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PROTOCOL ADXS001-06

PHASE 2 STUDY OF ADXS11-001 IN SUBJECTS WITH PERSISTENT/RECURRENT, LOCO-REGIONAL OR METASTATIC SQUAMOUS CELL CARCINOMA OF THE ANORECTAL CANAL

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IND NUMBER: 13712

EudraCT NUMBER: **2015-001053-33**

Original Version 1.0: March 9, 2015

Version 2.0/Amendment 1: April 27, 2015

Version 3.0/Amendment 2: July 31, 2015

Version 4.0/Amendment 3: December 1, 2015

Version 5.0/Amendment 4: March 8, 2016

PROTOCOL APPROVAL

Protocol Number: ADXS001-06

Title of Protocol: Phase 2 Study of ADXS11-001 in Subjects with Persistent/Recurrent, Loco-Regional or Metastatic Squamous Cell Carcinoma of the Anorectal Canal

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Prepared by:

[redacted]

08 March 2016
Date

Approved by:

[redacted]

08 March 2016
Date

INVESTIGATOR SIGNATURE PAGE

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By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by Advaxis, Inc. prior to seeking approval from the approving Institutional Review Board (IRB)/Ethical Review Committee (ERC).

This study will be conducted in accordance with Good Clinical Practices (GCPs), International Conference on Harmonisation (ICH) Guidelines, the Declaration of Helsinki, and local ethical and legal requirements.

Investigator Name:

_____ _____
Signature Date

_____ _____
PI Name (Printed) Site #

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ABBREVIATIONS

ADXS11-001	*Lm*-LLO Immunotherapy for HPV associated diseases
AEs	Adverse Events
APC	Antigen Presenting Cell
CD4	Cytotoxic T cell, effector T cell, Memory T cell
CD8	Helper T cell, Regulatory T cell
CAT	chloramphenicol acetyl transferase
CFU	Colony Forming Unit
CMP	Comprehensive Metabolic Panel
CR	Complete response
CRP	C-Reactive Protein
CTL	Cytotoxic T lymphocyte
DCR	Disease Control Rate
DLT	Dose limiting toxicity
DTH	delayed-type Hypersensitivity
ESR	Erythrocyte Sedimentation Rate
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GOG	Gynecologic Oncology Group
HPV	Human papilloma virus
HspE7	Heat Shock Fusion Protein-Based Immunotherapy
IV	Intravenously
IFN	Interferon
LFT	Liver Function Test
LLO	Listeriolysin O
Lm	*Listeria monocytogenes*
*Lm*dd	An attenuated strain of *Listeria monocytogenes* with deletions in two genes (*dal* and *dat*)
Lm-LLO	*Listeria monocytogenes* Listeriolysin O
MDSC	myeloid-derived suppressor cells
MHC	Major Histocompatibility Complex
MIC	Minimum inhibitory concentration
MMC	Mitomycin C
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NSAID	Non-Steroidal Anti Inflammatory Drugs

PI3K	Phosphoinositide 3-kinase
PR	Partial response
PSA	Prostate-specific antigen
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SD	Stable Disease
SOC	Standard of Care
TAA	Tumor Associated Antigen(s)
TCR	T-cell receptor
TNFα	Tumor necrosis factor alpha
TIL	Tumor infiltrating lymphocytes
tLLO	Truncated LLO
Tregs	Regulatory T cells
wt-Lm	wild type Listeria monocytogenes

1 SUMMARY

Study Title:	Phase 2 Study of ADXS11-001 In Subjects with Persistent/Recurrent, Loco-Regional or Metastatic Squamous Cell Carcinoma of the Anorectal Canal
Trial Phase	Phase II
Clinical Indication	Persistent/recurrent, loco-regional or metastatic squamous cell carcinoma (SCCA) of the anorectal canal
Trial Type	Interventional
Study Centers	Multicenter, USA
Route of Administration	Intravenous (IV)
Trial Blinding	Open label, unblinded
Number of Trial Subjects	Approximately 55 • 31 subjects in Stage 1 • 24 subjects in Stage 2
Estimated Duration of Trial	Approximately 6 years
Duration of Participation	Each subject will participate in the study for an average of approximately 6 years from the time the subject signs the informed consent form (ICF) through the final contact. Treatment will continue for up to 2 years or until the subject meets a discontinuation criterion (e.g., has either documented progression, unacceptable adverse events (AEs), withdrawn due to investigator's discretion, subject withdraws consent, pregnancy, or noncompliance with study procedures or treatments). Subjects who have been on therapy for >6 months and who attain a complete response (CR) may consider stopping the trial. Subjects who achieve a CR should receive at least 1 additional cycle of treatment. The study duration includes an active study treatment phase which may last up to a maximum of 36 months and a 3 year *Lm* Surveillance Monitoring Phase, which includes 6 months of oral antibiotic administration to commence upon completion of the active study treatment phase or upon study discontinuation. All subjects will be followed for adverse and serious adverse events (SAEs) for a minimum of 30 days. End of Study will be defined as 1 year after the last subject is enrolled on study. However, any ongoing subject, subjects who are still deriving clinical benefit from ADXS11-001 therapy at the end of their 2 year treatment period or at the end of the study may be enrolled into a separate extension study, as available.
Randomization Ratio	None
Methodology	This is a single arm Phase 2 study. Stage 1 and 2 of the study are monotherapy evaluations of ADXS11-001 in 31 and 24 subjects, respectively with persistent/recurrent, loco-regional or metastatic SCCA of the anorectal canal that have received at least 1 regimen for the treatment of advanced disease. Additionally, those deemed by their investigator as not optimal candidates for chemotherapy would be considered eligible.

Study Title:	Phase 2 Study of ADXS11-001 In Subjects with Persistent/Recurrent, Loco-Regional or Metastatic Squamous Cell Carcinoma of the Anorectal Canal
	In addition, all subjects will participate in a 3 year *Lm* surveillance period. The surveillance period will begin following the last dose of study treatment or at the time of study discontinuation. This period is intended to help ensure the eradication of *Lm* bacteria. This period will also include a 6 month course of trimethoprim/sulfamethoxazole which will be initiated approximately 72 hours after the completion of the last dose of ADXS11-001 or immediately following study discontinuation.
Objectives	Primary: • To evaluate efficacy as measured by the overall response rate and rate of 6 month progression-free survival (PFS) in subjects with persistent/recurrent, loco-regional or metastatic SCCA of the anorectal canal as determined by RECIST 1.1. Secondary: • To evaluate efficacy as measured by the overall response rate and rate of 6 month PFS in subjects with persistent/recurrent, loco-regional or metastatic SCCA of the anorectal canal as determined by irRECIST. • To evaluate the safety and tolerability of ADXS11-001 in subjects with persistent/recurrent, loco-regional or metastatic SCCA anorectal canal SCCA of the anorectal canal by NCI CTCAE 4.0 • To evaluate the additional parameters of efficacy (duration of response, PFS and overall survival) of ADXS11-001 in subjects with persistent/recurrent, loco-regional or metastatic SCCA of the anorectal canal as determined by RECIST 1.1 and irRECIST.
Criteria for Evaluation	Safety: recorded AEs, changes in physical examinations, vital signs measurements, clinical laboratory evaluations and *Lm* surveillance monitoring. Efficacy: Response rates as measured by RECIST 1.1 and irRECIST, duration of response, PFS

2 TRIAL DESIGN

Specific procedures to be performed during this trial, as well as the prescribed times and associated visit windows are outlined in the Schedule of Events- Section 6.1. Details of each procedure are provided in Section 7.1 - Trial Procedures.

This is a multi-center, open-label, 2 stage monotherapy study of ADXS11-001 in subjects with persistent/recurrent, loco-regional or metastatic SCCA of the anorectal canal that was previously treated in the metastatic setting. Stage 1 of the study will evaluate the safety and efficacy of ADXS11-001. After 31 evaluable subjects have been enrolled, further accrual will be temporarily stopped in Stage 1 to complete an interim efficacy

analysis evaluation. If the efficacy from Stage 1 demonstrates a response rate ≥10% by either RECIST 1.1 or 6-month progression free survival (PFS) rate ≥20%, enrollment will re-open to Stage 2. Enrollment will be complete in Stage 2 when an additional 24 evaluable subjects have been accrued (total 55).

Subjects will be treated with intravenous (IV) ADXS11-001 administered over [redacted] every 3 weeks at a dose of 5 x 10^9 CFU for up to 2 years or until a discontinuation criterion is met. A treatment cycle is defined as 9 weeks. Tumor assessments will occur every 9 weeks (Week 8 of every Cycle). Subjects will be monitored for adverse events (AEs) throughout the study; AEs will be graded in severity according to the guidelines outlined in the NCI Common Toxicity Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Safety follow-up will be conducted via telephone call 30 days (±5 days) after the last ADXS11-001 infusion to confirm the resolution of any ongoing AEs and SAEs. Survival Follow-Up will be conducted at each visit during the Lm Surveillance period and via a telephone call every 3 months (± 2 weeks) after the Lm Surveillance period to determine survival status for all subjects.

The end of the study will be defined as 1 year after the last subject has enrolled on study. However, any ongoing subjects, subjects who are still deriving clinical benefit from ADXS11-001 therapy at the end of their 2-year treatment period or at the end of the study may be enrolled into a separate extension study, as available.

Safety and efficacy analysis will be performed for both parts of the study. Subject disposition, demographic and baseline characteristics will be summarized separately for Stage 1 and Stage 2. Adverse events will be classified and summarized by system organ class (SOC) and preferred term, incidence, severity, and causality. All subjects who receive at least 1 dose of study treatment will be included in the safety analyses.

Efficacy analysis will be performed for Stage 1 separately (interim analysis) and both parts of the study combined. All subjects who have completed at least 1 cycle of study treatment will be included in the efficacy analyses.

3 OBJECTIVES & HYPOTHESIS

3.1 Primary Objectives & Hypothesis

Objective: To evaluate efficacy as measured by the overall response rate and rate of 6 month PFS in subjects with persistent/recurrent, loco-regional or metastatic SCCA of the anorectal canal as determined by RECIST 1.1

a. **Hypothesis**: ADXS11-001 will produce response rates ≥10% or 6 month PFS rates ≥20% in subjects with persistent/recurrent, loco-regional or metastatic SCCA of the anorectal canal.

3.2 Secondary Objectives

Objective: To evaluate efficacy as measured by the overall response rate and rate of 6 month PFS in subjects with persistent/recurrent, loco-regional or metastatic SCCA of the anorectal as determined by irRECIST

Objective: To evaluate the safety and tolerability of ADXS11-001 in subjects with persistent/recurrent, loco-regional or metastatic SCCA of the anorectal canal by NCI CTCAE 4.0.

