as palliative local radiotherapy, e.g., for brain or bone metastasis, during the trial is accepted unless this prohibits tumor evaluation according to the RECIST-criteria.

5.9 Monitoring Subject Compliance

Since LOAd703 and/or atezolizumab will be administered by the study personnel, compliance with study drug administration will be ensured and documented in the eCRF. Patient compliance with concomitant medications and protocol-specified assessments will be recorded in the eCRF.

6.0 STUDY EVALUATIONS

[redacted] Imaging will be used at several time points to determine tumor size. Patients will undergo their final follow-up evaluation visit [redacted]

6.1 Schedule of Events

All study evaluations are summarized in *14.1 Appendix I: Schedule of Events*.

6.2 Screening

Before beginning the screening visit, the patient will be informed about the trial and sign informed consent whereupon the patient is enrolled in the trial. The patient will be evaluated for health status, pregnancy (if applicable) and tumor load (by appropriate radiological imaging). If the patient has been subjected to radiology examination within three weeks prior to registration, this imaging can be reused for evaluation at the discretion of the Investigator.

Also, if samples have been taken for routine analysis <7 days prior to screening, the results can be used for eligibility evaluation at the discretion of the Investigator.

If all of the inclusion criteria and none of the exclusion criteria are met, the patient is registered to participate in the trial.

6.3 Treatment Study Visits

Figure 1 and Appendix 1 (Schedule of Events) shows the treatment schedule and timing of the study visits. Patients will undergo 12 LOAd703 treatments (q3w) administered by i.t. injection until study [redacted]. Atezolizumab infusions (q3w) will continue during the study until progression or toxicity requires treatment discontinuation. On the day of the treatment [redacted].

The treatments are scheduled on any of the designated study week working days. If the treatments are delayed to the next week, then they must be omitted in order to adhere to the protocol schedule.

[redacted]

If both treatments are discontinued, a modified follow-up schedule will apply (see section *6.4 Evaluation,* Modified Follow-Up and *Final Follow-Up Visit*).

6.4 Evaluation, Modified Follow-Up and Final Follow-Up Visit

During evaluation visits, the patient will be evaluated for health status, toxicity, and treatment effect on tumor size (radiology exam). [redacted] The final follow-up visit is scheduled at study [redacted] (see Figure 1).

If both LOAd703 and atezolizumab are discontinued (i.e., off-treatment patient), the patient should still be followed up and participate in the evaluation visits according to the Modified Follow-Up schedule, unless consent is withdrawn as well. Modified follow-up: patients should complete visits until visits [redacted] (see Appendix *III: Modified Follow-Up Schedule*).

For off-treatment patients, the final follow-up visit can be scheduled earlier but [redacted], if possible.

If another treatment is initiated due to progressive disease or other reasons, the patient will only be followed for survival (see section *7.5.3 Survival Follow-Up*). The final clinical follow-up visit [redacted]) should then be scheduled to collect endpoint data [redacted] as close to the start of new treatment as possible.

If patients are prematurely withdrawn from the study (i.e., survival follow-up patients), they will be followed for a minimum [redacted] The final clinical follow-up visit should be scheduled as soon as possible to collect endpoint data prior to the patient's withdrawal, if possible. After the final evaluation visit, patients enter survival follow-up and date of death will still be collected (see *7.5.3 Survival Follow-Up*).

7.0 STUDY ASSESSMENTS

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

7.2 Safety Parameters

7.2.1 Demographics

At screening only:

-Age
-Gender
-Race

7.2.2 Body Measurements

At screening only:

-Height

At screening and final follow-up visit:

-Weight

7.2.3 Medical History/Patient History

At screening only:

-Prior and ongoing medical illness and conditions
-Baseline symptoms
-Date of melanoma diagnosis
-Melanoma TNM staging
-Listing of known genetic tumor markers
-Previous anti-tumor therapy (e.g., surgery, chemotherapy, radiotherapy, targeted therapy)
-Previous or ongoing smoker

7.2.4 Physical Exam

-Physical assessment [redacted]). The physical assessment includes, but is not limited to, assessment of head/neck, chest/lungs, skin, abdomen, lymph nodes and the cardiovascular system. Other assessments should be added as applicable. The outcome will be recorded as "normal" or "abnormal". Abnormal findings will be assessed as "clinically significant" or "not clinically significant".

7.2.5 Continuation Criteria

Within -2 days prior to each LOAd703 and/or atezolizumab treatment ([redacted]), the Investigator will meet with the patient to confirm that he/she is eligible to continue treatment by reviewing:

- laboratory values
- No AEs/SAEs/DLTs have occurred that require dose reduction or discontinuation of treatment (see sections *5.5 Dose Limiting Toxicity (DLT), 5.6.8 LOAd703 Dose Modifications,* and *5.7.7 Atezolizumab Dose Modifications*). Note that additional treatments are not allowed if an ongoing related AE is still grade 3 or higher.
- No withdrawal criteria are fulfilled (see section *4.4 Withdrawal of Patients*).
- ECOG
- The patient is fit to receive another injection, in the opinion of the Investigator.

