Phase I/II Trial Investigating an Immunostimulatory Oncolytic Adenovirus for Cancer

EudraCT: [redacted]

Sponsor Study ID: LOKON002

Version Nr: 5.1, 2022-12-21

Sponsor: Lokon Pharma AB

[redacted]

[redacted] CEO, PhD

Changes to the protocol

Version 1.2	The first version used in the clinic.
Version 2.0 Dated 2019-04-08	Substantial changes: • Platinum-resistance disease has been added to the definition of the ovarian cancer population (section 2.7.4 and 4.1) • Continuation criteria to consider when assessing the patient prior to next LOAD703 injection, has been added, (section 5.1, 5.2) • Follow-up of patients after injection has been extended: overnight stays, vital signs, (section 5.1, 5.2) • Information on immediate reactions to the LOAd703 [redacted], has been added (section 9.4.1 and 9.4.3). • The use of corticosteroids during study has been added to as the pre-medication list under certain conditions (section 5.11) • Information on DLT assessment and dose adjustments, has been added (section 4.4, 5.1, 5.6 and 5.7) • [redacted] Administrative changes: • Clarifications regarding logs, lists and documentation of the study have been added. • Collection of data for demographics, physical examination and vital signs, have been clarified. • Details on storage and handling of LOAd703 has been clarified • Time window for LOAd703 injections, administration of concomitant Chemotherapy, blood sampling, [redacted], assessment of patient pre-injection and radiological examinations, have been added. [redacted]. Schedule of events has been updated accordingly. • The severity assessments of AEs and the SAE reporting logistics have been clarified. • Withdrawal of patient from study vs from treatment, including follow-up for off-treatment patients, have been clarified. • Follow-up patient post study has been clarified. • Spelling/writing errors, referrals to other sections in the protocol/latest version of IB/updated laws, and clarification that CTCAE version 4.03 is used, have been added.
Version 3.0 Dated 2019-11-15	Substantial changes: • Exclusion criteria nr 4: "patients on warfarin (or other anti-coagulants) are not eligible" has been changed to not exclude patients on other anti-coagulants than warfarin since the hospital guidelines regarding such patients has been changed. They are now eligible for injections and biopsy and can therefore be enrolled in this trial. Synopsis, section 4.2 and 6.3 are updated accordingly. • [redacted] is included as a new site and the trial is therefore not single center but multi center. [redacted]

	[redacted]. Synopsis, 1.4-6, 1.10.2, 3.3, 4, 5.4,1, 5.4.3, 7.1.1, 12.2 and 14.5 are updated accordingly. Administrative changes: • Information on the previous clinical results have been updated (section 2.4) • We have clarified that the number of study patients are referring to evaluable patients and does not include screen failures or non-evaluable patients. The definitions for DLT evaluable and efficacy evaluable patients have been clarified (synopsis, section 3.3, 10.2.1, and 10.2.2). • Clarification that DLT reporting always will be reported to Sponsor in an expedited manor independently of seriousness (section 5.7, 9.2.1 and 9.3.1) • Clarification that the CT at baseline should not be older than 4 weeks at the time of 1st injection and that [redacted] (sections 5.3, 6.2 and 7.5.1) • Clarifications have been made for timing of vital signs and ECOG (section 5.1, 5.2, 7.2.4 and 7.2.5), blood sampling instructions (section 7.2.9 and 7.2.8) and biobanking (section 7.1.2) • Instructions have been changed to comply with the latest approved IB regarding LOAd703 handling (section 5.5.3 and 5.5.5) • Clarification on how to follow-up withdrawn or non-compliant patients (section 4.5 and 4.6) • The medicinal product is a genetically engineered organism (GMO) which can also be called genetically engineered microorganism (GMM). The sponsor has decided to only refer to the product as a GMO to avoid confusion. Sections 5.4.2 and 5.5.1 are adjusted accordingly.
Version 4.0 **2020-01-02**	Substantial amendment Sections 5.5.3 and 5.5.5 are modified to allow [redacted]
Version 5.0 **2021-12-06**	Substantial changes: • [redacted]

[redacted]

- Update regarding reporting of chemotherapy-induced bone marrow toxicities (section 9.2)

Administrative changes:

- Update of contact information (section 1)
- Update of information regarding the previous clinical studies with LOAd703 (section 2.4)
- Update of adverse event description and study rationale (section 2.6 and 2.8)
- Minor clarification regarding efficacy assessment (section 5.2 and 7.5)
- Clarification of the criteria for taking patients off treatment and regarding patients who have been taken off study (section 4.4, 4.5, 5.1, 5.2 and 5.6)
- Minor update regarding imaging for screening (section 5.1, Appendix I, Table II).
- Removal of the batch number since all approved batch numbers with detailed product specification are listed in the effective version of IMPD (section 5.5.1 and 5.5.2)
- Minor clarification regarding treatment of biliary cancer patients (section 5.10.3)
- [redacted]
- Correction of time point for collection of [redacted] to comply with the text in the laboratory manual (section 7.3.3, Appendix I, Table II: Schedule of events for Study Visits)
- Minor clarification regarding unexpected events (section 9.1.3)
- Clarification regarding SAE reporting to the Sponsor (section 9.3.1)
- [redacted]
- Minor correction regarding reporting period in case of pregnancy (section 9.5)

	• Clarification regarding monitoring of concomitant medications (section 7.2.10 and 11.3) • Update to patient information and informed consent form to allow for samples to be analysed outside Sweden (section 7.1.2, 7.5.2 and 12.3) • Minor clarification that paper CRF copies are filed in the Investigator Site File (section 14.1) • Correction in the Appendix I, Table II: Schedule of events for Study Visits : [redacted]
Version 5.1 2022-12-21	<u>Administrative changes:</u> • Updated contact information (section 1.3, 1.6). • Corrections to the text to comply with the previously approved protocol amendment no. 5.0 dated 2021-12-06 (section 2.8 and 5.10.2) • Minor clarifications of adverse events description and study rationale (section 9.2, 9.2.1, 9.2.3, 9.3.1) • Minor update regarding SUSAR reporting (section 9.3.2) • Clarification regarding reporting to IRBs (section 9.3.3) [redacted]

TABLE OF CONTENTS

[redacted]

[redacted]

INVESTIGATOR'S STATEMENT

1. I have carefully read this amended protocol entitled "Phase I/II Trial Investigating an Immunostimulatory Oncolytic Adenovirus for Cancer" 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 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: Phase I/II Trial Investigating an Immunostimulatory Oncolytic Adenovirus for Cancer

Investigational Product: LOAd703, an oncolytic adenovirus serotype 5/35 expressing human trimerized CD40L and 4-1BBL under a CMV promoter.

Study Design: Single arm, open-label, multi-center trial.

Phase I: 3+3 patients receive 8x LOAd703 injections at three dose levels ($5x10^{10}$ VP, $1x10^{11}$ VP, $5x10^{11}$ VP) during standard of care (SoC) or gemcitabine conditioning, 9 DLT evaluable patients.

Phase II [redacted]: Phase II [redacted] includes a total of 18 evaluable patients (colorectal, pancreatic, biliary and ovarian cancer) treated at the highest virus dose $5x10^{11}$ VP (MTD). [redacted]

[redacted]

[redacted] Up to 35 efficacy evaluable patients will be recruited [redacted].

Objectives: The primary objective is to determine the tolerability of increasing doses of LOAd703 intratumoral injections during SoC or added conditioning chemotherapy.

The secondary objective is to determine the effects of LOAd703 intratumoral injections during SoC or added conditioning chemotherapy.

Endpoints: Primary Endpoints

Phase I

1. Tolerability is determined by physical examination, hematological and clinical chemistry analysis using CTCAE v 4.03.

[redacted]

Phase II

1. Tolerability is determined by physical examination, hematological and clinical chemistry analysis using CTCAE v 4.03.

[redacted]

Secondary Endpoints

Phase I

[redacted]

3. Local and distant anti-tumoral effects assessed by appropriate imaging dependent on tumor localization and by monitoring tumor marker/s when available. Responses are judged accordingly to RECIST 1.1.
4. Effects evaluated as time to tumor progression (TTP), progression free survival (PFS) and overall survival (OS).

Phase II

1. Local and distant anti-tumoral effects on tumor assessed by appropriate imaging dependent on tumor localization and by monitoring tumor marker/s when available. Objective responses are measured using RECIST 1.1.
2. Effect evaluated as TTP, PFS and OS.

[redacted]

Eligibility:

Inclusion criteria

1. Have histologic or cytologic evidence of colorectal carcinoma (CRC), pancreatic carcinoma (PC), biliary cancer, or epithelial ovarian carcinoma (EOC which may encompass epithelial ovarian, fallopian tube or primary peritoneal carcinoma).
2. Have advanced disease, defined as cancer that is either metastatic or locally advanced, unresectable, and for which radiotherapy or other locoregional therapies are not considered treatment of choice but systemic chemotherapy or no therapy is planned.
3. Have one of the following treatment situations apply:

   a) Colorectal carcinoma (CRC) , [redacted]

      I. A patient with refractory or recurrent metastatic CRC who has either received all conventional therapy; or is entering a "resting" phase between reasonable conventional treatments.

      II. A patient who is amenable to treatment with LOAd703 plus gemcitabine as a single agent conditioning regimen.

b) Pancreatic cancer

I. A patient with either locally advanced, unresectable or metastatic disease who is eligible to receive first or second line of conventional treatment consisting of gemcitabine and/or nab-paclitaxel.

II. A patient who is amenable to treatment with LOAd703 as an "add-on" to standard-of-care gemcitabine-based or nab-paclitaxel-based regimens or gemcitabine or nab-paclitaxel as single agents.

c. Biliary cancer, [redacted]

I. A patient with either locally advanced unresectable or metastatic biliary cancer who is either treatment-naïve or has received any number of lines of treatment.

II. Patient who is amenable to treatment with LOAd703 as an "add-on" to standard-of-care treatment consisting of gemcitabine combined with other agents (e.g. gemcitabine/low-dose cisplatin, gemcitabine/oxaliplatin, etc) in the first line setting or gemcitabine in a combination regimen or as a single agent in latter lines of treatment.

d. Ovarian Cancer

I. A patient with either epithelial ovarian, fallopian tube or primary peritoneal carcinoma.

II. The patient has either:

~~i) Residual disease following first line standard of care combination chemotherapy.~~

ii) Platinum-sensitive relapse (platinum free interval ≥6 months) and have previously received at least one line of chemotherapy and not eligible for PARP-inhibitor maintenance after chemotherapy.

iii) Platinum-resistant relapse (platinum free interval < 6 months), who have not received more than two lines of appropriate standard of care and not eligible for bevacizumab. Maintenance treatment does not count as a line of therapy.

iv) The patient has received appropriate therapy with PARP inhibitors if eligible.

III. Amenable to treatment with LOAd703 as an "add-on" to standard-of-care (excluding bevacizumab) as described in 5.10.4

4. Have a disease burden that is considered low (i.e. **low tumor burden**), which is defined on a patient-by-patient basis as per Principal Investigator's discretion. A rough guideline for defining low tumor

burden is that the sum of the product of the bidimensional measurements for all lesions is ≤ 70 cm^2.