Objective: To evaluate the additional parameters of efficacy (duration of response, PFS and overall survival) of ADXS11-001 in subjects with persistent/recurrent, loco-regional or metastatic SCCA of the anorectal canal as determined by RECIST 1.1 and irRECIST.

4 BACKGROUND & RATIONALE

4.1 Background

4.1.1 ADXS11-001 Immunotherapy

ADXS11-001 is a live attenuated *Listeria monocytogenes* (*Lm*)-LLO immunotherapy, developed for the treatment of human papilloma virus (HPV)-associated cancers. ADXS11-001 is bioengineered to secrete an antigen-adjuvant fusion protein (tLLO-HPV-E7) consisting of a truncated fragment of the listeriolysin O (tLLO) fused to the full length E7 peptide of HPV-16.

ADXS11-001 is phagocytized by antigen-presenting cells (APCs) and secretes Listeriolysin O (LLO)-tumor antigen fusion proteins within the cytoplasm of the APC thereby allowing the generation of a new population of tumor antigen specific cytotoxic T lymphocytes (CTLs) driven by the adjuvant properties of LLO. These tumor-specific CTLs can then take advantage of the acute immunologic response to the live vector to facilitate infiltration into the tumor, enabling them to access and destroy tumor cells.

The advantages that *Lm* possesses as a vector are rooted in its biology. It is a beta hemolytic Gram positive facultative intracellular bacterium that has been used to study cell mediated immunity for decades.[1] *Lm* are preferentially taken up by APCs and, unlike other intracellular bacteria like Salmonella, *Lm* escapes into the cytoplasm of the host cell by disrupting the phagosomal membrane. Also unlike Salmonella, *Lm* is a Gram positive organism, thus, does not release endotoxin, a rate limiting attribute of Salmonella. Because *Lm* quickly leaves the circulation becoming an intracellular infection and because it replicates in the cytoplasm, humoral immunity does not play a major role in combating listerial infections.

Lm has other useful properties, such as stimulating monopoiesis, stimulating the differentiation and maturation of APCs, and the generation of a particularly strong innate and adaptive cellular immune response.[1, 2] The ability to deliver antigen to the cytosolic compartment of APCs in order to develop human leukocyte antigen Class I

presentation to induce CD8+ cytotoxic T-cell responses appears to be an important aspect of developing an effective therapeutic antitumor therapy. Peptides derived from *Lm* in the phagolysosome and the cytosol can be presented by both the major histocompatibility complex (MHC) Class I and Class II molecules, inducing both CD4+ and CD8+ T cell responses. There is evidence that *Lm* also gets into tumors, probably carried by infected macrophages and neutrophils. One potential consequence of this is the observed ability of live *Lm* vector that secrete an LLO-antigen fusion, but not those that secrete only an antigen, to diminish regulatory T-cells (Tregs) within the tumor, but not in the spleen or normal peripheral tissues.

As a drug product, ADXS11-001 is administered as an IV infusion given every 3-4 weeks. It has no direct effect on tumor tissue, but is designed to stimulate the subject's own immune system to generate an effective immune response targeting a tumor-associated antigen like HPV-E7. Clinical benefit can manifest as a slowing of tumor growth, a stabilization of tumors, or a partial or complete response of the tumors.[3] Collectively, the spectrum of clinical benefits is captured as relative delays in tumor progression and/or apparent prolonged survival.

4.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for detailed preclinical and clinical data.

4.2 Rationale for Trial and Selected Subject Population

Human papilloma viruses are spread by direct human contact. Infection of squamous mucosal epithelial cells by high risk strains of HPV can result in the transformation of squamous epithelial to a pre-malignant phenotype that can progress to malignancy. High risk HPV strain E6 and E7 gene products interfere with the expression and function of the host tumor suppressor gene products of P53 and Rb in the host cell. This process can occur in the uterine cervix and can lead to cervical cancer, the oropharyngeal mucosa of the tonsils or base of the tongue, and lead to squamous cell carcinoma of the oropharynx, or the mucosal epithelium of the anus leading to anorectal cancer.

While it is estimated that 80% of sexually active individuals are exposed to oncogenic strains of HPV, the percentage that develop dysplastic or malignant lesions is considerably less.[4] This is presumably because many individuals can clear the viral infection immunologically. However, in some individuals, the virus is not cleared and expressions of viral gene products can lead to malignancy over time.

Various mechanisms have been proposed for the resistance of human solid tumors to immune recognition and obliteration, including the recruitment of regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSC), and local secretion of inhibitory cytokines that mediate immune tolerance in tissue or tumor microenvironments. The occurrence of HPV-induced cancer is strongly associated with failure to mount a strong HPV-specific type 1 T-helper and cytotoxic T-lymphocyte response.[5-7]

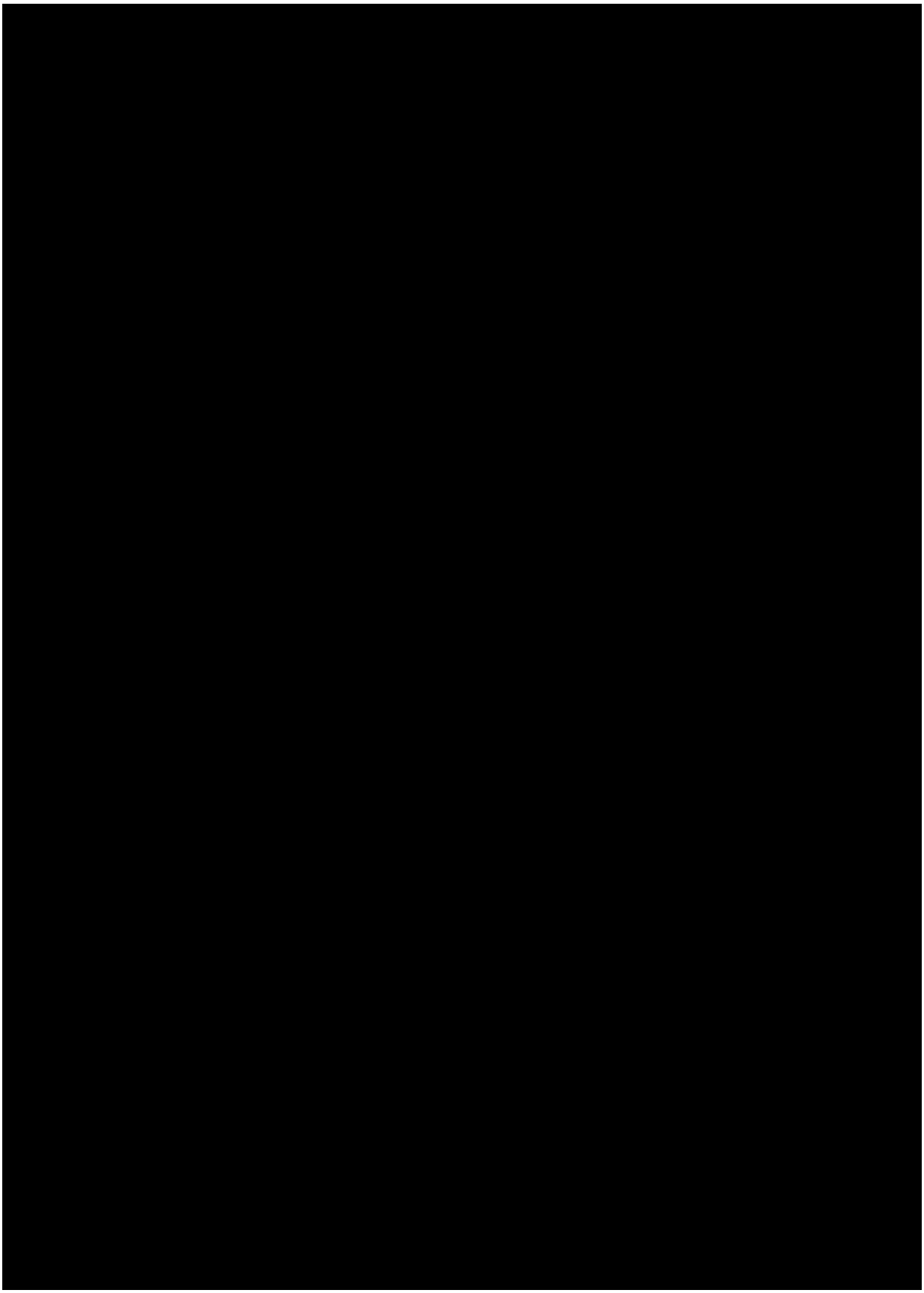
However, the inhibitory action of HPV-specific Tregs within the tumor microenvironment is not the only mediator of immune tolerance contributing to the immunologic resistance of HPV-associated malignancy. Recent evidence also suggests that tumors can co-opt physiologic mechanisms of tissue protection from inflammatory destruction via up-regulation of immune inhibitory ligands.