[redacted]

7.2.6 Vital Signs

At [redacted] and final follow-up visit: Blood pressure and pulse will be noted.

<u>Following LOAd703 treatments:</u> [redacted]

<u>Following atezolizumab treatments:</u> [redacted]

[redacted]

7.2.7 ECOG Performance Status

Assessed according to the ECOG score (14.2 *Appendix II: ECOG Performance Status*) at [redacted]. If treatments are discontinued, ECOG score will still be evaluated at all scheduled visits up to [redacted] (*14.3 Appendix III: Modified Follow-Up Schedule*).

7.2.8 Pregnancy Test

Urine or serum pregnancy test for females of childbearing potential is to be completed at [redacted].

7.2.9 12-Lead ECG

A 12-lead ECG will be performed after 5 minutes rest at [redacted], and the results will be judged clinically normal or abnormal by the Investigator. Any abnormality will be explained in the eCRF.

7.2.10 Blood Chemistry

[redacted]

However, if samples have been taken for routine analysis <7 days prior to screening, the results can be used for eligibility evaluation at the discretion of the Investigator, without need of subject the patients for new sampling for this reason.

If treatments are discontinued, samples should still be collected at all scheduled visits up to [redacted], and thereafter at the evaluation visits [redacted] (see *14.3 Appendix III: Modified Follow-Up Schedule*).

Blood samples are collected prior to the initiation of pre-medications or treatments according to local hospital routines and sent to the local laboratory for analyses.

[redacted]

7.2.11 Hematology

[redacted]

However, if samples have been taken for routine analysis <7 days prior to screening, the results can be used for eligibility evaluation at the discretion of the Investigator, without need of subject the patients for new sampling for this reason.

If treatments are discontinued, sampling should still be collected at all scheduled visits up to [redacted], and thereafter at the evaluation visits [redacted] (see *14.3 Appendix III: Modified Follow-Up Schedule*).

Blood samples are collected prior to the initiation of pre-medications or treatments according to local hospital routines and sent to the local laboratory for analyses.

7.2.12 Concomitant Medications

Concomitant medication includes ongoing medications/therapies, including contraception, at screening as well as between screening and the final follow-up visit.
Concomitant medication should be documented in the concomitant medication section in the eCRF with the generic name, dose, unit, route, frequency of administration, indication (referencing medical history or AE number), as well as start date (if started <2 weeks before screening) and stop date. At any subsequent visits, changes in dose and/or schedule for ongoing medications and new concomitant medications should be recorded, excluding LOAd703 and atezolizumab, which will be registered in the study treatment section of the eCRF. The eCRF is updated at every study visit.

For information about approved and non-approved concomitant medications, see section *5.8 Approved and Non-Approved Concomitant Treatment.*

Women of childbearing potential (i.e. not surgically sterile or had the last menstruation less than 1 year ago) that are study patients or partners to male study patients, should use one of these highly effective contraceptive methods during study treatment:

- combined (estrogen- and progesterone-containing)
- hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomized partner
- abstinence of heterosexual intercourse during the entire study period (depending on the preferred and usual lifestyle of the subject).

[redacted]

Male study patients should use condoms during intercourse during study participation and make sure that his partner, if woman of childbearing potential, use the adequate contraceptives.

7.2.13 Adverse Events (AE) Monitoring

AEs will be monitored continuously during the trial and AE data will be collected regardless of seriousness or causality. See section *9.0 Adverse Events (AE)* regarding AE reporting.

[redacted]

[redacted]

[redacted]

7.5 Efficacy Assessments

Response and tumor progression will be determined for all patients receiving [redacted]. However, patients receiving [redacted]

7.5.1 Tumor Size

Tumor size will be determined using a suitable imaging technique, depending on the localization of the tumor. Computer tomography (CT) will preferably be selected. Radiology exams will be performed every 9th week (±1 week) post-treatment initiation (i.e., [redacted]). However, at screening, if the patient has been subjected to radiology examination within 3 weeks prior to registration, this imaging can be used as baseline at the discretion of the Investigator. Definitions of measurable disease and response to treatment will follow RECIST 1.1 criteria. For research purposes, other methods such as immune-related (ir) RECIST may be compared to the RECIST v1.1 outcome. Further, a study-specific tumor evaluation will also be performed (see "*Instructions for lesion selection and effect evaluation"* provided by the Sponsor in the Investigator Site File).

Definition of Measurable Disease

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (irrespective of scanner type), 10 mm caliper measurement by clinical exam (when superficial), or 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).

PET

In addition to CT/MRI imaging, position emission tomography (PET) may be performed as a part of tumor assessment, at the discretion of the Investigator. If PET is used, the measures are documented according to the EORTC assessment. The PET evaluation will be exploratory.

7.5.2 Tumor Markers

Tumor-specific genetic markers such as BRAF mutation or mutations in DNA repair (i.e., mismatch repair-deficient cancers) will be listed if available during [redacted]. Otherwise, the tumor biopsy ([redacted] can be used for analysis. Genetic analysis of the biopsy within the study is done via the Research Laboratory, if applicable or send for analysis within Sweden and EU or third country (US, UK). After the analysis, sample will be destroyed or returned to the biobank.