5. Have a measurable disease by standard imaging techniques per RECIST criteria. Measurable lesions must be outside of any prior radiation field(s), unless disease progression has been documented at that disease site subsequent to radiation.
6. At least one non-irradiated (or irradiated but disease progression documented at the site subsequent to radiation) lesion must be suitable for image-guided intratumoral injection and needle biopsy.
7. Be medically suited to sedation if required during intratumoral injections.
8. Be at least 18 years-old.
9. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2.
10. Have no remaining acute toxic effects from previous anticancer therapy > grade 1, except for any grade of alopecia.
11. Have adequate baseline organ/hematological function, as demonstrated by the following:

a) Absolute neutrophil count (ANC) ≥1.0 x 10^9/l
b) Hemoglobin ≥90 g/l
c) Platelet count ≥ 100 x 10^9/l
d) Bilirubin < 1.5 times the institutional upper limit of normal (ULN)
e) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 (3, if liver metastases are present) times the institutional ULN.
f) Serum creatinine <2 times the institutional ULN or calculated creatinine clearance ≥35 mL/min
g) Prothrombin (INR)≤1.5 or prothrombin time (PT) ≤1.5 ULN; and either partial thromboplastin time or activated partial thromboplastin time (PTT or aPTT) ≤ 1.5 times the ULN.

12. The patient must understand and be willing to provide written informed consent.

Exclusion criteria

1. Any concurrent treatment that would compromise the study including but not limited to continuous high dose corticosteroids (>0.5mg/kg), lymphodepleting antibodies or cytotoxic agents.
2. Treatment with high dose immune inhibitors including lymphotoxic monoclonal antibodies such as alemtuzumab (Campath®), or sirolimus (Rapamune®) and its analogs, biological therapy, cytotoxic agents or any investigational agents within 21 days of registration.
3. Ovarian carcinoma patients should not be eligible to PARP inhibitor treatment.
4. Patients on warfarin are not eligible.
5. Women who are pregnant, lactating, or planning to become pregnant during the study period, or women of childbearing potential who are not using acceptable contraceptive methods. A woman is considered of childbearing potential if she is not surgically sterile or is less than 1 year since last menstrual period. Acceptable contraceptive methods are: 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.

6. Men who do not consent to the use of condom during intercourse during study participation.
7. Known active hepatitis B or C infection, or HIV infection.
8. Patients with active, severe, autoimmune disease.
9. Uncontrolled intercurrent illness including but not limited to psychiatric illness/social situations that in the opinion of the Investigator would compromise compliance of study requirements or put the patient at unacceptable risk.
10. Other malignancies within the past 2 years (not including basal and squamous cell carcinoma of the skin, localized prostate cancer or in situ cervix carcinoma).
11. Patients must agree to not to vaccinate with living vaccines during participation in the trial.
12. Prior treatment with an adenovirus-based gene therapy
13. 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: In Phase I, three doses (total viral load - $5x10^{10}$, $1x10^{11}$, $5x10^{11}$ VP) of LOAd703 are tested as "add-on" to SoC or conditioning gemcitabine chemotherapy. [redacted]

Phase II [redacted] with recruitment of 18 patients at $5x10^{11}$VP (MTD) and [redacted] with recruitment of PC and EOC patients at two dose levels: $1x10^{11}$ VP and $5x10^{11}$VP (MTD). [redacted]

Accrual Objective: **Up to** 53 efficacy evaluable patients in Phase II ([redacted].
The total number of patients to be enrolled in the study to achieve up to 53 evaluable patients shall not exceed 80.

Study Duration: 72 months

ABBREVIATIONS

[redacted]	[redacted]
Ad	Adenovirus
AE	Adverse event
[redacted]	[redacted]
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil count
aPPT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under curve
CBR	Clinical benefit rate
[redacted]	[redacted]
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
[redacted]	[redacted]
CRS	Cytokine release syndrome
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
CV	Curriculum vitae
[redacted]	[redacted]
DCF	Data clarification form
DLT	Dose Limiting Toxicity
DMP	Data management plan
DSUR	Drug safety update report
ECOG	Eastern cooperative oncology group
EOC	Epithelial ovarian cancer
GCP	Good clinical practice
[redacted]	[redacted]
GMM	Genetically modified microorganism
GMO	Genetically modified organism
[redacted]	[redacted]
IL	Interleukin
[redacted]	[redacted]
JEC	International ethics committee
LOAd	Lokon oncolytic adenovirus
[redacted]	[redacted]
MPA	Medial product agency
[redacted]	[redacted]
MTD	Maximum tolerated dose
[redacted]	[redacted]
ORR	Overall response rate
OS	Overall survival

PC	Pancreatic carcinoma
[redacted]	[redacted]
PD	Progressive disease
PDAC	Pancreatic ductal adenocarcinoma
[redacted]	[redacted]
PFS	progression free survival
PI	Principal investigator
PR	Partial response
PT	Prothrombin time
[redacted]	[redacted]
PTT	Partial thromboplastin time
[redacted]	[redacted]
RECIST	Response evaluation criteria in solid tumors
RSI	Reference safety information
SAE	Serious adverse event
SD	Stable disease
SoC	Standards of care
SUSAR	Suspected unexpected serious adverse reactions
[redacted]	[redacted]
TTP	Time to tumor progression
ULN	Upper limit of normal
VP	Virus particles
[redacted]	[redacted]

1. GENERAL INFORMATION

1.1. Protocol Number and Title of the Study

Sponsor Protocol Number: LOKON002

Title: Phase I/II Trial Investigating an Immunostimulatory Oncolytic Adenovirus for Cancer

1.2. Sponsor

Lokon Pharma AB

[redacted]

1.2.1. Chief Executive Officer

[redacted]

1.2.2. Sponsor Medical Advisor

[redacted]

1.3. CROs

1.3.1. Study conduct

[redacted]

1.3.2. SUSAR reporting to MPA/EMA

[redacted]

1.1. Investigators and Institutions

[redacted]

1.2. Research Nurse

[redacted]

1.3. Radiology (ultrasound-guided therapy)

1.4. Manufacturer

1.5. Importer & Pharmacy

1.6. Biobank

1.7. Laboratories

1.7.1. Research Analysis Laboratory

[redacted]

[redacted]

1.7.2. Clinical Analyses

[redacted]

[redacted]

2. BACKGROUND

2.1. Cancer Immunotherapy

2.1.1. Tumor Immunology and Cancer Immunotherapy

The immune system can recognize and kill tumor cells by 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 on major histocompatibility complex I (MHC-I) on the cells to CD8+ cytotoxic T lymphocytes (CTLs). Both virally-infected cells and tumor cells may prevent CTL recognition by down-regulating MHC molecules making the cells targets for natural killer (NK) cells. However, viruses initially activate an innate immune defense response, alerting antigen-presenting cells such as dendritic cells (DCs) to activate anti-viral immunity, while tumor cells do not induce the same degree of stimulation. Indeed, during cancer progression the tumor and its stroma produce substances that inhibit immune cells. Tumor immunity is restrained by blocking DC maturation and instead promoting differentiation and attraction of immunosuppressive cells to the tumor milieu. These suppressive cells are usually M2 macrophages, a variety of immature myeloid cells collectively called myeloid-derived suppressor cells (MDSCs) and T regulatory cells (Tregs). Such cells produce suppressive cytokines and growth factors such as IL10, TGFβ, Prostaglandin E2, Arginase I and myeloid peroxidase (1, 2). In the tumor milieu, activated CTLs are rapidly suppressed by these factors and become anergic, a state of reversible unresponsiveness, or die.

The essence 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 such as IFNγ, IL12, IL21 and TNF (3).

The implementation of checkpoint blockade antibodies targeting CTLA4 and PD1/PDL1 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, despite the success the majority of patients with solid malignancies are not responding to checkpoint blockade therapy. 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. One of these concepts is immunostimulatory gene therapy utilizing oncolytic viruses as gene delivery vehicles (6).

2.1.2. Immunostimulatory Gene Therapy

Immunostimulatory gene therapy aims to transfer genes coding for immunostimulatory proteins into the tumor area. The first studies using immunostimulatory gene therapy in experimental models were published in the late 1990s with promising results (7, 8). Different approaches were used in clinical trials as well but many failed to show sufficient efficacy. However, these studies were performed before the increased knowledge of suppressive immune cells infiltrating the tumor and the possibility to aid the immune responses using preconditioning or supportive chemotherapy that reduce the levels of these immunosuppressive cells (9). Further, the responses to immunotherapy follow a different course compared to traditional chemotherapy or irradiation. Initial swelling of the tumor due to inflammation may have been misinterpreted as progression leading to premature interruption of treatment (10). The combination of preconditioning or supportive chemotherapy together with awareness of how to interpret data will likely pave the way for immunostimulatory gene therapy as it has for other immunotherapies. Compared to the systemic delivery of soluble immunostimulatory cytokines, growth factors and antibodies, gene therapy can be delivered to a

distinct site with days to weeks of expressing the immunostimulatory transgenes depending on the vector used. This leads to a high concentration of the immunostimulatory proteins in the tumor reducing toxicity due to unnecessary withdrawal of tolerance to self-cells that can be seen upon systemic immune activation.

Therapeutic immunostimulatory genes are delivered to the tumor by many types of vehicles. Replication deficient adenoviruses have been commonly used since they can carry large transgene cassettes. Transgene expression is of limited duration because adenoviruses do not integrate into the host cell genome. The lack of integration renders this approach generally safety since the risk for mutagenesis of the host cell is unlikely. Moreover, humans are fully equipped to handle adenoviral infections. For example, most individuals have had upper respiratory tract infections due to adenoviruses and have pre-formed antibodies against several serotypes, and T cells cross-reactive to all (11). For immunostimulatory gene therapy, the immunostimulatory effects of the virus may enhance formation of anti-tumor responses by activating TLRs on tumor antigen-loaded DCs. Nevertheless, upon intratumoral delivery, the virus infects cells in the needle tract and there is a need to increase virus infection to prolong transgene expression. This may be achieved by using oncolytic viruses as gene delivery vehicles.

2.1.3. Oncolytic Virus (OV) Therapy

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, 12, 13). For full benefit, the OVs should infect all tumor cells, which can be a challenge if the tumor has metastasized. Since systemic viral spreading to distal tumor may be limited by the immune system, attempts are being made to develop less immunogenic OVs.

Instead of decreasing the immunogenicity of OVs, another approach is to utilize and boost their intrinsic immunostimulating capacity of the virus by adding immunostimulatory genes into the OV genome. Oncolytic adenoviruses armed with immunostimulatory transgenes successfully deliver them to the tumor and initiate an anti-tumor immune response active against both local and metastatic disease. The full efficacy of the combined oncolysis and immune stimulation is difficult to determine in murine models since the oncolysis is non-existing or rather limited in murine cells and the immunostimulatory effect cannot be evaluated in xenograft models in immunodeficient mice. There has been at least one published study using an oncolytic adenovirus carrying the full-length human CD40L gene to patients with end-stage cancer demonstrating feasibility and safety (14). There are other studies ongoing using GM-CSF armed oncolytic viruses and a herpes simplex virus armed with GM-CSF (talimogene laherparepvec) is approved for the treatment of patients with melanoma (15, 16).