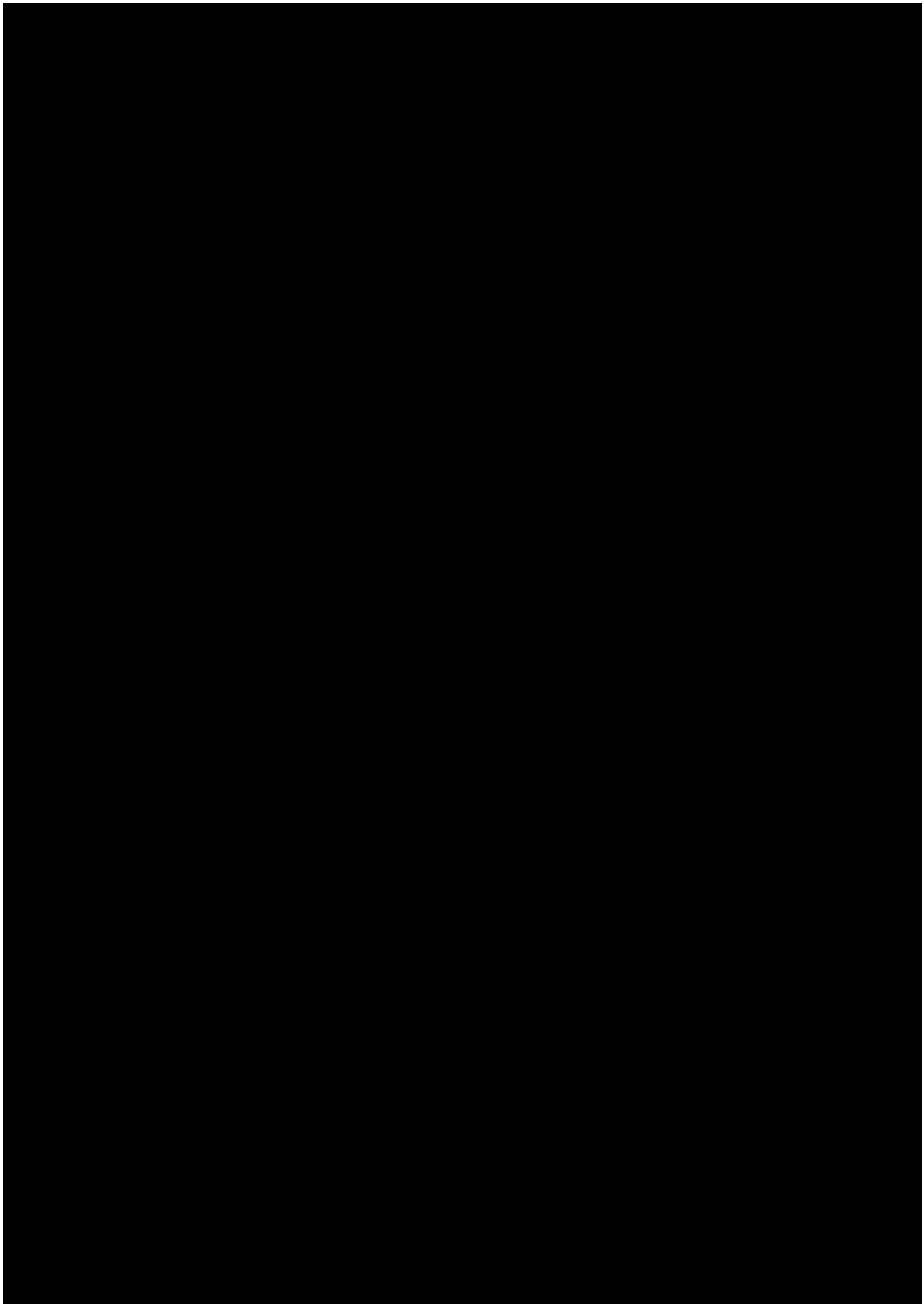
The mechanism of oncogenesis from high-risk HPV infection in squamous mucosal epithelium is consistent, whether the site of infection is the cervix or the oral or anal mucosa. Persistence of the virus and its inhibition of tumor suppressor functions can lead to the development of dysplasia or malignant carcinoma. Anorectal cancer, although relative rare has been steadily increasing over the last 50 years. And while both survival and locoregional control is good for patients with early stage anorectal cancer, for those patients with high risk and/or recurrent metastatic disease the unmet medical need remains high.[8, 9] The epidemiology of anorectal cancer demonstrates that high-risk HPV has been reported in approximatley 90% in patients with squamous cell cancer of the anorectal canal, with serotypes HPV 16 and 18 being the most common.[10] Given the activity that ADXS11-001 has demonstrated in metastatic squamous cell cancer of the cervix,[3] which are histologically and epidemiologically similar to anorectal cancer, evaluation of ADXS11-001 in patients with anorectal cancer seem logical.

Currently there is an ongoing clinical study in subjects with high-risk locally advanced squamous anal cancer which evaluates ADXS11-001 therapy prior to, and following standard of care radiotherapy and concurrent 5FU/mitomycin C (MMC) (NCT #01671488). To date 10 subjects have been enrolled. Preliminary safety data from this ongoing study are consistent with those observed with ADXS11-001 treatment to date. The current study seeks to evaluate ADXS11-001 in the metastatic population. The standard of care for patients with metastatic disease was established several years ago with a combination regimen of 5FU and cisplatin. Response rates with this combination range between 40-50% with median overall survival of 34.5 months.[11, 12] While efficacious, patients will recur and eventually succumb to their disease. The need to evaluate new therapies, particularly those targeted at HPV, such as ADXS11-001 is warranted.

4.2.1 Rationale for Dose Selection/Regimen/Modification

4.2.1.1 Summary of Safety of ADXS11-001





[redacted]

4.2.2 Delayed/Late Listeria Infection

In a Phase 1 clinical study, in the absence of antibiotics, *Lm* was rapidly cleared from the blood. No *Lm* was detected in the blood, urine or feces of any subject beyond 48 hours post-dosing and at the highest dose of ADXS11-001 tested (1×10^{10} CFU).[13]

wt-*Lm* is known to form and persist within biofilms especially on medical devices despite antibiotic treatment.[14] Although rare, medical device–related infections such as ventriculo-peritoneal shunt infection, peritoneovenous shunt infection, and prosthetic joint infection have been reported.[15-18] ADXS11-001is highly sensitive to antibiotics such as ampicillin and trimethoprim/sulfamethoxazole which can be an effective treatment regimen for listeria infection. Therefore, subjects with implanted medical device(s) that pose a high risk for colonization and/or cannot be easily removed are excluded from this study. In addition, all subjects will receive a course of oral antibiotics beginning on Day 4 (approximately 72 hours) after each dose of ADXS11-001 and for 6 months following the last dose of ADXS11-001 to aid in the eradication of the bacteria.

[redacted]

[redacted]

4.2.2.1 ADXS11-001 – Rationale for Dose Selection and Regimen

ADXS11-001 is a live attenuated strain of Listeria monocytogenes (*Lm*) that has been

[redacted]

The AEs associated with this class of agents seem to be directly related to innate immune effects associated with the infusion of the live attenuated bacteria. These typically consist of Grade 1 and 2 cytokine release symptoms (e.g., fever, chills, rigors, headache, nausea, vomiting, tachycardia, shortness of breath, hypotension, and rash) which typically occur 2-4 hours after ADXS11-001 infusion and usually resolve within 12-24 hours. The symptoms appear to be related to the number of CFU infused over time. Pretreatment with hydration, oral nonsteroidal anti-inflammatory drugs (NSAIDs), antihistamines, histamine H2-receptor antoagonists and antiemetics may reduce the incidence of these symptoms.

With ADXS11-001, live bacteria has not been recovered from subjects after 48 hours following completion of the infusion. A 7-day course of oral antibiotics is given beginning on Day 4 post dose to help ensure clearance of the vector. There is no specific target blood level that needs to be achieved in order for ADXS11-001 to compete with a target or bind to a receptor. Therefore, maximum concentration (C_{max}), minimum concentration (C_{min}), and half-life of ADXS11-001 are not relevant based on pharmacology.

[redacted]

[redacted]

The complex mechanism of action of ADXS11-001 includes elements that may be dose related. For example, the generation of T-cells may require a minimum effective dose in order for the body to respond. In previously completed, as well as ongoing clinical studies, a dose of 1 x 10^9 CFU has demonstrated clinical responses and appears to meet this minimum requirement. Additionally, in patients with advanced disease there may be an added benefit to treating with higher doses and repeating treatments until progression or complete response

Patients with metastatic or recurrent anorectal cancer have advanced disease, extremely limited treatment options and a poor long-term prognosis. Therefore, these patients should receive the most aggressive treatment that can be administered safely to optimize their opportunity for clinical benefit. Since the results from the ongoing Phase 1 study have shown that a dose of 1 x 10^{10} CFU can be safely adminstered and is well-tolerated by patients with an advanced HPV-related disease (cervical cancer), a dose of 5 x 10^9 CFU of ADXS11-001 has been selected for use in this clinical study. This dose has also be shown that it can be safely administered and was well-tolerated in a clinical study of patients with advanced HPV disease. It is also a dose level below the dose (1 x 10^{10} CFU) which has been established as the RP2D in a clinical study in an advanced disease HPV population. Finally, this dose was selected to offer patients with advanced anal cancer the greatest opportunity to receive clinical benefit during their participation in the study. The safety and tolerability of this dose will be evaluated in this population on an individual and cumulative subject basis. Defined stopping rules are in place which require safety data to be evaluated and the study 'stopped' if specific individual patient and/or cumulative patient criteria are met. The 5 x 10^9 dose will be evaluated when the study is 'stopped' based on meeting the protocol-defined criteria in order to determine if it is safe to proceed at this dose level or a lower dose should be considered. All subjects will

receive treatment for up to two years, until confirmed disease progression or until a complete clinical response is achieved.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The evaluation of efficacy for both the parts of the study will utilize CT or magnetic resonance imaging (MRI) to assess tumor response as well as PFS measured by RECIST 1.1 and irRECIST. These endpoints are well established and commonly used to evaluate signs of clinical activity and efficacy.

4.2.3.2 Safety Endpoints

The safety objective of this trial is to characterize the safety and tolerability of ADXS11-001 in subjects with metastatic SCCA of the anorectal canal. The safety analysis will be based on subjects who experience toxicities as defined by NCI CTCAE v 4.0. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received ADXS11-001, including SAEs.

The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, changes in physical examinations, vital sign measurments and clinical laboratory changes.

4.2.4 Study Stopping Rules

Rules for temporary suspension of study for death due to non-progressive disease, hematologic and non-hematologic events related to ADXS11-001 treatment

The Advaxis medical monitor and Project Manager as well as other key personnel associated with the trial (e.g. CRO Medical Monitor, Primary Investigator), as appropriate, will monitor death due to non-progressive disease and hematologic and non-hematologic toxicities for individual subjects in real-time and trial-level cumulative toxicities on a monthly basis. These events must be deemed by the Investigator at the site to have some degree of "relatedness" to ADVXS11-011 treatment (e.g. definitely, probably or possibly related) in order to be considered for evaluation. The assessment of cumulative trial-level toxicities will not begin until at least 5 subjects have received a dose of ADXS11-001 and evaluated for death and individual toxicity events following the completion of the initial 3-week treatment period. The guidelines below will be used to determine the threshold of cumulative events that will result in temporary suspension of enrollment for new subjects and dosing for any active subject until a thorough of the cumulative information is evaluated and a risk/benefit assessment conducted.

- Death (other than death related to disease progression) that occurs within 30 days of the ADXS11-001 infusion

- >30% Grade 3 or greater non-hematologic adverse events that are at least possibly related to ADXS11-001
- >30% Grade 4 or greater hematologic adverse events that are at least possibly related to ADXS11-001

The assessment of an individual subject event which meets the criteria as defined above and has been determined by the investigator to be related to ADXS11-001 treatment will begin as soon as all required and relevant information is received. The same project team personnel will review all of the information and determine an appropriate course of action (e.g., temporarily suspending enrollment and ongoing treatment in active subjects; temporarily suspending enrollment and allowing treatment in active subjects to continue) based on a thorough review pertaining to the event.

The Sponsor will send a written communication to the investigative sites when a decision is made based on all available information from an individual subject or the cumulative data to temporarily suspend future enrollment and/or the continued doing of active subjects. The communication will contain information about the event(s) and the immediate steps which must be taken in order to comply with the Sponsor's decision. The investigative sites will also receive written notification from the Sponsor when the enrollment of new subjects and dosing for active subjects may resume.

5 METHODOLOGY

5.1 Entry Criteria

5.1.1 Inclusion Criteria

This study will include subjects with persistent/recurrent, loco-regional or metastatic SCCA of the anorectal canal.