7.5.3 Survival Follow-Up

After the final clinical follow-up visit at the clinic, overall survival (OS) will be recorded [redacted]. OS will be collected until the trial is closed, i.e until LPLV. OS may be collected via medical records (Sweden, US) or by telephone/email (US) from the Investigator or research nurse/research coordinator to the patient and will consist only of questions regarding the patient's health. If the patient is initiating another anti-cancer treatment, the treatment will be documented if the information is available, since it may affect the OS. The day of death will be documented.

8.0 Response Criteria

8.1 RECIST

The tumor response will be evaluated using an appropriate imaging technique, depending on the localization of the tumor. Tumor regression or progression will be evaluated according to RECIST v1.1 criteria.

Complete Response (CR)

Complete macroscopic disappearance of all tumors.

Partial Response (PR)

A reduction of at least 30% in the sum of all tumor diameters from baseline.

Stable Disease (SD)

Neither PR nor progressive disease.

Progressive Disease (PD)

At least a 20% increase in the sum of all tumor diameters from the smallest tumor size and/or the appearance of new tumor lesion(s).

Confirmation of Progression: Due to the potential immunostimulatory capacity of the study treatments, it is possible that the induced immune stimulation may induce an inflammatory swelling of the tumor that initially may be mistaken for progression. Therefore, PD during study participation leading to discontinuation of repeated treatment needs to be confirmed by radiological imaging at a later time point (within 4-12 weeks) and/or by a biopsy and/or tumor serum marker to confirm tumor progression.

Mixed Response (MR)

One or more lesions fulfilling the criteria for PR and other(s) for PD.

Clinical Benefit Rate (CBR)

CBR is defined as MR or better.

Overall Response Rate (ORR)

ORR is defined as PR plus CR.

[redacted]

8.2 OS, TTP and PFS

Time-to-Tumor Progression (TTP)

TTP is the time from start of treatment to disease progression.

Progression-Free Survival (PFS)

PFS is the time from start of the treatment to progression or death.

Overall Survival (OS)

OS is defined as the time from the start of treatment to death due to any cause.

9.0 Adverse Events (AE)

Reference safety information (RSI) for LOAd703 and atezolizumab is listed in the Investigator's Brochure for each study drug. **Note** that both LOAd703 and atezolizumab are regarded as experimental drugs within this protocol and safety evaluation including attribution needs to carefully be considered for both agents.

9.1 Definitions

9.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence that does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable, unintended clinical sign, symptom, disease or clinically relevant change in laboratory variables or clinical tests temporally associated with the use of an investigational product, whether or not considered related to the investigation product, that requires clinical intervention or further investigation (beyond ordering a repeat/confirmatory test). Injury or accidents, medical conditions for operations that are not pre-planned, or deterioration of the concurrent illness are also considered as AEs.

9.1.2 Serious Adverse Event (SAE)

A serious adverse event is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (i.e., the patient was at risk of dying at the time of the event. It does not refer to an event that hypothetically may have caused death if it was more severe).
- Requires in-patient hospitalization or prolongation of existing hospitalization excluding that for pain management, disease staging/re-staging procedures, prolonged monitoring for possible AE, or catheter placement unless associated with other serious events.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based on appropriate

medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

The term "severe" is often used to describe the intensity (severity) of an event, even if the event itself may be of relatively minor medical significance (e.g., a severe headache). This is not the same as "serious" which is based on patient/event outcome or action criteria usually associated with events that pose a threat to the patient's life.

Planned or elective hospitalizations (e.g., for administration of protocol therapy) and the hospitalization *per se* should not be considered SAEs. However, should an adverse event occur during this planned or elective hospitalization due to the administration of protocol therapy, it will be regarded as an AE, unless the severity of the event would justify hospitalization, if the patient was not already hospitalized.

9.1.3 Suspected Unexpected Serious Adverse Reactions (SUSAR)

An unexpected adverse event is defined as any adverse drug experience where there is evidence to suggest a causal relationship, the specificity or severity of which is not consistent with the Reference Safety Information (RSI) in the current LOAd703 and/or atezolizumab IBs.

Unexpected, as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the IB) as opposed to the adverse drug experience not being anticipated from the pharmacological properties of the pharmaceutical product.

9.1.4 Serious Adverse Reactions (SAR)

A serious adverse reaction (SAR) is any AE for which there is evidence to suggest a causal relationship (reasonable possibility) between the study drug and the AE. By definition, all SARs are AEs, nevertheless, not all AEs are SARs. Both LOAd703 and atezolizumab are regarded as study drugs in this study.

9.1.5 Non-Serious Adverse Event

All AEs not fulfilling the previous definitions are classified as non-serious.

9.2 Evaluating and Documenting Adverse Events (AE)

AEs are graded in the study according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (refer to http://ctep.cancer.gov). All AEs (except for grade 1 and 2 laboratory abnormalities that do not require an intervention) are to be recorded on the AE page in the eCRF and source documentation.

During [redacted], the Investigator will note the occurrence and nature of each patient's existing medical condition(s). Occurrence and nature of AEs (including lab events) directly observed by the study personnel or spontaneously reported by the patient during the study will be reported. Each patient will be asked about AEs at each visit after the first dose of the investigational products LOAd703 and/or atezolizumab.