2.1.4. Preconditioning or Conditioning Chemotherapy

Preconditioning prior to cancer immunotherapy, or conditioning chemotherapy during cancer immunotherapy is often given to patients receiving immunotherapy to decrease immune inhibitory cells such as Tregs and MDSCs that may otherwise hinder the intended immune activation (9). Further, chemotherapy-induced lymphocyte or myeloid cell depletion may induce bone marrow cytokine production that restores the immune cell populations (*i.e.* by homeostatic replication), thereby favoring the activation of anti-tumor responses. Dependent on diagnosis and type of chemotherapy, tumor growth may also be decreased. Metronomic cyclophosphamide has been given to patients undergoing immunotherapy attempting to control suppressive immune cells (17). Such conditioning chemotherapy protocols may be of great value if they do not hamper the desired anti-tumor responses. Conditioning chemotherapies of interest that restrain immunosuppression but

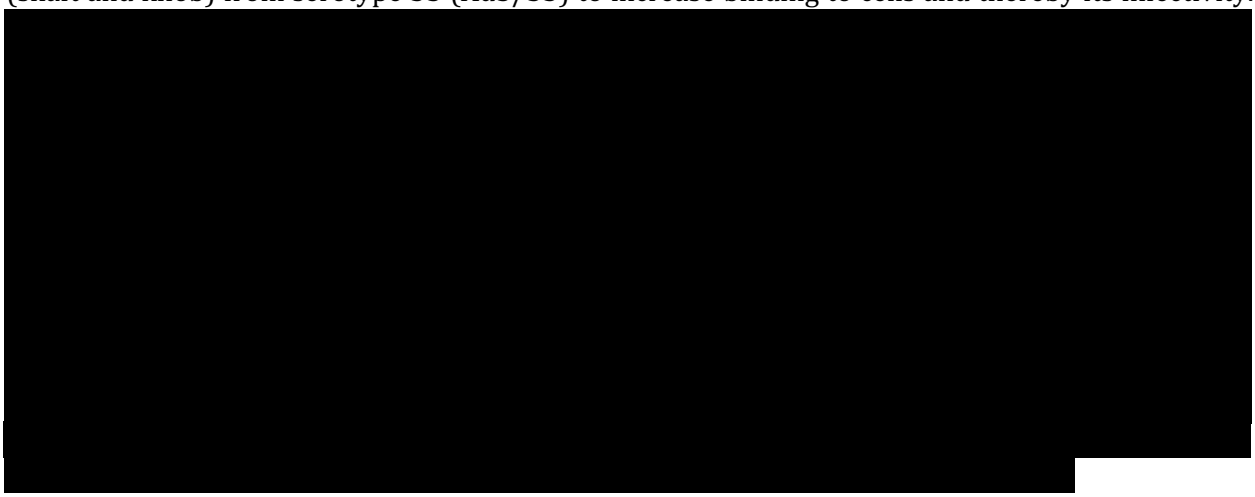
leave the capacity of lymphocytes in a responsive mode are gemcitabine, paclitaxel/nab-paclitaxel and platinum-based chemotherapies.

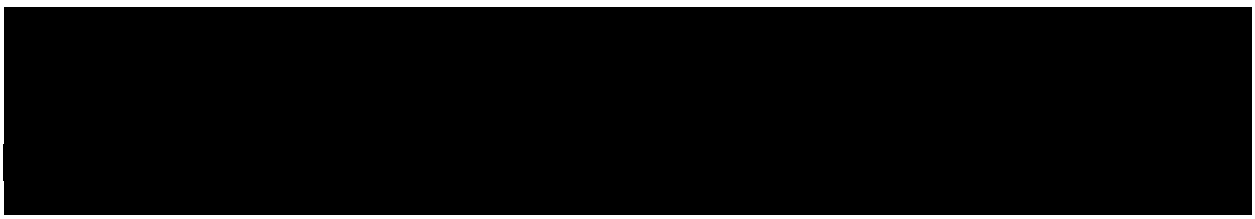
Gemcitabine is a nucleoside analog that replaces cytidine during DNA replication, and leads to growth arrest and apoptosis. Gemcitabine also targets ribonucleotide reductase thereby blocking the function of this enzyme. It is currently a component of standard of care (SoC) for pancreatic cancer both as adjuvant treatment to surgery and as treatment for advanced tumors +/- nab-paclitaxel. Although gemcitabine treatment of advanced metastasized tumors is only palliative, several studies, including our own, have shown that patients treated with gemcitabine have significantly lower levels of the immunosuppressive molecule TGFb, Tregs and MDSCs but a sustained level of activated T cells (18, 19). Recently it was shown that gemcitabine reduced MDSC recruitment to the tumor and accelerated the development of anti-tumor T cell responses, which aided combination therapy with an oncolytic retrovirus (20). In mice, gemcitabine reduced MDSCs and enhanced the efficacy of immunotherapy (21). Paclitaxel targets tubulin by binding to the beta-tubulin subunits. By its binding to tubulin, paclitaxel stabilizes tubulin polymers and prevents tubulin disassembly, thereby perturbing mitotic spindle assembly dynamics and cell division. It is also manufactured in an albumin-binding form (nab-paclitaxel), which appears to be associated with increased therapeutic indices in some tumor types. Platinum-based chemotherapies such as cisplatin and carboplatin crosslinks DNA. The crosslinking prevents DNA repair and/or DNA synthesis in cancer cells. Also taxanes and platinium compounds have shown to reduce immunosuppressive cells while favoring cytotoxic T cell responses both in animal models and in the clinic (22).

Hence, continuous conditioning of a patients with gemcitabine, paclitaxel/nab-paclitaxel and/or platinum-based chemotherapy during immunotherapy with LOAd703 may be beneficial.

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 binding to cells and thereby its infectivity.





[redacted]

[redacted]

[redacted]

2.3. Preclinical Studies

2.3.1. Summary of Preclinical Data

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.3.2. Summary of In Vivo Toxicity Data

[redacted]

[redacted]

[redacted]

2.4. Previous/ongoing Clinical Studies

LOAd703 is currently being tested in two other Phase I/IIa trials investigating safety and efficacy in patients with pancreatic cancer (LOKON001, [redacted]) and in patients with malignant melanoma (LOKON003, [redacted]).

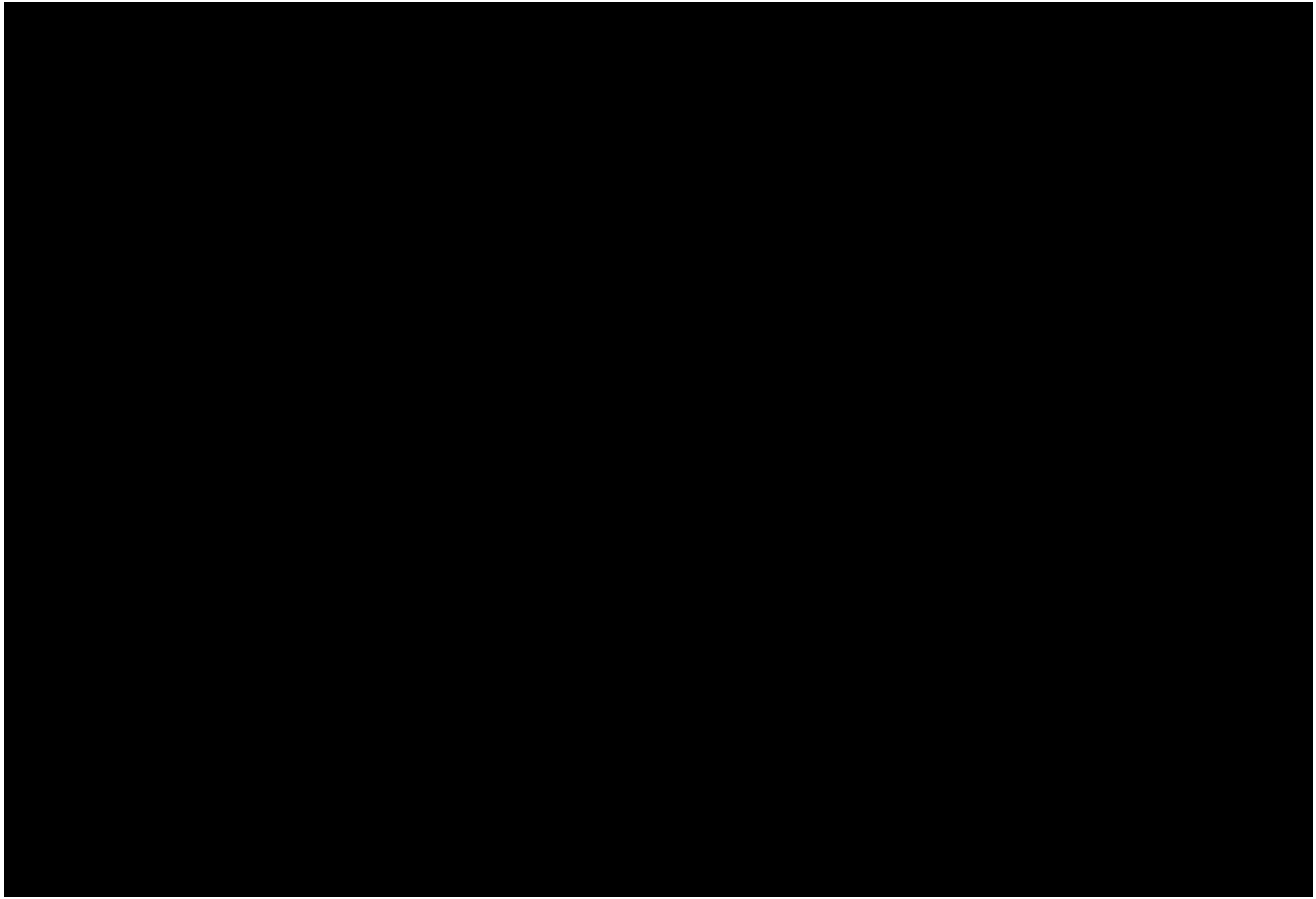
[redacted]

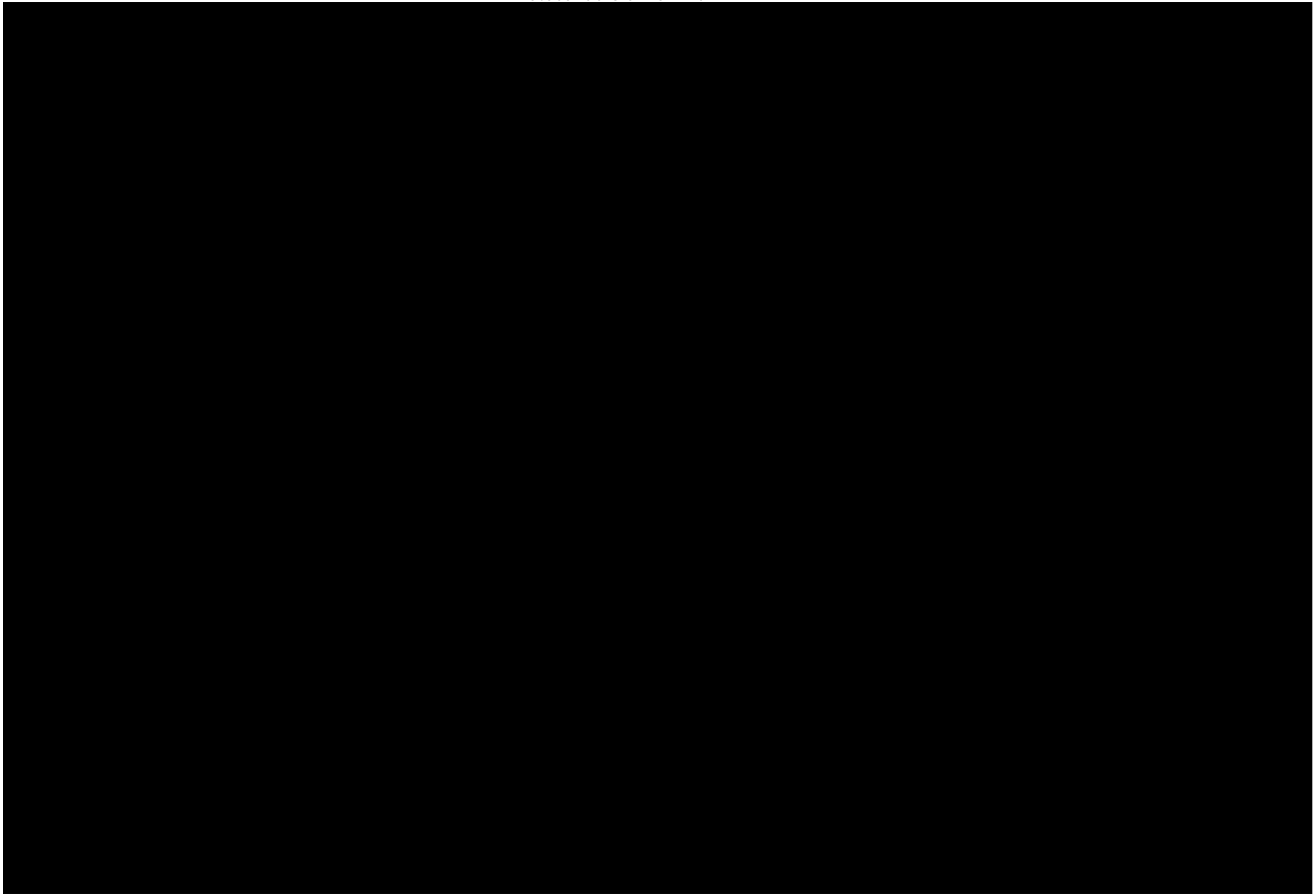
2.5. Potential Risks and Benefits

2.5.1. Potential Risks and Action Plan

In Table I, different risk factors are mentioned and summarized.