For subjects to be eligible they:

1. Must have histopathologic diagnosis of squamous cell cancer of the anorectal canal.
2. Must have received at least one line of therapy for their metastatic disease. However patients deemed by their investigator as not optimal candidates for chemotherapy (e.g., drug allergy, ototoxicity, renal insufficiency) would be considered eligible.
3. Be willing and able to provide written informed consent for the trial.
4. Be ≥18 years of age on day of signing informed consent.
5. Have measurable disease based on RECIST 1.1
6. Have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. Demonstrate adequate organ function as defined in Table 3.

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)[a]	≥1,000 /mcL
Platelets	≥75,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) OR ≥50 mL/min for subject with creatinine levels >1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤1.5 X ULN OR Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 ULN
AST (SGOT) and ALT (SGPT)	≤2.5 X ULN OR ≤5.0 X ULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or INR is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as aPTT is within therapeutic range of intended use of anticoagulants

[a] ANC, Platelets, Hemoglobin requirement cannot be met by the use of recent transfusions, or growth factor support (G-CSF, erythropoietin, etc) within 2 weeks prior to treatment initiation.
[b] Creatinine clearance should be calculated per institutional standard.

8. Female subjects of childbearing potential must not be breastfeeding and have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
9. Female subjects of childbearing potential should be willing to use 2 methods of birth control for the course of the study through 120 days after the last dose of study medication (see Section 5.7.2).
10. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
11. Must have a washout period of the following prior to first dose of study treatment:

a. **14 days** from completing prior standard of care therapy, with the exception of MMC and palliative radiation therapy for disease-related pain.

b. **6 weeks** from the last dose of MMC, given the delayed bone marrow suppression that can be experienced with MMC.

c. **28 days** from treatment with investigational device/therapy or 3 times the half-life in the case of monoclonal antibodies, whichever is longer

d. **7 days** from treatment with systemic steroid therapy or any other form of immunosuppressive therapy

e. **30 days** from treatment with live vaccine

Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, typhoid, and intranasal influenza vaccines (e.g., Flu Mist®). Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed.

5.1.2 Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Has not recovered (e.g., Grade ≤1 or at baseline) from AEs, with the exception of alopecia or Grade ≤2 neuropathy, due to a previously administered agent.

2. Has a diagnosis of immunodeficiency.

3. Has known additional malignancy that is progressing or requires active treatment. Treatment of an additional malignancy with chemotherapy, immunotherapy, biologic or hormonal therapy must have occurred 2 years prior. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

   a. Note: Local treatment of isolated lesions for palliative intent (e.g., by local surgery or radiotherapy), basal cell carcinoma of the skin, or squamous cell carcinoma of the skin, or ductal carcinoma in situ of the breast that has/have been surgically cured is acceptable.

4. Has known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided the metastases are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to the first dose of study treatment.

5. Has concurrent unstable or uncontrolled medical condition (e.g. active uncontrolled systemic infection, poorly controlled hypertension or history of poor compliance with an anti-hypertensive regimen, unstable angina, congestive heart failure, uncontrolled diabetes) or other chronic disease, which in the opinion of the investigator, could compromise the patient or the study.

6. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents.

    a. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule.

    b. Subjects that require intermittent use of inhaled steroids, bronchodilators or local steroid injections may be allowed with sponsor approval.

    c. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's Syndrome will not be excluded from the study.

7. Has an active infection requiring systemic therapy. Prior to dosing with study treatment(s), the subject must be at least 5 half-lives from their last dose of antibiotic.

8. Has any other serious or uncontrolled physical or mental condition/disease that, as judged by the investigator, could place the patient at higher risk derived from his/her participation in the study, could confound results of the study, or would be likely to prevent the patient from complying with the requirements of the study or completing the study.

9. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

10. Subject has implanted medical device(s) that pose a high risk for colonization and/or cannot be easily removed (e.g., prosthetic joints, artificial heart valves, pacemakers, orthopedic screw(s), metal plate(s), bone graft(s), or other exogenous implant(s)).

    a. Note: More common devices and prosthetics which include arterial and venous stents, dental and breast implants and venous access devices (e.g. Port-a-Cath or Mediport) are permitted. Subjects with any other devices or implants must be approved by Sponsor prior to participation.

11. Any patient currently requiring or anticipated to require tumor necrosis factor (TNF) blocking agent (e.g., infliximab) therapy for diagnosis of rheumatologic disease or inflammatory bowel disease (e.g., ankylosing spondylitis, Crohn disease, plaque psoriasis, psoriatic arthritis, rheumatoid arthritis or ulcerative colitis).

12. Patients who are currently receiving or who have received any PI3K inhibitor within 30 days prior to registration.

13. Subject has a contraindication (e.g. sensitivity/allergy) to trimethoprim/sulfamethoxazole **and** ampicillin.

14. Has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).

15. Has known active hepatitis B or hepatitis C.

16. Has a known allergy to any component of the study treatment(s) formulations.

17. Has contraindication to administration of NSAIDs.

18. Has undergone a major surgery, including surgery for a new artificial implant and/or medical device which is permitted by the protocol, within 6 weeks prior to the initiation of ADXS11-001 treatment

    a. Note: If the subject had a major surgery, all toxicities and/or complications from the intervention must have recovered to at least the baseline or Grade 1 prior to the initiation of ADXS11-001 study therapy. Consult with the Sponsor prior to enrolling subjects on the study who recently had a major surgery or have a new artificial implant and/or medical device.

19. In the opinion of the investigator has rapidly progressing disease, OR has life expectancy of <6 months, OR would be unable to receive at least 1 cycle of therapy.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 4.

Table 4 Trial Treatment

Drug	Dose	Regimen	Route of Administration	Regimen/Treatment Period	Use
ADXS11-001	5 x 10^9 CFU	Q3W	IV infusion	9-week cycle	Experimental

5.2.1 Dose Selection/treatment Modification

The dose to be used in each stage of the trial is described above. Treatment Modification Guidelines are described below in Section 5.2.1.2.

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.2.2.1. The dose of ADXS11-001 will be 5 x 10^9 CFU, however the sponsor reserves the right to change the dose up to 1 x 10^{10} CFU based on emerging data from ongoing clinical studies. If the dose is escalated, subjects who initiated therapy at 5 x 10^9 CFU may be be escalated up to 1 x 10^{10} CFU only after consultation with the sponsor.

The dose of 5 x 10^9 CFU will not be reduced for individual subject, however, the dose may be reduced for all subjects based on the stopping rules outlined in Section 4.2.4

Details on the dose calculation, preparation and administration are provided in the Pharmacy Manual.

5.2.1.2 Treatment Modification/Delay Due to Adverse Events

The most likely AEs associated with ADXS11-001 are comprised primarily of individual flu-like symptoms (e.g., fatigue, lethargy and low grade fever) or cytokine release symptoms (e.g., constitutional symptoms such as fever, chills, rigors, headache, nausea, vomiting tachycardia, shortness of breath, hypotension, and rash). These symptoms usually present within 2-4 hours after the completion of infusion and are often mild to moderate and transient in nature or respond quickly to symptomatic treatment. In rare instances they may last up to 24 hours. No cumulative or delayed toxicity has been observed.

Less likely AE's include increase heart rate, low blood pressure, muscle aches, headaches, allergic reaction, changes in blood chemistry, changes in blood counts, and short term changes in liver function.

Rare but serious AEs include high fever, difficulty breathing and hypotension.

[redacted] ADXS11-001 has a tropism for the liver. Transient asymptomatic elevations of ALT and alkaline phosphatase were observed after dosing in the Phase 1 trial without prophylactic medication administration. For that reason, patients with significant liver disease are excluded, and particular attention is to be paid to hepatic abnormalities. Treatment may be delayed or discontinued for drug related severe and life-threatening toxicities, as shown below in Table 5.

Table 5 Treatment Delay/Discontinuation Guidelines for Drug-Related Adverse Events

Toxicity	Grade	Hold treatment	Timing for restarting treatment	Discontinue subject
Hematologic	1,2,3	No	N/A	N/A
	4	Yes	Toxicity resolves to ≤Grade 1or baseline	Toxicity does not resolve to ≤Grade 1or baseline within 3 weeks
	1	No	N/A	N/A
	2-3	Yes	Toxicity resolves to ≤Grade 1 or baseline	Toxicity not resolved to ≤Grade 1 or baseline within 3 weeks of last infusion[a]

Non-hematologic, excluding cytokine release symptoms and DLTs	4	N/A	Permanent discontinuation	Permanent Discontinuation from Study

a With investigator and sponsor agreement, subjects with a non-heme AE (eg alopecia, neuropathy) still at grade 2 after 3 weeks, may continue treatment if only asymptametic and controlled

With Investigator and Sponsor agreement, subjects with a laboratory AE still at Grade 2 after 2 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the supportive care of AEs, see Section 5.6.

Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of ADXS11-001 should be discontinued from trial participation.

5.2.2 Administration of ADXS11-001

[redacted]

5.2.3 Timing of Dose Administration

ADXS11-001 should be initiated on Cycle 1/Day 1 after all procedures/assessments have been completed as detailed on the Schedule of Events (Section 6.1). Trial treatment may be administered up to 7 days before or after the scheduled treatment day due to administrative reasons but only after consultation with the Sponsor.

All trial treatments will be administered on an outpatient basis.

5.2.4 Pretreatment Prophylaxis Regimen

Mild to moderate cytokine release symptoms (e.g., constitutional symptoms such as fever, chills, rigors, headache, nausea, vomiting, tachycardia, shortness of breath, hypotension~~,~~ and rash~~.~~) are commonly seen and typically occur 2-4 hours after ADXS11-001 infusion and often resolve within 12-24 hours. Prophylactic medications are intended to reduce the inflammatory response. Subjects should receive the following pretreatment prophylaxis regimen:

IV Fluid Hydration:

- Normal saline (e.g., 500mL over 30 minutes)

Premedication Regimen:

- Antihistamine- PO or IV (e.g., diphenhydramine 25 mg or equivalent), once
- NSAIDs- PO, (e.g., naproxen, 220 mg or ibuprofen, 400 mg), once
- Antiemetic- PO or IV, (e.g., promethazine or ondansetron), once
- Histamine H2-receptor antagonist- PO or IV (e.g., famotidine 20 mg or equivalent), once

Pretreatment medication should be given on the day of dosing and completed at least 30 minutes prior to the start of the assigned study treatment. Additional NSAID doses and antiemetic administration should be given per label or package insert post initial administration on Day 1 and Day 2 , as needed. The prescribed dosage of the selected NSAID and antiemetic will be at the discretion of the Investigator.

Do not substitute acetaminophen for the selected NSAID for prophylactic treatment since acetaminophen does not have similar anti-inflammatory properties that could ameliorate cytokine release symptoms.