The general AE reporting period for this trial begins upon receiving the first LOAd703 and/or atezolizumab treatment and continues until final clinical follow-up visit at [redacted]

If both study treatments are prematurely discontinued, AEs should be recorded [redacted] see *4.4.1 Off-treatment patient*).

If patients are prematurely withdrawn from the study and enter survival follow-up (i.e., survival follow-up patients),they will be followed for a minimum [redacted]

[redacted] (see *4.4.2 Survival follow up patient*).

If a patient experiences an AE after signing the informed consent, but before treatment is started, the event will be recorded as an existing medical condition unless the Investigator believes that the event may have causal relationship to a study-specific procedure described in the protocol. If LOAd703 and/or atezolizumab have been administrated when an AE occurs, its relationship to the study drugs will be judged by the Investigator.

9.2.1 Severity Grading

The Investigator must determine the intensity of any AEs according to the NCI CTCAE Version 5.0 (see http://ctep.cancer.gov) and the causal relationship. Those AEs not covered by these criteria will be graded as follows:

1. Mild: Discomfort noticed, but no disruption of normal daily activity. Prescription drug not ordinarily needed for relief of the symptom but may be given because of the patient's personality/character.

2. Moderate: Discomfort sufficient enough to reduce or affect normal daily activity. Patient is able to continue in the study; treatment for the symptom may be needed.

3. Severe: Incapacitating, severe discomfort with inability to work or to perform normal daily activity. Severity may cause cessation of treatment with test drug; treatment for symptom may be given and/or patient hospitalized.

4. Life-threatening: Symptom(s) place the patient at immediate risk of death from the reaction as it occurred; does not include a reaction that, had it occurred in a more serious form, might have caused death.

5. Fatal: Event caused the death of the patient.

9.2.2 Attribution Definitions

The Investigator will attempt to assess the relationship of the event to the study drugs separately. An AE is considered to be associated with the use of any or both of the investigational products if the attribution is determined as possible, probable or definite. Attribution of AEs will be recorded in the CRF as:

- Unrelated: The AE is clearly NOT related to LOAd703 (or atezolizumab).
- Unlikely: The AE is doubtfully related to LOAd703 (or atezolizumab).
- Possible: The AE may be related to LOAd703 (or atezolizumab).
- Probable: The AE is likely related to LOAd703 (or atezolizumab).
- Definite: The AE is clearly related to LOAd703 (or atezolizumab).

Attribution will be specified for LOAd703, atezolizumab, treatment procedure (i.e., intratumoral injection and/or intravenous infusion), disease or other.

9.2.3 Duration of Event

The date of onset (and time if relevant), change of severity and the duration of the AE (i.e., date of resolution) will be recorded. Events that are ongoing at the time the patient completes follow-up will be documented as ongoing.

9.2.4 Action(s) Taken Regarding the Study Drugs

The method used to treat the AE, specifically any action taken with the study drugs, should be recorded. This includes, but is not limited to e.g., "dose reduced" or "discontinued".

9.3 Reporting Serious Adverse Events (SAE), Deaths, Unexpected AEs and DLTs

9.3.1 Reporting to Sponsor

AEs classified as serious require expeditious handling and reporting to the CRO as the Sponsor's representative, to comply with regulatory requirements. The Sponsor and its designees must be notified immediately (within 24 hours of becoming aware of the event) by email or telephone. Notification by email is preferred. The email and telephone numbers listed below may be used.

Initial notification via telephone or email does not obviate the need for the Investigator to provide a completed SAE form/eCRF entry within the designated reporting time frames.

[redacted]

The completed Serious Adverse Event Report Forms are submitted by email to [redacted] within 24 hours of becoming aware of the event.

The SAE form and detailed instructions describing the procedure for reporting SAEs are found in the Investigator's Site File.

[redacted]

Email: [redacted]
Phone: please see the Investigator Site File

9.3.2 Safety Report – Reporting by Sponsor

The Sponsor is responsible for submitting safety reports to the relevant regulatory authorities and ethics committees of any Suspected, Unexpected Serious Adverse Reactions (SUSARs). A SUSAR that is fatal or life-threatening should be reported as soon as possible, not later than 7 calendar days after the Sponsor becomes aware of the SUSAR, and with a follow-up report within another 8 days. Any other SUSARs should be reported within 15 days.

9.3.2.1 MPA/EMA Safety Report (EU)

The Sponsor is responsible for submitting safety reports to the MPA/EMA and IEC and this will be delegated to the CRO. A SUSAR that is fatal or life-threatening should be reported as soon as possible, not later than 7 calendar days after the Sponsor becomes aware of the SUSAR, and with a follow-up report within another 8 days. Any other SUSARs should be reported within 15 days.

SAEs that do not require expedited reporting should be listed together with SUSARs in the annual drug safety update report (DSUR), written by the Sponsor and submitted to the relevant regulatory authorities and ethics committees according to current legislation.