Table I: Risk and risk factors





[redacted]

[redacted]

2.5.2. Potential Benefits

[redacted]

2.6. Rationale for the Phase I/II Doses

[redacted]

2.7. Patient Populations

Below is a description of the targeted indications. Note that all patients enrolled will receiving palliative SoC treatment or gemcitabine conditioning.

2.7.1. Colorectal Cancer ( )

Colorectal cancer (CRC) is one of the most common cancers *(http://res.cloudinary.com /cancerfonden/image/upload/v1491294472/documents/cancerfondsrapporten-2017.pdf)*.
If possible, treatment is initiated with surgery to remove all or as much as possible of the tumor mass. Surgery is followed by chemotherapy. Chemotherapy with 5-flourouracil (5-Fu) is standard treatment in the advanced setting *(http://www.cancercentrum.se/globalassets/cancerdiagnoser /tjock--och-andtarmanal/ vardprogram/ nvpkolorektalcancer_2016-03-15.pdf)*. Capecitabine is an oral equivalent to 5-Fu and is as effective but hand-foot syndrome is a common adverse reaction (55). Irinotecan and oxaliplatin are the other two established chemotherapeutics (56, 57). Chemotherapy is sometimes combined with antibodies i.e. bevacizumab which binds to VEGF-A (58) or the anti-EGFR antibodies cetuximab (Erbitux^{R}) and panitumumab (Vectibix^{R}) (59). The infiltration of immune cells was found to be more important to predict prognosis than the TNM staging, indicating that the immune system may play a key role in CRC (60). The microsatellite instability (MSI) high CRC subtype is particularly immunogenic and FDA just approved the checkpoint blockade antibody pembrolizumab for the use in MSI-high tumors independently of tumor origin *(www.fda.gov)*. According to common practice, a treatment break is introduced after at least four months of chemotherapy (61). In this situation, all forthcoming treatments are regarded as palliative since cure cannot be expected. The same treatment is usually re-introduced when the disease progresses and the patients has a suitable health condition. The break constitutes a window of opportunity to evaluate new promising drugs such as immunotherapy. However, for active immunotherapy (e.g. activation of naïve T cells rather than stimulating pre-existing T cells like checkpoint blockade

antibodies) it is crucial to reduce immunosuppressive cells for effect. Conditioning chemotherapy is therefore needed. Several studies have demonstrated that the rather mild chemotherapeutic agent gemcitabine can enhance immune responses in many ways including the active suppression of myeloid-derived suppressor cells (MDSCs) (62-64). Hence, gemcitabine is a suitable conditioning to LOAd703 despites that it has no effect on its own in CRC.

This study will enroll subjects with refractory or recurrent CRC who have low tumor burden and either:

- Have received all reasonable conventional therapy.
- Are entering a "resting" phase during reasonable conventional palliative treatments (as indicated above)

LOAd703 will be administered only with gemcitabine as a single agent conditioning regimen in both CRC settings.

2.7.2. Pancreatic Cancer ([redacted])

With a 5-year survival rate of only 5%, pancreatic ductal adenocarcinoma (PDAC) is currently the fourth most common cause of cancer-related death in the US (65, 66) and is expected to raise to second place within a couple of decades. Due to the inherently aggressive biology of PDAC and the relatively late onset of cancer-related symptoms, most cases are not diagnosed until the tumor is unresectable due to involvement of adjacent vasculature and/or since it has already metastasized to distant sites. In fact, only 10-20% of PDAC patients are diagnosed with localized, resectable disease, and only 29% of these patients, after being treated with aggressive surgical resection and adjuvant chemotherapy, are alive 5 years after diagnosis (Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer, ESPAC-4) (67). All treatments of unresectable tumors are considered palliative. Combination regimens, such as gemcitabine/nab-paclitaxel and FOLFIRINOX (5-FU/irinotecan/oxaliplatin) have been shown to be more effective than single-agent regimens at shrinking or stabilizing advanced disease, but tumor control is relatively short-lived, and most patients with advanced PDAC still die of their disease within one year of diagnosis *(https://www.cancercentrum.se/globalassets/cancerdiagnoser/bukspottkortel/vardprogram/natvp_pankreascancer_20121030_final.pd)*. Novel treatment approaches are therefore greatly needed.

This study will enroll subjects with unresectable pancreatic cancer whom have low tumor burden and,

- Are eligible to receive first or second line of conventional palliative treatment consisting of gemcitabine with or without nab-paclitaxel

LOAd703 will be administered as an "add-on" to standard-of-care gemcitabine-based or nab-paclitaxel-based regimens or gemcitabine or nab-paclitaxel as single agents (section 5.10.2). Both gemcitabine and taxol-based therapy reduces immunosuppressive cells and are suitable conditioning treatments to immunotherapy.

2.7.3. Biliary Cancer ([redacted])

Biliary cancer includes cholangiocarcinoma and gallbladder cancer which both have a poor prognosis *(www.cancercentrum.se/globalassets/cancerdiagnoser/lever-och-galla/vardprogram/nat vp_ gallvagscancer _version1.0_170202_final.pdf)*. Patients with intrahepatic bile duct cancer have less than a 15% 5-year survival. while localized extrahepatic bile duct cancer has a better prognosis (30% 5-year survival). Patients who are diagnosed with metastatic disease have a median 5-year survival of only 2% *(www.cancer.org)*. Unfortunately, tumors are often diagnosed at later stages. Similarly, patients with gallbladder cancer are commonly not detected at an early stage and advanced gallbladder cancer has a 2-8% 5-year survival *(www.cancer.org)*. First line treatment after resection (if possible) is gemcitabine combined with low dose cisplatin based on the ABC study which demonstrated prolonged survival without additional side effects in patients treated with gemcitabine + low dose cisplatin compared to patients treated with gemcitabine alone (68). Other conventional first-line regimens include gemcitabine plus oxaliplatin. Treatment after resection or treatment of unresectable patients is considered palliative.

This study will enroll subjects with either locally advanced, unresectable or metastatic biliary cancer whom have low tumor burden and,

- Are eligible to receive any line of conventional palliative treatment consisting of gemcitabine combined with other agents (e.g. gemcitabine/low-dose cisplatin, gemcitabine/oxaliplatin, etc) in the first line or gemcitabine in a combination regimen or as a single agent (latter lines).

LOAd703 will be administered as an "add-on" to standard-of-care gemcitabine-based regimens or gemcitabine as a single agent in any line.

2.7.4. Ovarian Cancer ([redacted])

Epithelial ovarian carcinoma (EOC) is the deadliest gynecological malignancy and the 6th leading cancer-related cause of death in developed countries (77). Patients commonly respond well to first line chemotherapy given after surgery, but disease recurs in most patients, at which point it is not usually amenable to long remissions. Hence, treatments after surgery plus first line chemotherapy is considered palliative. Five-year survival for patients with late stage disease is less than 30%. Standard of care for both chemotherapy naive patients and after relapse with a platinum-free interval more than 6 months consists of carboplatin combined with paclitaxel, or gemcitabine, or liposomal doxorubicin administered every three weeks (69,70). For platinum-resistant patients (relapse within 6 months after platinum therapy) weekly paclitaxel in combination with bevacizumab is recommended (71,72). Patients with high-grade ovarian cancer may be eligible for PARP inhibitors after response to platinum treatment regardless of BRCA mutations. Studies indicate that paclitaxel also might be an effective conditioning drug similarly to gemcitabine (73,74).

This study will enroll patients with unresectable, palliative epithelial ovarian carcinoma (EOC) including epithelial ovarian, fallopian tube or primary peritoneal carcinoma whom have low tumor burden and either,

- Platinum-sensitive relapse (platinum free interval ≥ 6 months) received at least one line of standard-of-care combination chemotherapy and not eligible for PARP-inhibitor maintenance after chemotherapy.

  Platinum-resistant relapse (platinum free interval < 6 months) who have not received more than two lines of appropriate standard of care and not eligible for bevacizumab. Maintenance treatment does not count as a line of therapy.

- The patient has received appropriate therapy with PARP inhibitors if eligible.

LOAd703 will be administered as an "add-on" to standard-of-care regimens as described in section 5.10.4. [redacted]

2.8. Study Rationale

Patients diagnosed with solid tumors are commonly treated with surgery followed by cancer therapeutics such as chemotherapy. Cancer cells promote expansion of immature myeloid cells that act as immunosuppressive cells in the tumor microenvironment. Immunoactivating therapies, such as LOAd703, require conditioning of the patients to release the brakes of the immune system. Checkpoint blockade antibodies will likely be an interesting combination therapeutic for immune activating agents but for Phase I/II development, it is informative to perform studies with chemotherapy-conditioning during immunoactivating therapy since they have well-known therapeutic outcomes. Gemcitabine, nab-paclitaxel and platinum-based chemotherapy seem all to have the desired outcome on immunosuppressive cells while leaving expanding cytotoxic T cells unaffected (22). Hence, LOAd703 will be tested in this study in patients receiving such drugs. [redacted]

Up to 8 doses of LOAd703 will be given with SoC tailored for the indication. .

In this study, LOAd703 is given to patients with rapidly progressing cancers such as pancreatic cancer and biliary cancer, as an "add-on" therapy to any line of SoC treatment including first line since there are no curative treatments and short expected survival in these patients. For patients with CRC and ovarian cancer, LOAd703 is given only if the patients have not experienced complete responses to their respective first line SoC regimens, or experience a fast relapse post treatment, thus, have a high risk of rapid progression. Treatment of these patients with remaining approved options is considered palliative since cure is not any longer expected. Hence, patients with low tumor burden, with refractory or recurrent lesions will be enrolled. Since high tumor burden, end stage patients, do not have a satisfactory operating immune system, defining MTD in such patients may give misleading information on tolerability. Due to the well-known safety profile of oncolytic adenoviruses, this design with "add-on" virus therapy was chosen to utilize their standard chemotherapy as immune conditioning treatment. For patients with no current chemotherapy schedule, gemcitabine will be given as conditioning.

The study will demonstrate if LOAd703 administration is safe, if the immune system can be activated by LOAd703, if LOAd703 can be successfully delivered as "add-on" to different chemotherapy regimens, and if LOAd703 therapy will have clinical benefit that warrants further investigation.

3. TRIAL DESIGN

3.1. Objectives

The primary objective is to determine the tolerability of increasing doses of LOAd703 intratumoral injections during SoC or added conditioning gemcitabine chemotherapy.