5.2.5 ADXS11-001 Dosing

The dose for ADXS11-001 will be 5 x 10^9 CFU administered in 250 mL of normal saline infused over [redacted] Q3W in repeating 9-week treatment cycles.

The Pharmacy Manual contains specific instructions for ADXS11-001 storage, handling, dose calculation, reconstitution, destruction and ordering.

All subjects will also receive a 7 day course of oral antibiotics following each ADXS11-001 treatment. Specific details of the antibiotic regimen are provided in Section 7.1.6.2.

5.2.6 Treatment Duration

The study begins when the first subject signs informed consent.

The treatment duration is approximately 2 years.

5.2.7 Trial Blinding/Masking

This is an open-label trial. Therefore, the Sponsor, investigator and subject will know the treatment administered.

5.3 Randomization or Treatment Allocation

All subjects will receive ADXS11-001.

5.4 Stratification

There is no stratification.

5.5 Concomitant Therapies and Procedures (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from ADXS11-001 therapy may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on ADXS11-001 therapy requires the mutual agreement of the Investigator, the Sponsor, and the subject.

5.5.1 Acceptable Concomitant Therapies and Procedures

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication, therapies and procedures will be recorded on the electronic case report form (eCRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. Protocol-mandated prophylactic medications and antibiotics should also be captured in the eCRF. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should be included on the CRF. Only generic names should be used. Do not use trade names.

All concomitant medications received within 28 days before the first dose of trial treatment and up to 30 days after the last dose of trial treatment should be recorded.

5.5.2 Prohibited Concomitant Therapies

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Anti-cancer therapy including but not limited to, hormonal, chemotherapy, radiation therapy, treatment with targeting agents (eg, Tyrosine kinase inhibitors). However occasional radiation therapy for palliation of pain is allowed
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor. Radio-pharmaceuticals (e.g., radium, strontium, etc.) are not acceptable.
- Immunotherapy not specified in this protocol
- Investigational agents other than ADXS11-001

- PI3K inhibitors and TNFα blocking agents

- Live vaccines (eg, measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid) and intranasal influenza vaccines (eg, Flu-Mist®). Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed.

- Chronic use of systemic glucocorticoids has the potential to reduce the immune response therefore should not be used. However, glucocorticoids should be considered to manage symptoms related to cytokine release . Topical use of steroids is allowed. The intermittent use of steroids for the treatment of COPD and or asthma is allowed.

- Anti-infectives should be avoided. However, subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

- Acetaminophen is not to be used for premedication because it does not have anti-inflammatory properties required for AE amelioration but may be used for supportive care measures.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management may be removed from the trial after discussion with the sponsor. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria (Section 5.1.2) describe other medications that are prohibited in this trial. There are no prohibited therapies during post-treatment follow-up.

5.6 Supportive Care Guidelines

[redacted] Subjects should receive appropriate supportive care measures as deemed necessary by the treating Investigator including but not limited to the items outlined below.

5.6.1 Cytokine Release Symptoms

Cytokine Release Symptoms is a constellation of inflammatory symptoms resulting from cytokine elevations associated with T cell engagement and proliferation. Symptoms related to cytokine release may include constitutional symptoms such as fever, chills, rigors, headache, nausea, vomiting, rash tachycardia, hypotension, , and shortness of breath which usually presents several hours after the infusion and may last for up to 24 hours. These symptoms are caused by an increase in cytokines such as TNFα, IFNγ and

IL-6, all of which have been shown to occur after ADXS11-001 administration, resulting from the body's immune response to the therapy. Although, symptoms are often grade 1-2 and transient, resolving with symptomatic management within 30 minutes-1 hour, in rare instances (~1%) grade 3-4 hypotension has been seen. Therefore, close monitoring of blood pressure is strongly recommended at baseline, and during the post-infusion period. Increased levels of IL-6, has been strongly associated with capillary leak which manifests as hypotension due to the cytokines involved. We have observed elevated IL-6 levels after infusion of ADXS11-001, with peak levels occurring 2-4 hours after infusion. Emerging evidence indicates that IL-6 antagonists, such as Tocilizumab, has demonstrated good results in treating cytokine-induced hypotension [19-22] and is therefore recommended for cases of severe hypotension refractory to supportive care (e.g. fluids and/or pressors).

The management of cytokine release symptoms and guidelines for subsequent treatment for patients who have experienced these adverse events are shown in Table 6.

Table 6 Recommended Management Guidelines for Adverse Events Associated with Cytokine Release

Toxicity	NCI CTCAE Grade or Severity	Treatment	Modification for Subsequent infusions
Hypotension	1 Mild	• Supportive care	• Increase pretreatment IV fluids (e.g., 500 ml - 1L normal saline)
Fever, Constitutional symptoms	1	• Supportive care	• No modification
Hypotension	2 Moderate	• Fluids and 1 dose of pressor (e.g. 0.3 mg epinephrine IM) • Increase monitoring of vital signs • If hypotension persist for more than one hour consider low dose corticosteroids (e.g. hydrocortisone 100 mg IV over 30 seconds	• Extend infusion time to 2 hours. Increase pretreatment IV fluids (e.g. 500 ml -1L normal saline) • Incorporate Glucocorticoid- Hydrocortisone or equivalent- 50 mg, IV, as premedication
All other cytokine release symptoms (e.g. chills, rigors, fever, nausea, vomiting)	2	• Appropriate supportive care measure	• Extend infusion time to 2 hours. • Consider increasing doses of prophylactic medications
Hypotension	3 Severe	• Fluids, high dose pressors (e.g. Dopamine 10 µg/kg/min) +1 dose tocilizumab*(4mg/kg over 1 hour) • If hypotension worsens or is unresponsive to above measures, administer corticosteroids • If the patient's condition does not improve or stabilize within 24 hours of the tocilizumab dose, administration of a second dose of tocilizumab +/- corticosteroids should be considered.	• Discuss with Sponsor

Toxicity	NCI CTCAE Grade or Severity	Treatment	Modification for Subsequent infusions
All other cytokine release symptoms (e.g. chills, rigors, fever, nausea, vomiting)	3	• Appropriate supportive care measures	• Extend infusion time to 2 hours. • Consider increasing doses of prophylactic dose of NSAID, or antiemetic as appropriate
Hypotension/Organ toxicity, mechanical ventilation	4 Life threatening	• Vigilant supportive care • Fluids, • High dose pressors, • Tocilizumab (4mg/kg over 1 hour) +/- corticosteroids (hydrocortisone 100 mg IV infused over 30 seconds administered every 2 hours until symptoms resolve to <Grade 1)	• Permanently discontinue

* Tocilizumab is a humanized, immunoglobulin G1k (IgG1k) anti-human IL-6R mAb approved for treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to Disease-Modifying Anti-Rheumatic Drugs (DMARDs), for the treatment of active polyarticular juvenile idiopathic arthritis (PJIA), and active systemic juvenile idiopathic arthritis (SJIA) in patients 2 years of age and older. Tocilizumab works by preventing IL-6 binding to both cell-associated and soluble IL-6Rs. Although, it is not indicated for the treatment of cytokine release symptoms emerging clinical experience at several institutions has concluded that tocilizumab is an effective treatment for severe or life-threatening cytokine release symptoms**.[19-22]**

5.6.2 Nausea/vomiting

Nausea and vomiting should be treated aggressively. In addition to the prophylactic antiemetic therapy subjects receive prior to each infusion, consideration should be given to subsequent administration of antiemetic therapy every 8 hours, as needed according to standard institutional practice. Subjects should also be strongly encouraged to maintain liberal oral fluid intake.

5.6.3 Infusion Reaction

While there is some overlap between infusion reactions symptoms and cytokine release symptoms, infusion reactions symptoms, typically occur during the infusion, while cytokine release symptoms typically occur after the infusion and are mediated by a different mechanism of action. Signs/symptoms of infusion reactions may include: allergic reaction/ hypersensitivity (including drug fever); arthralgia (joint pain); bronchospasm; cough; dizziness; dyspnea (shortness of breath); fatigue (asthenia, lethargy, malaise); headache; hypertension; hypotension; myalgia (muscle pain); nausea; pruritic/itching; rash/ desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); and vomiting. Table 7 below shows the management guidelines for subjects who experience an infusion reaction associated with administration of the study treatment.

Table 7 Management Guidelines for Infusion Reactions

NCI CTCAE Grade	Treatment
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	1. Stop Infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics 2. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.
Grades 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilatory support indicated	1. Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine 2. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. 3. Hospitalization may be indicated. 4. Subjects who experience a Grade 4 reaction should be permanently discontinued from study. Subjects who experience a grade 3 reaction may be discontinued. Discussion with the Sponsor is recommended

5.6.3.1 Listeriosis and Listeria Infection - Identification and Management

A person with (wt) listeriosis usually presents with fever and muscle aches, sometimes preceded by diarrhea or other gastrointestinal symptoms. Almost everyone who is diagnosed with listeriosis has an "invasive" infection, in which the bacteria spread beyond the gastrointestinal tract. The symptoms vary with the infected person. Pregnant women typically experience fever and other non-specific symptoms, such as fatigue and aches. However, infections during pregnancy can lead to miscarriage, stillbirth, premature delivery, or life-threatening infection of the newborn. In people other than pregnant women, symptoms can include headache, stiff neck, confusion, loss of balance, and convulsions in addition to fever and muscle aches. Listeriosis can present in different ways. In older adults and people with immunocompromising conditions, septicemia and meningitis are the most common clinical presentations.[23] Subjects may need immediate evaluation with a brain CT scan or MRI and a lumbar puncture with the analysis of spinal fluid to rule out meningitis.

For symptomatic patients, diagnosis is confirmed only after isolation of *Lm* from a normally sterile site, such as blood or spinal fluid (in the setting of nervous system involvement), or amniotic fluid/placenta (in the setting of pregnancy). Stool samples are of limited use and are not recommended. *Listeria monocytogenes* can be isolated readily on routine media, but care must be taken to distinguish this organism from other Gram-positive rods, particularly diphtheroids. Selective enrichment media improve rates of isolation from contaminated specimens. You can expect that the cultures will take approximately 1-2 days for growth. Importantly, a negative culture does not rule out infection in the presence of strong clinical suspicion. Serological tests are unreliable, and not recommended at the present time.[23]

Listeriosis is treated with a wide range of antibiotics. In preclinical studies, wt-*Lm* and ADXS11-001 are susceptible to the lowest tested concentration of the following antimicrobial agents: [redacted]

5.6.4 Management and Surveillance of Listeria During Study Participation

A subject who experiences a fever (CTCAE Grade 1 or greater) 24 hours following the completion of ADXS11-001 infusion should be started on NSAIDS, hydration and other appropriate measures to treat the fever. In the event that the fever persists or worsens 48 hours following the completion of ADXS11-001 infusion then oral or broad spectrum IV antibiotics should be considered based on the subject's medical condition. If the fever remains unresponsive to oral/IV antibiotics 72 hours following the completion of the infusion then a blood culture should be obtained to evaluate for listeremia and determine the appropriate treatment course for the subject.