9.3.2.2 IND Safety Report (US)

Under Title 21 Code of Federal Regulation (CFR) Part 312.32, the Sponsor (or designee) is required to notify the FDA ([redacted]) and all participating Investigators (i.e., all Investigators to whom the Sponsor is providing drug under its IND or under any Investigator's IND) of any of the following:

Any SAR, that is both serious and unexpected, and if there is evidence to suggest a causal relationship between the study drug and the event, such as:

- A single occurrence of an event that is uncommon and known to be drug related.
- One or more occurrences of an event that is not commonly associated with the drug but is otherwise uncommon in the population exposed to the drug.
- An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug-treatment group than in a concurrent or historical control group.

In addition, the Sponsor must report the following:

- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the Sponsor, that suggest a significant risk in humans exposed to the drug.
- Any findings from laboratory animals or *in vitro* testing, whether or not conducted by the Sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure dose.
- Any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or IB.

SAEs that do not require expedited reporting should be listed together with SUSARs in the annual DSUR, written by the Sponsor and submitted to the relevant regulatory authorities and ethics committees according to current legislation.

9.3.3 Reporting to IEC/IRB

Investigators must report SAEs and AEs to his/her IRB or IEC per institutional guidelines and/or other applicable guidelines.

9.3.4 Procedures in Case of Medical Emergency

The Investigator should ensure that the necessary procedures and expertise are available to cope with any emergencies during the study.

If an emergency occurs, please notify [redacted]

Email: [redacted]
Phone: please see the Investigator Site File

[redacted]

[redacted]

9.5 Handling of Pregnancy

Any pregnancy diagnosed during the study participation must be reported immediately to the Sponsor. Women of childbearing potential and male with a partner of child bearing potential, will be thoroughly informed about contraceptive medication (see section 7.2.12 *Concomitant Medications*) before trial participation and to immediately inform the Investigator if pregnancy should occur during study participation. Pregnancy, in and of itself, is not regarded as an AE, unless there is suspicion that study medication may have interfered with the effectiveness of a contraceptive medication. If the patient becomes pregnant while participating in the study, the study drugs should be immediately discontinued. Pregnancy information about a female patient or a female partner of a male patient should be reported immediately from the time the Investigator first becomes aware of a pregnancy or its outcome. This will be performed by the Investigator by completing a Pregnancy Form.

Any pregnancy complication, spontaneous abortion, elective termination of a pregnancy for medical reasons, outcome of stillbirth, congenital anomaly/birth defect, or SAE in the mother will be recorded as an SAE and reported.

10.0 STATISTICS

10.1 Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be prepared as a separate document and will include a more technical and detailed description (including templates for Tables, Listings, and Figures) of the planned statistical summaries regarding safety and effect evaluation. The SAP will be finalized before initiating any statistical analysis. Unless otherwise stated, tabulation of summary statistics and data analysis will be performed using SAS® Version 9 or later.

Statistical Methods

Statistics will be displayed for response evaluation for the patients treated at MTD.

[redacted]

Demographic and efficacy analyses will be carried out using all toxicity and response evaluable patients.

Patient disposition, including reason for withdrawal, will be summarized by dose group.

Demographics and disease baseline characteristics, pregnancy test results, medical history and prior medications will be tabulated.

10.2 Sample Size

10.2.1 Safety

[redacted]

The study will be conducted using a Bayesian Optimal Interval (BOIN) design with a target DLT rate of 0.3.[39] This design has algorithmic escalation/de-escalation rules like a traditional 3+3 design but allows for specification of the target DLT rate and expanded accrual beyond N=6 with continued consistent toxicity monitoring (i.e., the assessment of DLT rate continues throughout the study which gives a well-defined safety evaluation of Phase I/II studies).

Two LOAd703 dose levels will be tested together with a fixed dose of atezolizumab. The BOIN design allows for enrollment of 3 patients in a cohort and the number of patients with DLT determines whether additional patients are treated with the current dose or if the dose is decreased or increased. In general, we will escalate the dose if the observed toxicity rate at the current dose is <= 0.2365, and we will de-escalate the dose if the observed toxicity rate at the current dose is >= 0.3585. If the observed toxicity rate is between 0.2365 and 0.3585, 3 additional patients will be treated at the current dose. For cohorts of size 3, the decision boundaries are shown in Table 3.

Additional cohorts will be added in the unlikely event that more than N=25 participants at a single dose level are needed.

Table 2. DLT Regulation of Dose Escalation

Number of Patients treated in a Defined Dose Cohort	3	6	9	12	15	18	21	24	25
Escalate dose if number of DLT≤	0	1	2	2	3	4	4	5	5
Treat additional 3 patients at current dose if number of DLT=	1	2	3	3,4	4,5	5,6	5-7	6-8	6-8
De-escalate dose if number of DLT≥*	2	3	4	5	6	7	8	9	9
Eliminate** dose level and all higher doses from further use if number of DLT≥	3	4	5	7	8	9	10	11	12

* At the lowest dose level, if the recommendation is to de-escalate AND the dose level has not been eliminated from consideration, 3 additional patients can be accrued at the same dose level; otherwise the trial will be stopped.
** Note that if the DLT level reach the elimination limit, this dose level is abandoned from the study independently of DLT events at lower dose levels[39].