The secondary objective is to determine the effects of LOAd703 intratumoral injections during SoC or added conditioning gemcitabine chemotherapy.

3.2. Endpoints

Primary Endpoints

Phase I

1. Tolerability is determined by physical examination, hematological and clinical chemistry analysis using CTCAE v 4.03.

Phase II

1. Tolerability is determined by physical examination, hematological and clinical chemistry analysis using CTCAE v 4.03.

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Secondary Endpoints

Phase I

3. Local and distant anti-tumoral effects assessed by appropriate imaging dependent on tumor localization and by monitoring tumor marker/s when available. Responses are judged accordingly to RECIST 1.1.
4. Effects are evaluated as time to tumor progression (TTP), progression free survival (PFS) and overall survival (OS).

Phase II

1. Local and distant anti-tumoral effects on tumor assessed by appropriate imaging dependent on tumor localization and by monitoring tumor marker/s when available. Objective responses are measured using RECIST 1.1.
2. Effect evaluated as TTP, PFS and OS.

3.3. Summary of Trial Design

The trial is a multi-center, open label, single arm, dose-escalation Phase I/II trial. The trial dose escalation in Phase I has a standard 3+3 design to determine maximum tolerable dose (MTD).

3.4. Duration of Study

The patients will receive 8 LOAd703 injections every other week during chemotherapy cycles. The study is estimated to take 72 months.

3.5. End of Study

The end of study is defined as the date of the last visit of the last patient.

4. SELECTION AND WITHDRAWAL OF PATIENTS

This is a multi-center study conducted at two sites in Sweden: Study patients will be recruited among patients taken care of at this department but may also include patients among those referred from other hospitals. Once a patient is enrolled in the trial, the responsibility of the patient remains with the study Principal Investigator independently of indication. The trial sites are described in section 5.4.

4.1. Inclusion Criteria

Patients must meet all of the following criteria for inclusion into the study:

1. Have histologic or cytological evidence of colorectal carcinoma (CRC), pancreatic carcinoma (PC), biliary cancer, or epithelial ovarian carcinoma (EOC which may encompass epithelial ovarian, fallopian tube or primary peritoneal carcinoma).
2. Have advanced disease, defined as cancer that is either metastatic or locally advanced, unresectable, and for which radiotherapy or other locoregional therapies are not considered treatment of choice but systemic chemotherapy or no therapy is planned.
3. Have one of the following treatment situations apply:

a) Colorectal carcinoma (CRC), [redacted]

i. A patient with refractory or recurrent metastatic CRC who has either received all conventional therapy; or is entering a "resting" phase between reasonable conventional treatments.

ii. A patient who is amenable to treatment with LOAd703 plus gemcitabine as a single agent conditioning regimen.

b) Pancreatic cancer

i. A patient with either locally advanced, unresectable or metastatic disease who is eligible to receive first or second line of conventional treatment consisting of gemcitabine and/or nab-paclitaxel.

ii. A patient who is amenable to treatment with LOAd703 as an "add-on" to standard-of-care gemcitabine-based or nab-paclitaxel-based regimens or gemcitabine or nab-paclitaxel as single agents (section 5.10.2).

c) Biliary cancer, [redacted]

I. A patient with either locally advanced unresectable or metastatic biliary cancer who is either treatment-naïve or has received any number of lines of treatment.

II. Patient who is amenable to treatment with LOAd703 as an "add-on" to standard-of-care treatment consisting of gemcitabine combined with other agents (e.g. gemcitabine/low-dose cisplatin, gemcitabine/oxaliplatin, etc) in the first line setting or gemcitabine in a combination regimen or as a single agent in latter lines of treatment.

d) Ovarian Cancer

I. A patient with either epithelial ovarian, fallopian tube or primary peritoneal carcinoma. The patient has either:

~~i) Residual disease following first-line standard-of-care combination chemotherapy.~~

ii) Platinum-sensitive relapse (platinum free interval ≥ 6 months) and have previously received at least one line of chemotherapy and not eligible for PARP-inhibitor maintenance after chemotherapy.
iii) Platinum-resistant relapse (platinum free interval < 6 months) who have not received more than two lines of appropriate standard of care and not eligible for bevacizumab. Maintenance treatment does not count as a line of therapy.
iv) The patient has received appropriate therapy with PARP inhibitors if eligible.

II. Amenable to treatment with LOAd703 as an "add-on" to standard-of-care (excluding bevacizumab) as described in 5.10.4.

4. Have a disease burden that is considered low (i.e. low tumor burden), which is defined on a patient-by-patient basis as per Principal Investigator's discretion. A rough guideline for defining low tumor burden is that the sum of the product of the bidimensional measurements for all lesions is ≤ 70 cm^2.
5. Have a measurable disease by standard imaging techniques per RECIST criteria. Measurable lesions must be outside of any prior radiation field(s), unless disease progression has been documented at that disease site subsequent to radiation.
6. At least one non-irradiated (or irradiated but disease progression documented at the site subsequent to radiation) lesion must be suitable for image-guided intratumoral injection and needle biopsy.
7. Be medically suited to sedation if required during intratumoral injections.
8. Be at least 18 years-old.
9. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2.
10. Have no remaining acute toxic effects from previous anticancer therapy > grade 1, except for any grade of alopecia.
11. Have adequate baseline organ/hematological function, as demonstrated by the following:
    a) Absolute neutrophil count (ANC) ≥1.0 x 10^9/l
    b) Hemoglobin ≥90 g/l
    c) Platelet count ≥ 100 x 10^9/l
    d) Bilirubin < 1.5 times the institutional upper limit of normal (ULN)
    e) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 (3 if liver metastases are present) times the institutional ULN
    f) Serum creatinine <2 times the institutional ULN or calculated creatinine clearance ≥35 mL/min
    g) Prothrombin (INR) ≤1.5 or prothrombin time (PT) ≤1.5 ULN; and either partial thromboplastin time or activated partial thromboplastin time (PTT or aPTT) ≤ 1.5 times the ULN.
12. The patient must understand and be willing to provide written informed consent.

4.2. Exclusion Criteria

1. Any concurrent treatment that would compromise the study including but not limited to continuous high dose corticosteroids (>0.5mg/kg), lymphodepleting antibodies or cytotoxic agents.
2. Treatment with high dose immune inhibitors including lymphotoxic monoclonal antibodies such as alemtuzumab (Campath®), or sirolimus (Rapamune®) and its analogs, biological therapy, cytotoxic agents or any investigational agents within 21 days of registration.
3. Ovarian carcinoma patients should not be eligible to PARP inhibitor treatment.
4. Patients on warfarin are not eligible.
5. Women who are pregnant, lactating, or planning to become pregnant during the study period, or women of childbearing potential who are not using acceptable contraceptive methods. A woman is considered of childbearing potential if she is not surgically sterile or is less than 1 year since last menstrual period. Acceptable contraceptive methods are: 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.
6. Men who do not consent to the use of condom during intercourse.
7. Known active hepatitis B or C infection, or HIV infection.
8. Patients with active severe autoimmune disease.
9. Uncontrolled intercurrent illness including but not limited to psychiatric illness/social situations that in the opinion of the Investigator would compromise compliance of study requirements or put the patient at unacceptable risk.
10. Other malignancies within the past 2 years (not including basal and squamous cell carcinoma of the skin, localized prostate cancer or in situ cervix carcinoma).
11. Patients must agree to not to vaccinate with living vaccines during participation in the trial.
12. Prior treatment with an adenovirus-based gene therapy.
13. 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 Log, Registration and Identification Log and Numbering of Subjects

It is the responsibility of the Principal Investigator that all patients, considered as candidates for the study, are listed in the “Screening and enrolment log”. The reason for rejecting a patient before informed consent is obtained should be specified in the comment field of the log. Patients will receive a consecutive study number when signing the informed consent and are thereafter considered enrolled as study patients. The trial site will keep a Registration and Identification log for all enrolled patients connecting a subject to the study number.

Study patients who have been screened and are excluded before week 1-visit are considered screen failures and noted in the “Screening and enrolment log”. The reason for excluding the patient from entering the study should be specified in the comment field of the “Screening and enrolment log”.

When the inclusion and exclusion criteria have been fulfilled and confirmed in the eCRF, the patient is registered in the study.

4.4. Off-treatment and off-study patients

A patient can discontinue the study treatment at any time if it is medically necessary, as judged by the Investigator or the Sponsor.

Modified Follow-Up Criteria: The patient would not continue to receive treatment but would continue to be followed as otherwise specified in this trial if the following criteria are met:

1. The development of toxicity, which, in the Investigator's judgment, precludes further treatment.
2. A response 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 request to discontinue treatment.
4. Female patient becomes pregnant.
5. If a DLT has been observed, that will not warrant dose reduction (or addition of corticosteroids pre-injection), or if a DLT occurs also after a dose reduction and/or addition of corticosteroids, the patient will be withdrawn from treatment, but will continue follow up according to the study schedule.
6. Confirmed progressive disease without any other treatment options available.

Hence, if the patient discontinue treatment, analysis of late toxicity, virus persistence, immunological reactions and effect can still be continued within the study accordingly to timelines in the protocol.

Off-Study Criteria: A patient has the right to withdraw consent for the study at any time without giving any specific reason. The patient will be withdrawn from participation in this trial at any time if any of the following criteria is met:

1. Progressive disease that will require another treatment regimen.
2. Patient request to be removed from the trial (withdrawn consent).
3. Lost to follow-up/noncompliance to protocol.
4. Study termination.

4.5. Withdrawn Patients

After treatment discontinuation or premature withdrawal a patient from the trial, the Investigator will clearly document the reason in the case report form.

Off treatment patients should continue to be followed and assessed as specified in the trial, i.e. all LOAd703 visits (despite no virus is injected) and evaluation visits up to the final follow-up visit, if possible.

If the patient is withdrawn from this protocol (off-study), the final follow-up visit should be scheduled as soon as possible to collect end-point data prior the patient's discontinuation, if possible. Nevertheless, these patients will be followed for a minimum of [redacted] treatment for ongoing or occurrence of new AEs if possible.
If the patient withdraw consent, this follow up should be done outside the study, i.e. no data will be collected in the study.

4.6. Noncompliance

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

5. TREATMENT OF PATIENTS

5.1. Phase I

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 eligibility, including assessment of health status and radiological evaluation. Imaging obtained [redacted] prior of first LOAd703 injection and blood tests done [redacted] of screening may be used for baseline evaluations at the discretion of the Investigator. Patient registration will occur following successful screening and confirmation of all eligibility criteria via eCRF.

[redacted] post registration the patients will initiate their biweekly LOAd703 injections [redacted]) given in combination with SoC chemotherapy, or gemcitabine conditioning if there are no current chemotherapy schedule available (Figure 1, Section 5.3). The patients will be given a total of 8 LOAd703 injections. Three cohorts consisting of at least three patients per cohort will be evaluated in Phase I. The dose will be escalated, one dose per cohort, evaluating the doses $5x10^{10}$ VP/injection (cohort 1), $1x10^{11}$ VP/injection (cohort 2) and $5x10^{11}$ VP (cohort 3). The treatment will be administered by image-guided intratumoral injection either percutaneously (preferred) or endoscopically, depending on the tumor location. Patients who will receive their injections of LOAd703 by endoscopic route may require sedation as determined by the endoscopist and performed as per standard practice at the Hospital.

[redacted]

[redacted]

Prior each LOAd703 injection ([redacted]) the Investigator must make a complete AE evaluation and assess the toxicity screening to assure that the patient is able to receive further LOAd703 injections.

[redacted]

[redacted]

[redacted] Radiological assessment will be performed at enrollment and thereafter every other month as per routine at the hospital. [redacted] post the final LOAd703 administration, patients will undergo a final follow-up analysis and come off-study. [redacted] Date of death will be captured and will be reported as descriptive addendum to the study report when all subjects can be concluded.