All subjects will receive a 6 month course of an oral antibiotic regimen as a prophylactic measure approximately 72 hours following the completion of the last dose of ADXS11-001 treatment or at the time of study discontinuation. This additional safety measure is intended to eradicate *Lm* from the body.

Lm surveillance monitoring will also be initiated following the completion of the last dose of ADXS11-001 treatment or at the time of study discontinuation. This monitoring will include obtaining a blood sample for CBC, CMP, including CRP and ESR, and blood cultures for the detection of listeria. Testing will be performed on all subjects who have received at least one dose of ADXS11-001 and occur every 4 months (±2 weeks) for 3 years.

Should a diagnosis of listeriosis occur at any point after treatment with ADXS11-001 is completed immediate, intensive IV antibiotic treatment (e.g. Ampicillin +/- Gentamicin or other IV antibiotic regimen as indicated) is required. An infectious disease consult should be obtained. Based on each individual subject's case and at the discretion of the treating physician, the removal of any foreign medical object that has been present since treatment with ADXS11-001 was initiated may be warranted. It is extremely important that the investigator, his/her research staff, other healthcare providers involved in the care of the subject as well as each subject participating in this study are educated and made aware of the signs and symptoms of listeriosis and the potential for delayed listeremia/listeriosis. Educational materials for the investigator, research staff, health care providers and patients will be prepared and educational training performed.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.7.2 Contraception

ADXS11-001 may have adverse effects on a fetus in utero. Furthermore, it is not known if ADXS11-001 has transient adverse effects on the composition of sperm. Prior to enrollment, all male and female study candidates with reproductive potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Women of childbearing potential is defined as females who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), are not postmenopausal (defined as amenorrhea ≥12 consecutive months or women on hormone replacement therapy with a documented serum follicle stimulating hormone level >35 mIU/ml). Even women who are using oral, implanted, or injectable contraceptive hormones or mechanical products, such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides), to prevent pregnancy, who are practicing

abstinence, and who have a sterile partner (eg, vasectomy) should be considered of childbearing potential.

All women of childbearing potential must have a negative pregnancy test within 72 hours prior to receiving ADXS11-001. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of human chorionic gonadotropin. If the pregnancy test is positive, the patient must not receive ADXS11-001 and may not be enrolled in the study.

Male subjects may be enrolled if they are willing to use an adequate method of contraception. Women of childbearing potential may be enrolled if they are willing to use 2 methods of birth control. The 2 birth control methods can be 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study all males and female study candidates of reproductive potential must adhere to the contraception requirement (described above) from Visit 1 through 120 days post last ADXS11-001 administration. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a SAE (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

It is unknown whether ADXS11-001 is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.7.5 Major and Minor Surgeries and ADXS11-001 Treatment

No formal studies of the effect of ADXS11-001 on wound healing have been conducted. However, based on its mechanism of action it is not expected that administration of ADXS11-001 would complicate wound healing. Therefore, a subject may initiate or resume study treatment 2 weeks after minor surgery (i.e. surgery involving little risk to the life of the patient; specifically an operation on the superficial structures of the body or a manipulative procedure that does not involve a serious risk) if the wound has completely healed and there are no wound healing complications. A subject who has wound healing complications following minor surgery, received major surgery or requires newly implanted artificial (prosthetic) joints, implants and/or devices which is permitted by the protocol during the course of the study, must wait a minimum of 6 weeks and must have recovered from any toxicity (e.g. return to baseline or Grade 1) and/or complication before the next infusion of study treatment. Sponsor consultation is required prior to resuming study treatment for these subjects. If the treatment is delayed due to concomitant surgery beyond 12 weeks the subject may be discontinued from the study.

On study, surgeries and/or procedures must be scheduled following the completion of 7 day course of prophylactic antibiotics post ADXS11-001 infusion. In addition, "recommended antibiotic prophylaxis" per institution standards for respective surgeries/and or procedures must be followed.

5.8 Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.5.

A subject can be discontinued from the treatment for any of the following reasons:

- Screen Failure
- Adverse Event/Serious Adverse Event
- Lost to Follow-Up
- Disease Progression, radiographic and/or clinical
- Death
- Withdrawal of Consent by Subject
- Investigator Decision/Study Non-Compliance by Subject

- Achieved Complete Remission
- Completed Study (maximum 24 months of study treatment)
- Other (specify)

In all cases, the reason for and date of withdrawal must be recorded in the eCRF and in the patient's medical records. The patient must be followed up to establish whether the reason was an AE, and, if so, this must be reported.

When a subject discontinues/withdraws prior to treatment completion, all applicable activities scheduled for the final assessment (End of Therapy assessments) should be performed at the time of discontinuation. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2.

The investigator must make every effort to contact subjects who discontinue the study prematurely or are lost to follow-up and to schedule the end of therapy assessments. Attempts to contact such subjects must be documented in the patient's records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter).

5.9 Subject Replacement Strategy

Non-evaluable subjects will be replaced in order to achieve the total number of subjects.

5.10 Treatment after Initial Evidence of Radiologic Disease Progression

Immunotherapy may produce antitumor effects by potentiating endogenous cancer-specific immune response. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions. If radiological imaging shows progressive disease (PD), subjects may continue on study with the option of continuing treatment**,** provided there is:

- no deterioration in ECOG performance status
- absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- absence of rapid progression of disease
- absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

Tumor assessment should be repeated ≥4 weeks later to confirm PD. If repeat imaging shows CR, partial response (PR) or stable disease (SD) compared to the baseline scan, treatments may be continued or resumed. If repeat imaging shows continued progression

of disease, subjects will be discontinued from study therapy, unless the basis for the PD assessment is enlarged tumor-draining lymph nodes in the presence of a target tumor reduction. In determining whether or not tumor burden has increased or decreased, Investigators should consider all target lesions as well as non-target lesions.

5.11 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

- Quality or quantity of data recording is inaccurate or incomplete
- Poor adherence to protocol and regulatory requirements
- Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
- Plans to modify or discontinue the development of the study treatment

In the event of Sponsor decision to no longer supply study treatment, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6 STUDY EVALUATIONS

6.1 Schedule of Events

Study Procedure	Screening[2]	9 Week Treatment Cycle[1]									End of Therapy[3]	Follow-Up
		Weeks										
		1	2	3	4	5	6	7	8	9		
Administrative Procedures												
Informed consent	X											
Eligibility Criteria / Subject ID Card	X											
Demographics/Medical History	X											
Prior Cancer History	X											
Prior/Concomitant Therapies & Procedures	X	X			X			X			X	X[4]
Prophylactic Medication[6]		X			X			X				
ADXS11-001 Administration[7]		X			X			X				
Dispense/Prescribe Oral Prophylactic Antibiotics [8]		X			X			X				X
Phone Call												X[4,5]
Clinical Procedures/Assessments												
Review Adverse Events[9]	X	X			X			X			X	X[4]
Vital signs/Weight[10]	X	X			X			X			X	
Physical Examination	X	X			X			X			X	
ECOG Performance Status	X	X			X			X			X	
Laboratory Procedures/Assessments[11]												
CBC with Differential	X	X			X			X			X	
Serum Chemistry Panel	X	X			X			X			X	
Coagulation Profile	X	X			X			X			X	

Study Procedure	Screening[2]	9 Week Treatment Cycle[1]									End of Therapy[3]	Follow-Up
		Weeks										
		1	2	3	4	5	6	7	8	9		
Urine Dipstick	X	X			X			X			X	
Urine Pregnancy Test[12]	X	X			X			X			X	
Lm Surveillance Monitoring[13]												X
Efficacy Measurements												
Tumor Imaging[17]	X								X			

[1] Repeating 9-week treatment cycles. Study cycles will be numbered sequentially.
[2] Screening/Baseline tumor evaluations will be performed within 28 days prior to first dose of study treatment.
[3] End of Therapy is not a visit. Assessments noted here must be completed upon the decision to discontinue a subject from study treatment.
[4] Safety Follow-Up will be conducted via a telephone call *30 days (± 5 days) after the last ADXS11-001 infusion* to confirm the resolution of any new or ongoing adverse events and serious adverse events. All ongoing events must be followed through resolution.
[5] Survival Follow-Up will be conducted at each visit during the Lm Surveillance period and via a telephone call *every 3 months (± 2 weeks) after the Lm Surveillance period* to determine survival status for all study subjects.
[6] Subjects will be pretreated with prophylactic regimen at least [redacted] before each ADXS11-001 infusion.
[7] The initial ADXS11-001 administration will identify Day 1 of Cycle 1. ADXS11-001 may be administered ± 7 days within each scheduled infusion.
[8] All Subjects will receive a 7-day course of oral antibiotic therapy starting approximately 72 hours after administration of ADXS11-001. All subjects will also receive an additional 6 month oral antibiotic course to be initiated approximately 72 hours following the last dose of study treatment or anytime upon discontinuation of study treatment.
[9] Adverse events and serious adverse events will be assessed from the time Informed Consent is obtained through 30 days after the last ADXS11-001 infusion is administered.
[10] Height will be measured at screening only. Monitor vital signs immediately [redacted] for the first 4 hours following the completion of every ADXS11-001 infusion.
[11] C1D1 Safety labs do not need to be repeated if screening labs are collected within 3 days of dosing. All laboratory procedures are to be completed and assessed by the investigator within 3 days prior to the administration of ADXS11-001 to confirm lab criteria for study treatment are met.
[12] Urine pregnancy tests must be performed within 72 hours prior to each ADXS11-001 infusion for female subjects of childbearing potential. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
[13] *Lm* Surveillance Monitoring will include a 6-month course of oral antibiotics and routine monitoring of CBC, CMP (including CRP, ESR) and blood cultures. Following completion of the last dose of study treatment or following study discontinuation, all assessments will be performed every 4 months (±2 weeks) for 3 years.
[14] Baseline tumor imaging and assessments must be performed within 28 days prior to the first ADXS11-001 infusion in the first study cycle. Subsequent tumor imaging and assessments will be conducted at Week 8 (±1 week) for the duration of study participation. Radiologic progression, not accompanied by clinical deterioration, should be confirmed ≥4 weeks later.

7 TRIAL PROCEDURES

7.1 Trial Procedures

The Schedule of Events - Section 6.1 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

Consent must be documented by the subject's dated signature on the most current Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved ICF document along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated ICF should be given to the subject before participation in the trial.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must receive the IRB/IEC's approval/favorable opinion in advance of use. The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

7.1.1.2 Eligibility Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card after the subject provides written informed consent.

7.1.1.4 Demographic/Medical History

Demographic information and a medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions and any condition that are considered to be clinically significant by the Investigator.