10.2.2 Effect

[redacted]

[redacted]

10.3 Safety Reporting

Summary statistics will be presented descriptively for the following safety endpoints by dose group:

- Adverse Events - the number of adverse events, the proportion of patients having at least one adverse event and adverse events by MedDRA® coded terms will be presented.
- Serious Adverse Events - the number of serious adverse events, the proportion of patients having at least one serious adverse event and serious adverse events by coded terms will be presented.
- Related Adverse Events - the number of related adverse events to LOAd703 or atezolizumab, the proportion of patients having at least one related adverse event and related adverse events by coded terms will be presented separately and pooled.

Note: Only treatment emergent AEs (commencing after exposure to study medication) will be included in the AE summaries. Non-treatment emergent events (starting prior to exposure to study medication) will be included in the patient listings and not included in the above summaries.

- Clinical Laboratory Evaluation values [redacted].

Note: Values outside normal ranges will be flagged in the individual patient listings.

- Results of quantitative and qualitative evaluations for urinalysis will be presented in a similar way as the laboratory parameters.
- Vital sign parameters [redacted]
- ECOG [redacted]

10.4 Efficacy Reporting

[redacted]

For the variables of progression-free survival (PFS), time-to-progression (TTP) and overall survival (OS), Kaplan-Meier curves and estimates including medians and 95% CIs will be provided.

[redacted]

[redacted]

11.0 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Direct Access to Source Data/Documents

The Investigator(s)/institution(s) will permit study-related monitoring, audits, review and regulatory inspection(s) and will provide access to source data/hospital records. The Sponsor verifies that each patient has consented in writing to grant access to the original source data/hospital records by means of the written patient information and signed informed consent.

During monitoring, the data recorded in the CRFs by the Investigator or designee will be checked for consistency with the source data/hospital records by the Monitor (i.e., source data verification). Any data discrepancies will be documented and explained in the monitoring reports.

11.2 Source Data

The requirements for the information contained in the patient's medical records corresponds to the requirements of the "Patientdatalagen" (SFS 2008:355), "The Medical Product Agency's regulations on clinical trials of medicinal products for human use" (LVFS 2011:19), and Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508 which means that in addition to information that is pertinent to the care and well-being of the patient, the following minimum study-specific information must be recorded:

- Date when patient information was given and when signed informed consent was obtained
- Patient study number
- The name of the study, EudraCT /IND/NCT number and short study description
- Fulfilment of inclusion criteria
- Diagnosis
- Dates of all visits during the study period
- Any information relating to AEs
- All treatments and medications prescribed/administered (including dosage)
- Date of study termination

For information that is study specific and of no interest to the medical care of the patient, other documents may be considered as source data. Prior to study start, the site Principal Investigator/study nurse/coordinator and the Monitor must identify and document the expected location of the source data (e.g., medical record notes, laboratory reports, etc.). This will be done by completing a site-specific source data verification log (Origin of Source Data). The site must clearly communicate any deviation from the expected source data location to the Monitor.

11.3 Monitoring

In accordance with the principles of Good Clinical Practice (GCP), the Sponsor is responsible that the trial is adequately monitored. In this study, the CRO will be responsible for monitoring activities on behalf of the Sponsor. During the study, the Monitor will have regular contacts with the study site, including monitoring visits to ensure that the study is conducted and documented properly in compliance with the protocol, GCP and applicable regulatory requirements.

The Monitor will ensure that accountability of investigational products is performed and will review source documents to verify consistency with the data recorded in the CRFs. All patients that have performed any study-specific assessments will be monitored for signed informed consent and all patients that have received study drug will be monitored for date of study visits, inclusion/exclusion criteria and AE/SAE.

The Monitor will also check the Investigator Site File and provide information and support to the Investigator(s). The extent of monitoring will be described in a monitoring plan, which will be approved by the Sponsor.

The study site may be subject to quality assurance audit(s) by the Sponsor as well as inspection by regulatory authorities. The Investigator and other responsible personnel must be available during the monitoring visits, audits and inspections and should devote sufficient time to these processes.

For investigational sites in the EU: All site Principal Investigators should provide a curriculum vitae (CV) to the CRO to be responsible for the study. All Sub-Investigators and other responsible personnel should be listed on the delegation list, together with their study responsibilities, and provide their CVs to the CRO. GCP certificates for the Principal Investigator and all study team members on the delegation log must be provided.

For investigational sites in the US: All site Principal Investigators will be required to provide a current signed and dated CV, medical license, proof of human subject research protections training, a completed FDA Form 1572 (required in the US) and a financial disclosure statement (required in the US) to the CRO. All Sub-Investigators will be required to provide a current NIH biosketch or CV, medical license, proof of human subject research protections training and a financial disclosure statement (required in the US) to the CRO. GCP certificates for the Principal Investigator and all study team members on the delegation log must be provided.