The informed consent form includes a specific question if the patients are willing or not for the study team to follow up on their condition regularly after final follow-up visit. Patients will participate for survival monitoring even if they disagree to the extended follow up post study.

[redacted]

When the first patient has received at least three doses of virus without DLT (as evaluated at the next AE evaluation [redacted] after third dose), the next two patients in the first cohort can begin LOAd703 treatment. No patients are dosed the same day in Phase I. Note that enrollment plus screening is allowed if slots are available in a cohort at any time. If a patient does not complete the three doses for a reason other than virus- or administration route-related DLT, this patient will be replaced by another subject and not regarded as a DLT. For details regarding DLT, see section 5.7.

Treatment with an escalated virus dose, can be initiated when at least three patients at the previous dose have received at least three doses of LOAd703 virus without DLT prior the AE assessment before [redacted] The decision for the next cohort to escalate dose, or stay at current dose, is taken by the Sponsor after a safety meeting including the Sponsor, the Clinical Project Manager (for taking notes only), the Medical Advisor and the Principal Investigator.

Note: at least 1 of 3, or 2 of 6, patients per dose cohort should be represented by a patient within one of the orphan indications pancreatic, biliary or ovarian cancer.

The justification of cohort sizes is outlined in chapter 10 (Statistics).

5.2. Phase II [redacted]

The Phase II[redacted] is initiated when maximum tolerated dose (MTD) is determined in Phase I by a safety meeting in which the Sponsor, the Clinical Project Manager (for taking notes only), the Clinical Advisor and the Principal Investigator participate.
Phase II[redacted] is initiated after approval of Amendment no.5.

The same procedures are followed for Phase II[redacted]:

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 eligibility, including assessment of health status and radiological evaluation. Imaging obtained [redacted] prior to screening and blood tests done [redacted] of screening may be used for baseline evaluations at the discretion of the Investigator. Patient registration will occur following successful screening and confirmation of all eligibility criteria via eCRF.

[redacted] LOAd703 injections [redacted]) (Figure 1, Section 5.3) given in combination to SoC or gemcitabine conditioning if there are no current chemotherapy options available. The patients will be given a total of 8 LOAd703 injections. The treatments will be administered by image-guided intratumoral injection either percutaneously (preferred) or endoscopically, depending on the tumor location. Patients who will receive their injections of LOAd703 by endoscopic injection may require sedation as determined by the endoscopist and performed as per standard practice at the Hospital.

[redacted]

[redacted]

[redacted]

Prior each LOAd703 injection ([redacted]) the Investigator must make a complete AE evaluation and assess the toxicity screening to assure that the patient is able to receive further LOAd703 injections.

[redacted]

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

[redacted] Radiological assessment will be performed at enrollment and thereafter every other month as per routine at the hospital. [redacted] post the final LOAd703 administration, patients will undergo final follow-up analysis and come off-study. [redacted] Date of death will be captured and will be reported as descriptive addendum to the study report when all subjects can be concluded. The informed consent form includes a specific question if the patients are willing or not for the study team to follow up on their condition regularly after final follow-up visit. Patients will participate for survival monitoring even if they disagree to the extended follow up post study.

[redacted]

5.3. Treatment Schedule for Study Visits

LOAd703 will be given every 14 days [redacted]) as "add-on" to SoC chemotherapy, or with gemcitabine conditioning if there are no standard options available. [redacted] he LOAd703 treatment schedule and study visits is described in Figure 1.

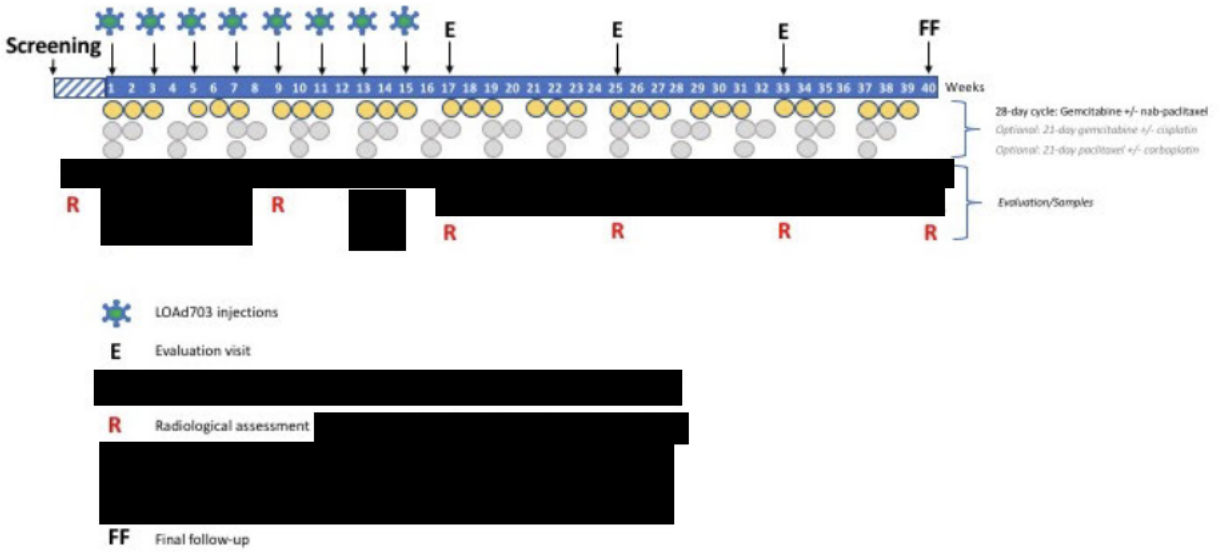


Figure 1. *Treatment schedule for LOAd703 treatments, sampling and follow-up visits.* [redacted] *The LOAd703 study will be added to standard care (SoC) treatment which will commonly be given in a 28-day cycle (yellow circles indicate infusion days). If no SoC is available, the PI can use gemcitabine conditioning which is also given at a 28-day cycle. Some patients may need SoC using a 21-week cycle and infusion days are shown in as grey circles. Chemotherapy can be omitted at any time as per hospital guidelines. Independently of chemotherapy regimen, the study visits are always at the same weeks.* [redacted]

Chemotherapy schedule and dose, dose modifications and omissions will be instituted per standard guidelines. Missed LOAd703 or chemotherapy doses will not be made up in order to maintain adherence to the protocol schedule. [redacted]

5.4. The Trial Sites

5.4.1. [redacted]

The patients recruited in this trial will participate in the trial activities at either respective trial site under guidance of the Principal Investigator. As soon as a patient is enrolled in the trial, the Principal Investigator is responsible for the patient, supported by the oncologist that internally referred the patient to the Principal Investigator.

Trial visits and most activities such as meeting the physician, nurse, blood and shedding sampling as well as administration of SoC chemotherapy is taking place at the oncology unit. Since LOAd703 is administered by image-guided intratumoral injection, a radiologist or endoscopist performs the injection upon request from the Principal Investigator. The lesion/s to be injected is decided by the Principal Investigator after recommendation of the radiologist/endoscopist. Biopsy is handled similarly.

The patients are treated in a hospital including a fully equipped emergency care unit. The hospital personnel involved in this trial are trained using immunostimulatory adenovirus-based treatments and the coordinating PI has experience from previous trials with a similar product administrated by ultrasound-guided intratumoral injection. The study nurse brings the patient and the LOAd703 virus to the injection suite and stays during the injection, where after the patient is transferred to the oncology unit for monitoring and chemotherapy administration.

5.4.2. GMO Regulation at Trial Site

The LOAd703 virus will be handled only by genetically modified organism (GMO)-educated staff and handled in hospital suites appropriately labelled with biohazard signs. When the suite is used for LOAd703 injection, only GMO-educated staff is allowed in the room. The Sponsor is responsible for the GMO education. Staff that receives education is considered GMO-certified and sign off that they have received education. A GMO folder with education material including rules and regulation, how to handle GMO, activities upon accidents with GMO and list of certified staff is available at both the Oncology and Radiology departments.

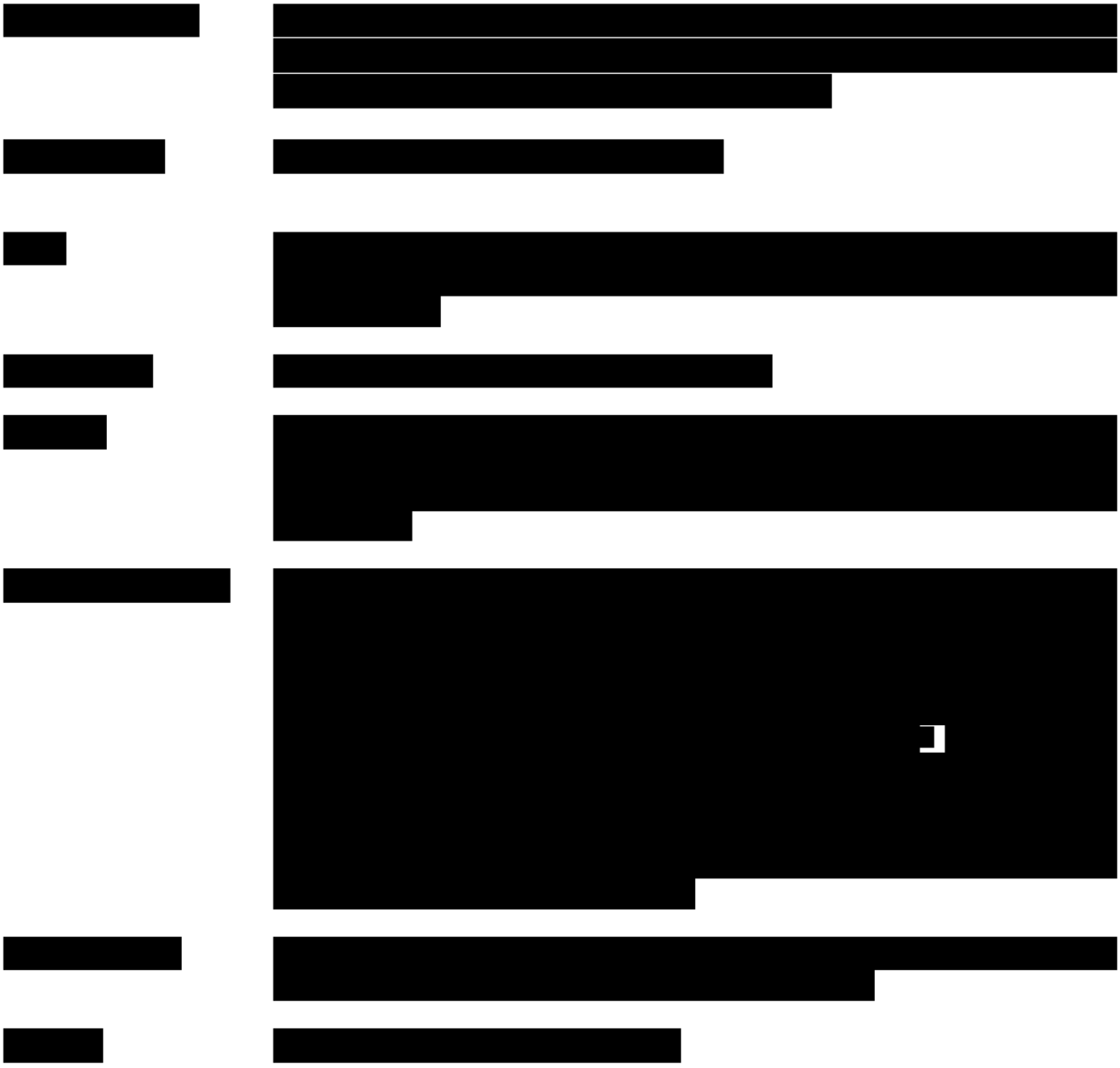
5.4.3. Referrals from National Swedish Hospital

Patients can be referred to the trial sites by another Swedish hospital, commonly within the region, to participate in this trial. The patient will participate in the trial activities at [redacted]. However, SoC treatment (e.g. chemotherapy treatments

part of their routine treatment) at time points when no trial activities occur can be given by the referring hospital at the discretion of the principal Investigator to limit the patients need of multiple travels to the trial site. Such logistics require that the Principal Investigator has agreed with the referring Oncologist that they continue to give the patient SoC at defined time points. It also requires that the study nurse is in contact with the referring site to confirm administration and dose and make notes in the eCRF. Nevertheless, all study activities and assessments, including RECIST and AE evaluations, will be done at the trial site and under close supervision by the Principal Investigator. The Principal Investigator is responsible for all trial patients during their participation in the trial.