7.1.1.5 Prior Cancer History

The investigator or qualified designee will obtain prior and current details regarding disease status, including histopathologic confirmation of cancer, all prior cancer treatments and best response(s), if applicable (eg, systemic, radiation and surgeries).

7.1.1.6 Prior/Concomitant Therapies and Procedures

The investigator or qualified designee will review all prescription and nonprescription medication (excluding vitamins and nutritional supplements) taken by the patient from 28 days prior to screening and up to and including 30 days after the last administration of ADXS11-001; the information will be recorded in the medical record and on the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Generic names should be used to eliminate confusion that may result from trade names. Protocol-mandated prophylactic medications and antibiotics should also be captured in the eCRF.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse/Serious Adverse Event Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening serious events from the time written informed consent is obtained through 30 days after the last ADXS11-001 dose is administered. Adverse experiences. Serious events experienced during this time will be graded, reported and recorded on the eCRF according to NCI CTCAE v 4.0 (Section 12.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to Section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Physical Examination

The investigator or qualified designee will perform an evaluation by body system.

7.1.2.3 Vital Sign Measurement

The investigator or qualified designee will measure and record vital signs (including blood pressure, pulse rate, respiratory rate, and temperature) at Screening, prior to each ADXS11-001 administration and [redacted] for the first 4 hours following each infusion. Weight will be collected prior to each ADXS11-001 infusion. Height will be measured at screening only.

7.1.2.4 Eastern Cooperative Oncology Group Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.1).

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood to be drawn over the course of the trial (from pre-trial to trial discontinuation), including approximate blood volumes drawn by visit and by sample type per subject will be based on local laboratory requirements.

7.1.3.1 Laboratory Safety Evaluations

Laboratory tests for hematology, chemistry, urinalysis, *Lm* surveillance and others are specified in Table 8.

Subjects must meet all lab criteria prior to dosing. Laboratory tests can be performed no more than 3 days prior to dosing. If screening laboratory tests are performed within 3 days prior to initial study treatment, they can be used for C1D1 labs. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

Table 8 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	*Lm* surveillance* blood cultures
Absolute Neutrophil Count	Carbon Dioxide ‡ *(CO_2 or bicarbonate)*	Urine pregnancy test †	
	Calcium		
	Chloride		
	Creatinine		
	C-Reactive Protein (CRP)*		
	Erythrocyte Sedimentation Rate (ESR)*		
	Glucose		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
‡ If considered standard of care in your region.
**Lm* surveillance Monitoring will include routine monitoring of CBC, CMP (including CRP, ESR) and blood cultures. Following completion of study treatment all assessments will be performed every 4 months (±2 weeks) for 3 years.

7.1.4 Efficacy Measurements

7.1.4.1 Tumor Imaging and Assessment of Disease

CT and MRI will be considered the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT should be performed with contiguous cuts of 10 mm or less. Spiral CT scan should be performed using a 5 mm contiguous reconstruction algorithm (as a general rule, lesion diameter should be no less than double the slice thickness). Lesions on chest x-rays will be acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable. Ultrasound is not an acceptable method to measure disease.

Assessment of disease will be done using both RECIST 1.1 criteria and irRECIST criteria. All subjects who have completed one 9-week cycle of ADXS11-001 treatment will be considered evaluable for response.

7.1.4.2 Measurable and Non-Measurable Lesions and Disease

Measurable lesions will be those that can be accurately measured in at least one dimension with the longest diameter ≥2.0 cm (for spiral CT scan or MRI scan, ≥1.0 cm). Measurable disease will be present if the subject has 1 or more measurable lesions.

Non-measurable lesions/disease will be all other lesions (or sites of disease), including small lesions (those with all measurements <2.0 cm or <1.0 cm with spiral CT/MRI), or any of the following: bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitis, cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions, and lesions occurring within a previously irradiated area unless they are documented as new lesions since the completion of radiation therapy.

7.1.4.3 Target/Non-Target Lesions

All measurable lesions, up to a maximum of 2 per organ and 5 in total, should be identified as target lesions to be measured and recorded at baseline. The target lesions should be representative of all involved organs. Target lesions will be selected based on their size (the lesion with the longest diameter) and suitability for accurate repeated measurements. At baseline, a sum of the longest diameters for all target lesions will be calculated and recorded as the baseline tumor burden. The baseline sum will be used as the reference point to determine the objective tumor response of the target lesions.

Measurable lesions other than the target lesions and all sites of non-measurable disease will be identified as non-target lesions and will be recorded at baseline. Non-target lesions will be evaluated at the same time points as target lesions.

7.1.4.4 Response in Measurable Lesions (RECIST 1.1)

At baseline, the sum of the longest diameters (SumD) of all target lesions (up to 2 lesions per organ, up to total 5 lesions) is measured. At each subsequent tumor assessment, the SumD of the target lesions and of new, measurable lesions (≥10; up to 2 new lesions per organ, total 5 new lesions) are added together to provide the total measurable tumor burden (TMTB):

TMTB = SumD target lesions + SumD new, measurable lesions

Percentage changes in TMTB per assessment time point describe the size and growth kinetics of both old and new measurable lesions as they appear. At each tumor assessment, the response in target and new measurable lesions is defined based on the change in TMTB.

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

7.1.4.5 Immune-Related Response in Measurable Lesions (irRECIST)

In addition to evaluation using RECIST 1.1 criteria, an immune response adaptation of RECIST will be applied to this trial. The essential differences between irRECIST and RECIST criteria are as follows:

- New measureable lesions do not necessarily constitute progressive disease and they should be added into the total tumor burden. New non-measurable lesions do not constitute disease progression but will prevent the determination of an irCR.

- Apparent disease progression should be confirmed after 4 weeks in the absence of symptoms consistent with clinical deterioration.

At baseline, the sum of the longest diameters (SumD) of all target lesions (2 per organ and 5 in total) is measured. At each subsequent tumor assessment, the SumD of the target lesions and of new, measurable lesions (≥10 mm [lymph nodes ≥15 mm in shortest diameter]; up to 2 new lesions per organ, total 5 new lesions) are added together to provide the total measurable tumor burden (TMTB):

TMTB = SumD target lesions + SumD new, measurable lesions

Percentage changes in TMTB per assessment time point describe the size and growth kinetics of both old and new measurable lesions as they appear. At each tumor assessment, the response in target and new measurable lesions is defined based on the change in TMTB (after ruling out irPD) as follows:

Complete Response (irCR): complete disappearance of all target and new, measurable lesions, with the exceptions of lymph nodes which must decrease to <10 mm in short axis

Partial Response (irPR): decrease in TMTB ≥30% relative to baseline (see below)

Stable Disease (irSD): not meeting criteria for irCR or irPR, in absence of irPD

Progressive Disease (irPD): increase in TMTB ≥20% relative to nadir

7.1.4.6 Response in Non-Measurable Lesions (RECIST 1.1)

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively.

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

- Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

When the patient also has measurable disease, to achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

In the event that the patient has only non-measurable disease, the same general concepts apply as noted above, however, in this instance there is no measurable disease assessment

to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease (ie, an increase in tumor burden representing an additional 73% increase in 'volume' which is equivalent to a 20% increase diameter in a measurable lesion).

7.1.4.7 Immune-Related Response in Non-Measurable Lesions (irRECIST)

At each tumor assessment, the presence of any new, non-measurable lesions is assessed. The presence of such lesions will rule out an overall response of irCR. An increase in the size or number of new, non-measurable lesions does not necessarily imply an overall response of irPD; if these lesions become measurable (≥10 mm) at a subsequent tumor assessment, their measurement will at that point start to contribute to the TMTB.

In addition, the response in non-target lesions is defined as follows:

Complete Response (irCR): complete disappearance of all non-target lesions

Stable Disease (irSD): non-target lesions are stable

Progressive Disease (irPD): unequivocal increases in number or size of non-target lesions. To achieve unequivocal progression of non-target lesions, there must be an overall level of substantial worsening of non-target disease that is of a magnitude that the treating physician would feel it is important to change therapy.

NOTE: Equivocal findings of progression of non-target lesions (eg, small and uncertain new lesions; cystic changes or necrosis in existing lesions) should be considered irSD, and treatment may continue until the next scheduled assessment.

7.1.4.8 Overall Response

Overall response will be determined based on RECIST 1.1 criteria and by irRECIST criteria (Table 9). Overall response according to irRECIST is derived from the responses in measurable lesions (based on TMTB) and the presence of any non-measurable lesions.

Table 9 Tumor Response Evaluation: Comparison of RECIST 1.1 and irRECIST

Criteria	RECIST1.1	irRECIST
New measurable lesions (≥ 10 mm)	Always represents PD	Incorporated into tumor burden

Criteria	RECIST1.1	irRECIST
New non-measurable lesions (< 10 mm)	Always represents PD	Does not define progression but precludes irCR
Non-Target lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions	Disappearance of all lesions
PR	≥ 30% decrease in the sum of the longest diameter of all target lesions compared with baseline, in absence of new lesions or unequivocal progression of non-target lesions	≥ 30% decrease in tumor burden compared with baseline
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study	Neither a 30% decrease in tumor burden compared with baseline nor a 20% increase compared with nadir can be established
PD	At least 20% increase in sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. The appearance of one or more new lesions is also considered progression.	At least 20% increase in tumor burden compared with nadir (at any single time point)[a]

irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; BOR = best overall response; CR = complete response; irCR = immune-related complete response; PD = progressive disease; PR = partial response; SD = stable disease;

[a] Patients with an initial finding of progressive disease (irPD) before or at the 8-week imaging assessment, but without rapid clinical deterioration, require confirmation of irPD with a second, consecutive scan obtained ≥ 4 weeks from the initiation documentation. Patients will continue to receive study treatment until irPD is confirmed at this later time point. Best overall response (BOR) will therefore include responses occurring at any time before disease progression and after early progression (i.e., within the first 9 weeks of the study).

7.1.4.8.1 Best Overall Response (RECIST 1.1)

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions (Table 10).

Table 10 Best Overall Response (RECIST 1.1)

Target Lesions	Non-Target Lesions		Overall Response
Baseline (Index) and New Measurable Lesions	Baseline Lesions	Unequivocal New Lesions	
CR	CR	No	CR

Target Lesions	Non-Target Lesions		Overall Response
Baseline (Index) and New Measurable Lesions	Baseline Lesions	Unequivocal New Lesions	
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable at a particular time point; PR = partial response; SD = stable disease; PD = progressive disease

7.1.4.8.2 Immune-Related Best Overall Response (irRECIST)

The immune-related best overall response (irBOR) is the best irRC overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment prior to subsequent therapy (including tumor resection surgery) for the individual subject in the study (Table 11). As with the primary definitions of tumor response, early progression (i.e., irPD occurring prior to Week 8) will not preclude an irBOR of irCR, irPR or irSD resulting from the Week 8 assessment. An assessment of irPD at or after Week 8 will preclude a subsequent irBOR of irCR, irPR or irSD. However, any post-progression clinical activity in subjects with irBOR of irPD may be summarized for exploratory purposes.