12.0 ETHICS

12.1 Protocol Modifications

No modification of the protocol should be implemented without the prior written approval of the Sponsor. Any such changes, which may affect a patient's treatment or informed consent, especially those increasing potential risks or scientific quality of the study, must receive prior approval by the relevant regulatory authorities/ethics committees before implementation. The exception to this is where modifications are necessary to eliminate an immediate hazard to trial subjects, or when the change involves only logistical or administrative aspects of the trial (e.g., change in Monitor or telephone number). Other administrative revisions, which may impact the clinical portion of the study, will be duly reported to the regulatory authority by the Sponsor and/or ethics committee by

the site Principal Investigator, or designee, under the guidance of the CRO and with the approval of the Sponsor.

12.2 Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

It is the responsibility of the site Principal Investigator to obtain approval of the study protocol, protocol amendments, patient information and informed consent from the relevant IEC/IRB before enrollment of any subject into the study.

The Sponsor or designees shall report all SUSARs to the IEC/MPA. If a study stops prematurely at a study center for any reason, the IEC must be informed. At the end of the study, the Sponsor/site Principal Investigator should notify the IEC.

The Sponsor/site Principal Investigator should file all correspondence with the relevant IEC/IRB and provide the other party with copies.

12.3 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, applicable regulatory requirements, GCP, and the ethical principles of the latest version of the Declaration of Helsinki.

12.4 Patient Information and Informed Consent

It is the responsibility of the Investigator to provide each subject with full and adequate verbal and written information about the objectives, procedures and possible risks and benefits of the study. All subjects should be given the opportunity to ask questions about the study and should be given sufficient time to decide whether or not to participate in the study. The written patient information must not be changed without prior discussion with the Sponsor.

The subjects will be notified of their voluntary participation and of their freedom to withdraw from the study at any time and without giving any particular reason. Subjects must also be informed that withdrawing from the study will not affect their future medical care, treatment or benefits to which the subject is otherwise entitled.

The Investigator is responsible for obtaining written informed consent from all subjects (or their legally acceptable representatives and/or witnesses, where applicable) prior to enrollment in the study.

Upon signing informed consent, the subject consents to:

- Participating in the study.
- Allowing personnel connected with the Sponsor or regulatory authorities to gain full access to hospital records to check study data.
- Recording, collection, processing and storing of data in a database.
- Possible transfer of study information to countries outside of the European Union (EU)/United States (US).
- Storing of study samples in a biobank when required (i.e., European sites require a biobank).

It should be clearly stated that the data will not identify any subject taking part in the study, in accordance with the national guidelines for handling personal data.

The Investigator who gave the verbal and written information to the subject shall sign and date the informed consent form. A copy of the patient information and the informed consent form should be given to the subject. The Investigator should file the signed informed consent forms in the Investigator Site File for possible future audits and inspections. The Investigator Site File shall be archived according to the applicable regulations.

13.0 DATA MANAGEMENT

13.1 Data Management

The CRO is responsible for Data Management and will write a study-specific Data Management Plan (DMP) where further details will be specified. All data will be recorded in electronic CRFs (eCRFs). The Investigator is responsible for ensuring the accuracy, completeness and legibility of the data reported in the eCRFs, and this will be checked by the Monitor.

13.1.1 Data Entry and Data Validation

Data will be entered into the study eCRF and will be subject to both logical computerized checks and manual validation checks against listings in accordance with the study-specific DMP. All inconsistencies detected during these procedures will be resolved through electronic Data Clarification Forms (DCFs) in the eCRF, issued to the Monitor or investigational site personnel.

13.1.2 Database Closure

When all patients have been completed, all data have been entered into the eCRF database, all coding is done and approved, and all queries are solved, the Database Closure procedures will begin. Decisions will be made on how to classify patients into analysis populations, and how to handle protocol violations and deviating or missing data. All decisions will be dated and documented in a Database Closure document. After finalization of the Database Closure document, the database will be locked. Any changes in the database thereafter will be documented.

13.2 Electronic Case Report Forms (eCRFs)

The Investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the eCRFs. An eCRF is required and should be completed for each included subject on a visit-by-visit basis. The eCRF should be completed, monitored and corrected (if needed) within 6 months from the last visit of the study patient. The subject's identity must always remain confidential. All information in the eCRFs should be in English. If necessary, the Monitor should translate any information or comments recorded in other languages.

The completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties (except for authorized representatives of relevant regulatory authorities) without written permission from the Sponsor. All eCRF electronic files should be kept in the Sponsor's Trial Master File and a copy of all eCRFs electronic files should be kept in the Investigator Site File.

In this study, clinical data including AEs and concomitant medications will be entered into a 21 CFR Part 11-compliant eCRF [redacted]. The eCRF includes password protection, audit trails and internal quality checks, such as automatic range checks to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. Backups of the data are automatically performed on a regular basis. Backups are stored and encrypted on both magnetic and optical media in a separate physical location. This process guarantees the minimum data loss in the events of a disastrous failure.

13.3 Record Keeping

To enable audits and evaluations by the Sponsor and inspections by regulatory authorities, the Investigator shall keep records (essential documents) of the study for at least 10 years after final report. This includes any original source data related to the study, the subject identification list (with subject identification numbers, full names and addresses), original signed informed consent forms, copies of all eCRF-generated files and detailed records of the investigational product's disposition.

13.4 Study Report

The survival follow-up will continue until LPLV and the study is thereafter completed.