5.5. LOAd703 Drug Product

5.5.1. LOAd703 Brief Description



5.5.2. Packaging and Labeling

[redacted]

[redacted]

5.5.3. Storage and Handling

[redacted]

5.5.4. Accidents

[redacted]

[redacted]

5.5.5. Preparation of LOAd703 Prior Treatment

[redacted]

5.5.6. Administration of LOAd703

[redacted]

[redacted]

5.5.7. Unused Clinical Trial Supplies

[redacted]

5.6. LOAd703 Dose Modifications

[redacted]

[redacted]

5.7. Dose Limiting Toxicity

DLT is defined as a CTC adverse event (CTCAE) Version 4.03, grade 3 or higher that can be attributed (definitely, possibly or probably) to LOAd703. A DLT will be reported to Sponsor in an expedite manor, following the procedures for SAE reporting, regardless if the event fulfil the serious criteria or not, see section 9.3.1.

[redacted]

5.8. Maximum Tolerated Dose

Maximum tolerated dose (MTD) is defined as the highest safe dose tested in Phase I, in which DLT does not occur in $\geq$1 of 3, or $\geq$2 of 6 treated patients.

5.9. Continuation of Treatment

If subjects are judged by the Investigator to be deriving significant clinical benefit (at least partial response) from LOAd703 once all scheduled injections (maximum 8) have been administered,

additional treatments need to be approved by the Sponsor, the ethical review board and by the Medical Products Agency.

5.10. Chemotherapy Standard of Care/Gemcitabine Conditioning Schedules

LOAd703 is given as an "add-on" to standard of care (SoC). If no regimen is available, gemcitabine conditioning can be used instead. Below are options that can be combined with LOAd703 in this protocol. The dose can be omitted or reduced as per standard guidelines at the Hospital.

5.10.1. Colorectal Cancer ([redacted])

Patients with colorectal cancer will receive LOAd703 treatments "add-on" to gemcitabine conditioning if there are no standard options or the patients is in a scheduled treatment break (e.g. resting between standard options). [redacted]

Gemcitabine 1000mg/m^2 is given intravenously in repeated 28-day cycles with treatments day 1, 8 and 15.

5.10.2. Pancreatic Cancer

Patients with pancreatic cancer will receive LOAd703 treatments "add-on" to SoC gemcitabine with or without nab-paclitaxel.

Gemcitabine (1000mg/m^2) with or without nab-paclitaxel (125mg/m^2) are given intravenously in repeated 28-day cycles with treatments day 1, 8 and 15.

5.10.3. Biliary Cancer ([redacted])

Patients with biliary cancer will receive LOAd703 treatments as an "add-on" to SoC gemcitabine combined with other agents (e.g gemcitabine/low dose cisplatin, gemcitabine/oxaliplatin etc) in the first line setting or gemcitabine in a combination regimen or as a single agent in latter lines of treatment.
Gemcitabine (1000mg/m^2) with or without cisplatin (25 mg/m^2) are given intravenously in repeated 21-day cycles with treatments day 1 and 8.

5.10.4. Ovarian Cancer

Patients with ovarian cancer with platinum-sensitive relapse will receive LOAd703 treatments "add-on" to SoC treatments at the discretion of their physician: 1) liposomal doxorubicin (40mg/m^2) and carboplatin (AUC5) at a 28-day cycle with treatments on day 1 or, 2) gemcitabine (800mg/m^2) and carboplatin (AUC5) at a 21-day cycle with treatments on day 1.

Patients with platinum-sensitive relapse who are felt not to be appropriate candidates for the platinum-based regimens, as per the discretion of their treating physician, may be treated with LOAd703 added on to either paclitaxel or gemcitabine according to the schedules below.

Patients with ovarian cancer with platinum-resistant relapse will receive LOAd703 treatment added on to the following standard-of-care treatments at the discretion of their treating physician: 1) paclitaxel (80mg/m^2) on a 28-day cycle with treatments on day 1, 8, 15 and 21; or 2) Gemcitabine (1000mg/m^2) conditioning on a day 1, 8 and 15 schedule.

5.11. Concomitant Treatment

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

[redacted]

5.12. Monitoring Subject Compliance

As LOAd703 will be administered by the clinical study medical personnel, compliance with study drug administration will be ensured. Patient compliance with concomitant medications and protocol-specified assessments will be recorded at the study visits.

6. STUDY EVALUATIONS

[redacted]

6.1. Schedule of Events

All study evaluations are summarized in Table II (Appendix I).

6.2. Screening

During the screening phase, the patient will be informed about the trial and sign informed consent. The patient will be evaluated for health status, pregnancy (if applicable) and tumor load (appropriate radiological imaging). If the patient has been subjected to radiology examination within the past [redacted], the previous imaging can be reused for evaluation at the discretion of the Investigator. However, the imaging should not be older than [redacted] at the time for first LOAD703 injection. If all of the inclusion criteria and none of the exclusion criteria are met, the patient is enrolled to participate in the trial.

6.3. LOAd703 Visits

The patients will undergo maximum 8 biweekly ( ) repeated treatments with LOAd703. LOAd703 is administered by image-guided intratumoral injection.

Prior each administration ( ) the Investigator must see the patient to make a complete AE evaluation and assess the toxicity screening to assure that the patient is able to receive further LOAd703 injections. For continuation criteria, see section 5.1 for Phase I and section 5.2 for Phase II.

Chemotherapy should be given

6.4. Evaluation Visits

During evaluation visits, the patient will be evaluated for health status, toxicity, and treatment effect on tumor size (radiology exam and tumor marker when available every other month).

6.5. Collection of Information After /Study End

If the patient consented to collection of information on his/her condition after study end, information on tumor evaluations and further treatment will be collected from the medical record.
All patients will be followed for survival after study end.

7. STUDY ASSESSMENTS

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

7.2. Safety Parameters

7.2.1. Demographics

- Age ([redacted])
- Gender ([redacted])
- Race

7.2.2. Medical History/Patient History

- Prior and ongoing medical illness and conditions ([redacted])
- Date of diagnosis ([redacted])

- Diagnosis stage and extent of the disease ([redacted])
- Previous anti-tumor therapy and response to the respective treatment ([redacted])
- Previous or ongoing smoker [redacted]

[redacted]

7.2.3. Physical Exam

- Full physical examination ([redacted])
- Physical assessment [redacted]). For details, see section 5.1 for Phase I and section 5.2 for Phase II.
- Baseline symptoms ([redacted])

7.2.4. Vital Signs, height and weight

[redacted]

[redacted]

[redacted]

- Height ([redacted])
- Weight ([redacted])

After injection [redacted].

7.2.5. ECOG Performance Status

To be assessed according to the ECOG score (Appendix II). [redacted]

7.2.6. Pregnancy Test

Urine or serum pregnancy test for females of child-bearing potential is to be completed at [redacted]

7.2.7. 12-Lead ECG

A 12-led ECG will be performed after 5 min rest [redacted], and will be judged clinically normal/abnormal by the Investigator. Any clinical abnormalities should be described.

7.2.8. Blood Chemistry

[redacted]

Blood sampling for safety should be taken [redacted] before each injection. However, if [redacted] virus injection no 1, these results are considered as baseline and no new sampling is needed. Further, if samples have been taken for routine analysis [redacted] enrollment, the results can be used for screening evaluation at the discretion of the Investigator without need of subject the patients for new samples.

[redacted].

7.2.9. Hematology

Hemoglobin, WBC with differential count, platelet count at screening, LOAd703 visits, evaluation visits and at final follow-up.
Blood sampling for safety should be taken [redacted] before each injection. However, if screening samples are taken [redacted] virus injection no 1, these results are considered as baseline and no new sampling is needed. Further, if samples have been taken for routine analysis [redacted] enrollment, the results can be used for screening evaluation at the discretion of the Investigator without need of subject the patients for new samples.

7.2.10. Concomitant Medications

All on-going medications should be listed at screening with start and stop time, excluding LOAd703 and chemotherapy, and those already registered as concomitant medications at a prior visit. The list is updated at every study visit if applicable. Since patients usually are prescribed numerous concomitant medications, of which many are to be used per needed, the actual medication list in the medical records should be confirmed with the patient by the study nurse/Investigator at each visit.

7.2.11. Adverse Events Monitoring

Adverse events will be monitored continuously during the trial and data on all AEs will be collected regardless of severity and causality. See section 9 about AE reporting.

[redacted]

[redacted]

[redacted]

7.5. Efficacy Assessments

Response and progression will be determined for all patients [redacted]

7.5.1. Tumor Size

Tumor size will be determined with suitable imaging depending on the localization of the tumor. Computer tomography (CT) will preferably be selected. Radiology exams will be performed every other month post treatment initiation: [redacted]). However, at screening: if the patient has been subjected to radiology examination within the [redacted], the previous imaging can be reused for evaluation at the discretion of the Investigator. Note that the baseline CT should not be older than [redacted] at the time of first LOAd703 injection. Definitions of measurable disease and response to treatment will follow RECIST 1.1 criteria.

[redacted]

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 10mm by CT scan (irrespectively of scanner type) [redacted]

7.5.2. Tumor Markers

Serum markers, if available, will be evaluated simultaneously to tumor size imaging ([redacted] These samples are sent together with the clinical chemistry samples in section 7.2.8. The level of a serum marker will not be considered in the response criteria. [redacted] After the analysis, sample will be destroyed or returned to the biobank.

8. Response Criteria

8.1. RECIST

The tumor response will be evaluated using appropriate imaging technique depending on the localization of the tumor. Tumor regression or progression will be evaluated accordingly with RECIST 1.1 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 partial response 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.

[redacted]

Clinical Benefit Rate (CBR)
CBR is defined as MR or better.

Overall Response Rate (ORR)
ORR is defined as PR or better. The below Table is used for guiding overall response.

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)
Overall survival is defined as the time from the start of treatment to death due to any cause.

9. Adverse Events (AE)

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 require clinical intervention or further investigation (beyond ordering a repeat/confirmatory test). Injury or accidents, the medical condition for operations not pre-planned, or deterioration in concurrent illness are also considered as AEs.

9.1.2. Serious Adverse Event (SAE)

A serious AE 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 death 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, 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; 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 a patient's life.

Planned or elective hospitalizations (e.g., for administration of protocol therapy) should not be considered SAEs.

9.1.3. Suspected Unexpected Serious Adverse Reactions (SUSAR)

An unexpected AE 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 current Investigator's Brochure with Reference Safety Information (RSI); or, if an Investigator's Brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in this protocol or in the regulatory agency study authorization application.
Unexpected, as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the Reference Safety Information in the Investigator Brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

9.1.4. Non-Serious Adverse Event

All other 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 4.03 (see: http://ctep.info.nih.gov). All AEs (except grade 1 and 2 laboratory abnormalities that do **not** require an intervention) are to be recorded on the AE page in the case report form (eCRF) and source documentation.

All AEs fulfilling the criteria for Serious (section 9.1.2) should also be reported as a serious adverse event (SAE) with the following exception: bone marrow toxicities induced by chemotherapy will only be reported as an SAE if the event leads to hospitalization or death, or in any other way deviates from what the Investigator considers to be expected.

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 investigational product LOAd703.

The AE reporting period for this trial begins upon receiving the first cycle of LOAd703/chemotherapy and ends at study termination (e.g. at final follow-up). 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 has been administrated when an AE occurs, its relationship to LOAd703 will be judged by the Principal Investigator.

9.2.1. Severity Grading

The Investigator must determine the intensity of any AEs according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (see http://ctep.info.nih.gov) and their 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 symptom but may be given because of personality of patient.
2. Moderate: Discomfort sufficient to reduce or affect normal daily activity. Patient is able to continue in study; treatment for 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: Life-threatening consequences, urgent intervention may be required;
5. Fatal: Event caused the death of the patient.

For AEs of grade 3 or higher related to the LOAd703 virus, DLT should be considered. See section 5.7.

9.2.2. Attribution Definitions

The Investigator will attempt to assess the relationship of the event to LOAd703, the injection procedure, chemotherapy, underlying cancer disease or other reason. An AE is considered to be associated with any of these reasons if the attribution is determined as possible, probable or definite. Attribution of AEs for each of the reasons will be recorded in the CRF as:

- Unrelated: The AE is clearly NOT related
- Unlikely: The AE is doubtfully related
- Possible: The AE may be related
- Probable: The AE is likely related
- Definite: The AE is clearly related

9.2.3. Duration of Event

The date of onset (and time if relevant) and the duration of the AE (i.e. date of resolution) will be recorded, as well as changes in severity and/or Seriousness over time (see the Data Handling Instructions for the eCRF).
Events that are ongoing at the time the patient completes follow or dies will be documented as ongoing. For the AE with outcome death, the date of death will be recorded as stop date.

9.2.4. Action/s Taken Regarding the Study Drug

The method used to treat the AE, specifically, action taken with the study drug should be recorded, for example, but not limited to, "dose reduced", "discontinued".
For details on dose reduction, see section 5.6.

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

9.3.1. Reporting to Sponsor

Adverse events classified as serious and/or DLT require expeditious handling and reporting to the Sponsor and [redacted] to comply with regulatory requirements.

For any serious adverse event (SAE) and/or DLT that occurs while a patient is on-study; regardless of any opinion as to the relationship of the SAE to the study drug, the Sponsor must be notified immediately (within 24 hours of becoming aware of the event) by e-mail a completed Serious Adverse Event Report Form to Sponsor Safety Inbox and the CRO ([redacted]):

[redacted]

An initial notification can also be done by email (preferred) or telephone call to the contact persons listed below. However, the initial notification should always be followed by a completed Report Form emailed to the safety mail addresses [redacted] as soon as possible.

[redacted]

[redacted]

[redacted]

Detailed instructions describing the procedure of reporting SAEs are found in the Investigator Site File.

9.3.2. Safety Report – Reporting by Sponsor

The Sponsor is responsible for informing MPA/EMA and IEC of any Suspected, Unexpected Serious Adverse Reactions (SUSARs). SUSARs that is fatal or life-threatening, should be reported as soon as possible and not later than 7 calendar days after first knowledge by the Sponsor, and with a follow-up report within another 8 days. Any other SUSARs should be reported within 15 days.

The third party vendor will be delegated the task to report SUSAR to the MPA/EMA and IEC as per regulations.

SAEs that are not objects for expedited reporting, should be listed together with SUSARs in the annual drug safety update report (DSUR), written in cooperation between Principal Investigator, Sponsor and UCR, and submitted to MPA and IEC according to current legislation.

9.3.3. Reporting to IRBs

Investigators must report SAEs and unexpected AEs to his/her IRB or ethics committee according to national legislation and per the institutional guidelines.

9.3.4. Procedures in case of Medical Emergency

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

If an emergency occurs, please notify the Sponsor and [redacted]:

[redacted]

[redacted]

9.5. Handling of Pregnancy

Any pregnancy diagnosed during the study, or that occurs within the AE reporting period after stopping study medication, must be reported immediately to the Sponsor. Women of childbearing potential will be informed about contraceptive medication during 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 on-study, the study drug 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 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 serious AE in the mother will be recorded as an SAE and will be reported as described.

10. STATISTICS

10.1. Description of Objectives and Endpoints

The primary objectives of the Phase I component are to evaluate toxicity, including DLT, of image-guided intratumoral repeated injection of LOAd703 in patients with solid cancer. The endpoint is tolerability to highest trial dose.

The primary objective for the Phase II component is to confirm safety of MTD and evaluate efficacy on tumor upon image-guided intratumoral, repeated dose, injection of LOAd703 in patients with solid cancer. The endpoints are confirmed tolerability and response.

10.2. Sample Size

10.2.1. Phase I

[redacted]

10.2.2. Phase II

[redacted]

[redacted]

10.3. Safety Reporting

Safety data will be tabulated for the safety population. AEs will be tabulated by body system, preferred term, severity, seriousness, and relationship to treatment. Each value will be classified as falling above, below, or within the normal range. Laboratory parameters will also be tabulated by the maximum NCI-CTCAE severity grade. AE terms will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA).

10.4. Efficacy Reporting

Efficacy will be tabulated by response category per the RECIST1.1 criteria for the efficacy evaluable population. The clinical benefit rate and overall response rate (ORR) will be determined. [redacted]

11. 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), providing access to source data/hospital records. Sponsor verifies that each patient has consented in writing to direct access to the original source data/hospital records by the use of written patient information and signed Informed Consent.

During the monitoring, the data recorded in the CRFs by the Investigator will be controlled for consistency with the source data/hospital records by the study monitor (source data verification). Any discrepancies of data will be documented and explained in the monitoring reports.

11.2. Source Data

The requirements regarding information in the medical records follows the "Patientdatalagen" (SFS 2008:355), the General Data Protection Regulation (GDPR: EU2016-679) and "The Medical Product Agency's regulations on clinical trials of medicinal products for human use" (LVFS 2011:19:), which means that except information that are of importance for the wellbeing and care 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 and the EudraCT number
- 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 details and information that is study specific and of no interest for the medical care of the patient, CRF and other documents may be considered as source data. Prior to study start, the Principal Investigator/study nurse and the Monitor must identify and document the expected source location of source data (e.g. medical record notes, laboratory reports and the CRF itself). 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 study monitor. Note that the patient journal shall include a short description of the study.

11.3. Monitoring

In accordance with the principles of Good Clinical Practice (GCP), monitoring of the study will be performed by Sponsor. In this study, [redacted] 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 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 for verification of consistency with the data recorded in the CRFs. All patients that have performed any study specific assessment will be monitored for Signed Informed Consent and all patients that have received study drug will be monitored for date of visits, inclusion and exclusion criteria and AE/SAE.

Since patients usually are prescribed numerous concomitant medications, of which many are to be used per needed, the actual medication list in the medical records should be confirmed with the patient by the study nurse/Investigator at each visit.
The monitor will compare the eCRF only with the notes in the medical records, except for periods of hospitalization (SAE) when concomitant medication will be checked against the medicinal dispensing lists. When start/stop dates, doses or indications are missing in the medical records, the CRF will be considered source data.

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

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

The Investigator should provide a curriculum vitae (CV) or equivalent documentation of suitability to be responsible for the study. All Sub-investigators and other responsible personnel should be listed together with their function in the study on the delegation list and provide their CVs.

11.4. 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 MPA and the International ethics committee (IEC) 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, change in telephone number). Other administrative revisions, which may impact the clinical portion of a study, will be duly reported to the MPA by the Sponsor and/or IEC by the Principal Investigator, or designee, under guidance of [redacted] and with approval of the Sponsor.

12. ETHICS

12.1. Independent Ethics Committee

It is the responsibility of the Principal Investigator to obtain approval of the study protocol/protocol amendments, the patient information and the Informed Consent from the IEC before enrolment of any subject into the study.

The Sponsor shall report all SUSARs to the IEC. 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 should notify the IEC.
The Sponsor/Principal Investigator should file all correspondence with the IEC and provide the other party with copies.

12.2. 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 Declaration of Helsinki.

This Phase I/II-study is conducted at 2 clinics in Sweden: [redacted] Medical staff with appropriate level of training is available at both sites. The sites have procedures for handling emergency situations.

12.3. 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 enrolment in the study.

The subjects will consent to:

- Participating in the study.
- Personnel concerned at the Sponsor and regulatory authorities to gain full access to hospital records, to control the data collected in the study.
- Recording, collection and processing of data and storing of data in a database.
- Possible transfer of information from the study to countries outside the European Union (EU).
- Storing of study samples in a biobank.
- Allow for samples to be analysed in within EU or outside EU (third country).
- Further follow-up of their condition via the medical records after final follow-up visit (Yes/No)

It should be clearly stated that the data will not identify any subject taking part in the study, in accordance with the EU General Data Protection Regulation (2016/679).

A copy of the patient information and the Informed Consent form should be given to the subject. The Investigator who gave the verbal and written information to the subject shall sign the Informed Consent form. The Investigator should file the signed Informed Consent forms in the Investigator's File for possible future audits and inspections.

It is suitable to notify the subject's family doctor of the subject's consent to participate in the study.

13. DATA MANAGEMENT

13.1. Data Management

[redacted] will be responsible for the 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 (e)CRFs. The Investigator is responsible for ensuring the accuracy, completeness and legibility of the data reported in the eCRFs. The monitor will check the accuracy, completeness and legibility of the data reported in the eCRFs.

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. In addition, selected key variables will be proofread. All inconsistencies detected during these procedures will be resolved through electronic Data Clarification Forms (DCF's) in the eCRF, being 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 done and approved, and all queries solved, the Database Closure procedures will start. Decisions will be made 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.

14. DATA HANDLING AND RECORD KEEPING

14.1. Electronic Case Report Forms (eCRF)

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 [redacted] to the last visit of a 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 Swedish.

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 appropriate regulatory authorities) without written permission from the Sponsor. A paper copy of the electronic CRFs should be kept in the Sponsor's Study File and and in the Investigator Site File.

The Investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the eCRFs.

In this study, clinical data including AEs and concomitant medication swill be entered into a 21 CFR Part 11-compliant eCRF ([redacted]) provided by [redacted]. The eCRF includes password protection 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 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. This loss will be limited to all data recorded during the last 8 hours prior to the failure in the worst case.

14.2. 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 10 years. This includes any original source data related to the study, the subject identification list (with subject numbers, full names and addresses), the original signed Informed Consent forms, copies of all eCRFs and detailed records of investigational products disposition.

14.3. Study Report

A full study report should be submitted to EudraCT by Sponsor within 12 months from last patient's last visit. The PI and study site must provide necessary information by completing the eCRF for every patient no later than 6 months from last patient's visit to allow close out activities including monitoring and correction of eCRFs if necessary.

14.4. Insurance

Patients in the study are covered by the [redacted]

14.5. Publication Policy

The investigation is considered as collaboration between Uppsala University, Uppsala University Hospital, Karolinska University Hospital and the Sponsor. The Investigator agrees to inform the Sponsor of any publication or presentations on the study. 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. Employees at the Sponsor or representatives of the Sponsor should be coauthors should they have provided scientific input to the study design, data interpretation etc.

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16.0 APPENDICES

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Table II. Schedule of Event

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