A full study report should be submitted to the regulatory authorities by the Sponsor within 12 months from the completion of the study. The site Principal Investigator and study site personnel must provide the necessary information by completing the eCRF for every patient no later than 3 weeks from the LPLV to allow for close-out activities such as monitoring and correction of the eCRFs if necessary.

13.5 Publication Policy

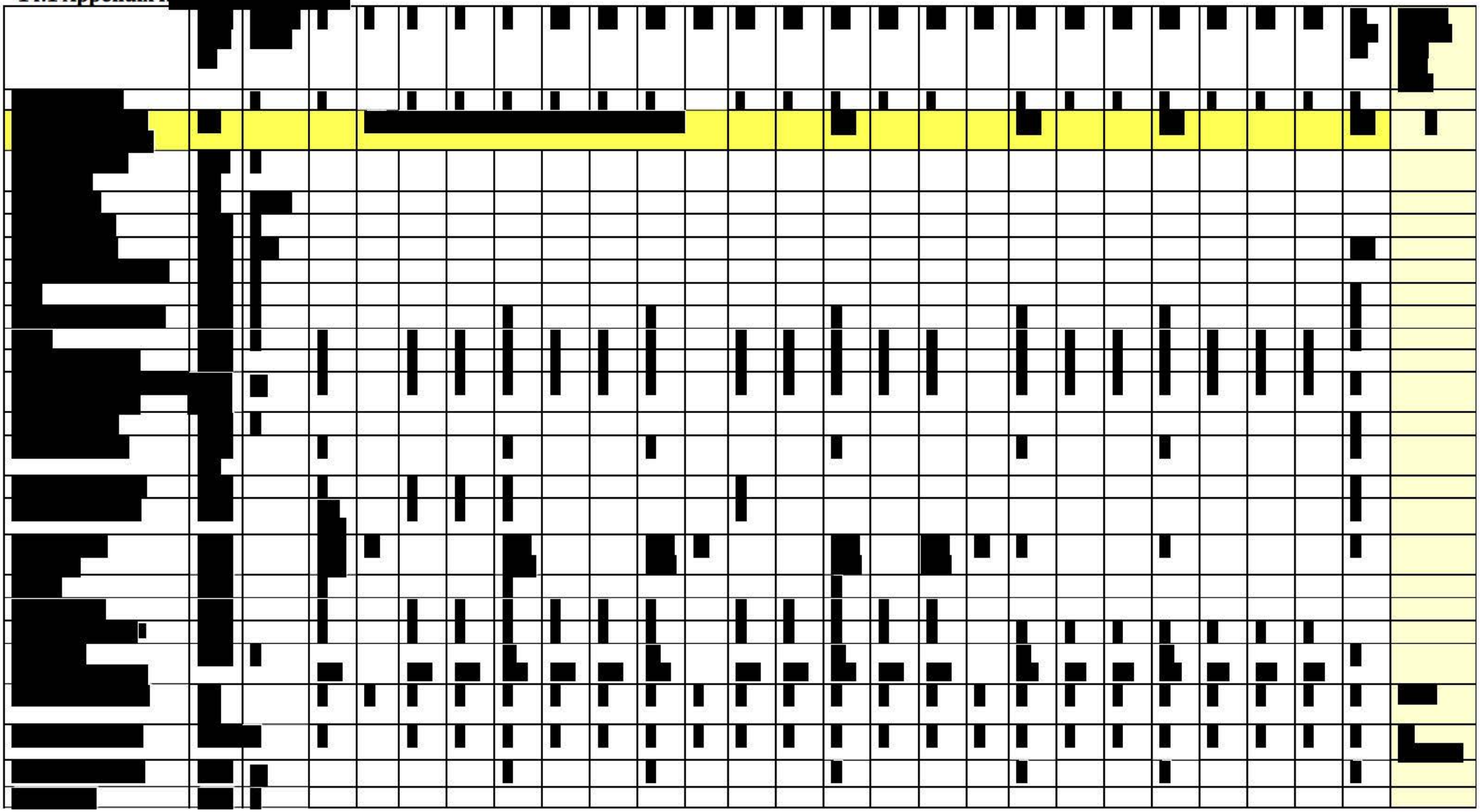
The investigation is considered as a collaboration between the clinical sites, Hoffmann LaRoche Ltd and the Sponsor. Publication ideas for manuscripts, abstracts or presentations will be jointly discussed and prepared. All manuscripts, abstracts or presentations (in outline form with copies of slides, if available) will be submitted to the Sponsor at least 30 days prior to the submission of the data for publication in order for the Sponsor to protect proprietary information. The Sponsor will review the submitted material within a reasonable period of time and will not unreasonably withhold publication permission. Investigators as well as employees or representatives of the Sponsor and Hoffmann LaRoche Ltd should be listed as co-authors in the event that they have provided scientific input into the study design, data interpretation, etc.

13.6 Insurance

Study patients enrolled in Sweden are covered by the Swedish Patient Insurance (LÖF) and the Swedish Pharmaceutical Insurance, [redacted]. Study patients enrolled in the US are insured by [redacted], held by Sponsor.

14.0 APPENDICES

14.1 Appendix I[redacted]



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