Table 11 Immune-Related Best Overall Response (irBOR)

Target Lesions Baseline (Index) and New Measurable Lesions	Non-Target Lesions[a]		irRC Overall Response
Total Measurable Tumor Burden	Baseline Lesions	Unequivocal New Lesions	
irCR	irCR	No	irCR
irCR	irSD	No	irPR
irPR	irCR or irSD	No	irPR
irSD	irCR or irSD	No	irSD

Target Lesions Baseline (Index) and New Measurable Lesions	Non-Target Lesions[a]		
Total Measurable Tumor Burden	Baseline Lesions	Unequivocal New Lesions	irRC Overall Response
irPD	Any	Yes or No	irPD
Any	Unequivocal Progression	Yes or No	irPD
Any	Any	Yes	irPD

irCR = immune-related complete response; irPR = immune-related partial response; irSD = immune-related stable disease; irPD = immune-related progressive disease

[a] Any increase in the size or number of non-measurable lesions does not necessarily imply an overall response of irPD. If these lesions become measurable (≥10 mm) at a subsequent assessment, their measurement will at that point start to contribute to the total measurable tumor burden. To achieve unequivocal progression of non-target lesions, there must be substantial worsening in non-target disease that is of a magnitude that the Investigator feels it is important to change therapy. Equivocal findings of progression of non-target lesions (e.g., small and uncertain new lesions; cystic changes or necrosis in existing lesions) should be considered irSD, and treatment may continue until the next assessment.

7.1.5 Other Procedures

7.1.5.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

Treatment may continue until a study discontinuation criterion is met or for up to 2 years. Subjects who achieve a CR should receive at least 1 additional cycle of treatment.

Any subject who is still deriving clinical benefit from ADXS11-001 therapy at the end of their 2 year treatment period or has achieved CR and subsequently progressed within 1 year of stopping study treatment may be enrolled into a separate extension study, as available.

7.1.6 Visit Requirements

Visit requirements are outlined in Section 6.1 – Schedule of Events. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.6.1 Screening

Screening period – will start when the first screening evaluation is performed. This does not include signing of informed consent or wash out periods. Screening evaluations will be performed within 28 days prior to the first treatment administration, unless otherwise specified.

Informed Consent - each subject must sign a copy of the most current IRB/IEC approved informed consent document. A copy of the signed document will be maintained with the subject's records.

Inclusion/Exclusion Criteria - all inclusion and exclusion criteria will be reviewed by the Investigator or qualified designee to ensure that the subject qualifies for the trial.

Prior/Concomitant Therapies and Procedures - past or current medical conditions, current medications, medications taken within 28 days of study entry, histological confirmation of cancer, tumor staging (refer to the most current American Joint Committee on Cancer Staging Manual, the 5th edition or higher), and prior cancer therapies and best response(s), if applicable.

Pregnancy test - A rapid pregnancy test will be performed for all women of child bearing potential. A positive rapid pregnancy test must be confirmed by serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of βHCG).

Laboratory Procedures (hematology, chemistry, urinalysis, other) – see Section 7.1.3.

Tumor Imaging/Disease Assessment - CT scan or MRI for determination of unidimensional measurements and disease response. Baseline tumor imaging/disease assessment must be performed within 28 days prior to the first dose of ADXS11-001. Then imaging studies and tumor assessments will be performed every 9 weeks starting on Week 8 of every Cycle.

7.1.6.2 Treatment Period

Subjects should arrive at the study center early on the days of their scheduled treatment in order to be evaluated, have laboratory specimens collected before treatment commences, allow for infusion timing, and take study prophylactic regimen as described in Section 5.2.4.

During the time the subjects are at the study site, the infusion line will be left in place to administer parenteral drugs, if necessary. Subjects will remain at the study center for a minimum of 4 hours after ADXS11-001 administration for safety observation, and if necessary, treatment of side effects. Subjects may receive NSAIDs and antiemetics per label or package insert on Day 1 and Day 2, as needed.

Adverse Event Monitoring - The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Schedule of

Events and more frequently if clinically indicated. AE/serious events will be graded, reported and recorded on the eCRF according to NCI CTCAE v 4.0. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Physical Examination - evaluation by body system.

Vital Signs - blood pressure, pulse rate, respiratory rate, and temperature will be checked and recorded prior to administration of ADXS11-001 and every [redacted] for the first 4 hours following the infusion. Height and weight will be measured at screening, and weight will be measured pre-dose at every visit.

ECOG Performance Status - according to ECOG criteria.

Laboratory Procedures - according to Section 7.1.3.

Prophylactic Medications – will be pretreated with prophylactic regimen on the day of dosing and completed at least 30 minutes before each ADXS11-001 infusion as outlined in Section 5.2.3.

Prophylactic Antibiotics with Instructions –
(1) During Study Treatment Phase - All subjects will receive a 7 day course of oral antibiotic therapy starting approximately 72 hours (Day 4) after administration of ADXS11-001. Antibiotic therapy should consist of either 160 mg trimethoprim/800 mg sulfamethoxazole (DS) tablet administered three times during the 7 consecutive days or 80 mg trimethoprim/400 mg sulfamethoxazole administered daily for 7 consecutive days or for subjects with sulfa allergies, ampicillin 500 mg four times daily for 7 consecutive days. ADXS11-001 is resistant to both streptomycin and chloramphenicol. In the event a subject experiences a persistent fever present at 72 hours after receiving ADXS11-001, the oral regimen will be replaced by broad spectrum IV antibiotics administration until a blood culture is obtained and results are available. At this time, a specific IV antibiotic regimen may be prescribed based on the results of the blood culture. Should a diagnosis of listeriosis be made intensive IV antibiotic treatment must be initiated. Ampicillin +/- Gentamicin is the preferred treatment regimen but other IV antibiotics may be used based on the subject's tolerance, culture and sensitivity results. An ID consult should be obtained.
(2) Post Study Treatment - All subjects will receive a 6 month course of oral trimethoprim/sulfamethoxazole or ampicillin for subjects with sulfa alleriges to be initiated approximately 72 hours following the last dose of study treatment or at the time of study discontinuation. Trimethoprim/sulfamethoxazole therapy should consist of either 160 mg trimethoprim/800 mg sulfamethoxazole (DS) tablet administered three times a week or 80 mg trimethoprim/400 mg sulfamethoxazole administered daily for 7 consecutive days. The dose of ampicillin consists of 500 mg four times daily for 6 months.

Tumor Imaging/Disease Assessment - CT scan or MRI for determination of unidimensional measurements and disease response. Imaging studies and tumor assessments will be performed every 9 weeks starting at Week 8 of Cycle 1.

Pregnancy test - A rapid pregnancy test will be performed within 72 hours of each treatment administration (combination or monotherapy) for all women of child bearing potential prior to treatment. A positive rapid pregnancy test must be confirmed, prior to dosing, by a serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of βHCG).

7.1.6.3 Safety Follow-up/Post-Treatment Visits

Safety follow-up will be conducted via telephone call 30 days (±5 days) after the last ADXS11-001 infusion to confirm the resolution of any ongoing AEs and SAEs. Additional unscheduled visits may be considered as needed and at the discretion of the investigator.

Surveillance monitoring for the detection of *Lm* will be initiated at the completion of study treatment according to the protocol or at the time of study discontinuation if earlier. This surveillance monitoring phase will consist of a 6 month course of oral antibiotics, obtaining a blood sample to monitor CBC, CMP, including CRP and ESR, and blood cultures at regular intervals. This testing will be performed on all subjects who have received at least one dose of ADXS11-001. It will occur every 4 months (±2 weeks) for 3 years beginning after the last dose of study treatment. If a persistent increase in CRP and/or ESR is observed with negative blood cultures for listeria during this time the subject should be evaluated and treated, as appropriate, for another possible cause. In the event that a definite cause has not been identified then subjects must continue to be monitored closely, including another additional testing and a blood culture, for possible signs/symptoms of listeriosis. This testing may be performed at the investigative site or at another acceptable location following consultation with the Sponsor.

7.1.6.4 Survival Follow-up

Survival Follow-Up will be conducted at each visit during the Lm Surveillance period and via a telephone call every 3 months (± 2 weeks) after the Lm Surveillance period to determine survival status for all subjects.

7.2 Assessing and Recording Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant

adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an AE.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered AEs. Examples of this may include, but are not limited to, onset of menses or menopause occurring at a physiologically appropriate time.

The Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Advaxis for human use.

AEs may occur during the course of the use of Advaxis' product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

AEs may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

All AEs will be recorded from the time the consent form is signed through 30 days following cessation of treatment on the Adverse Event CRF forms/worksheets. The reporting timeframe for AEs meeting any serious criteria is described in Section 7.2.3.1.

7.2.1 Overdose

For purposes of this trial, an overdose will be defined as any ADXS11-001 dose exceeding the prescribed dose. No specific information is available on the treatment of overdose of ADXS11-001. In the event of an ADXS11-001 overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an AE(s) is associated with ("results from") the overdose of an Advaxis product, the AE(s) is reported as a SAE, even if no other seriousness criteria are met.

If a dose of Advaxis' product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as an AE.

All reports of overdose with and without an AE must be reported within 24 hours to inVentiv Health Clinical Pharmacovigilance (Attn: iHC SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@inventivhealth.com).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered AEs, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours of awareness to inVentiv Health Clinical Pharmacovigilance (Attn: iHC SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@inventivhealth.com).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any AE occurring at any dose or during any use of Advaxis' product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

Progression of the cancer under study is not considered an AE unless it results in hospitalization or death.

Any SAE, or follow up to a SAE, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 30 days following cessation of treatment, whether or not related to Advaxis'

product, must be reported within 24 hours to the Sponsor at inVentiv Health Clinical Pharmacovigilance (Attn: iHC SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@inventivhealth.com).

Additionally, any SAE, considered by an investigator who is a qualified physician to be related to Advaxis' product that is brought to the attention of the investigator at any time outside of the time period specified above also must be reported immediately to the Sponsor.

SAE reports and any other relevant safety information are to be forwarded to inVentiv Health Clinical Pharmacovigilance (Attn: iHC SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@inventivhealth.com).

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Advaxis Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to inVentiv Health Clinical Pharmacovigilance (Attn: iHC SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@inventivhealth.com) at the time of submission to FDA.

All subjects with SAEs must be followed up for outcome.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all AEs according to the NCI CTCAE v 4.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRF/worksheets.

All AEs regardless of CTCAE grade must also be evaluated for seriousness.

The following attribution categories (Table 12) will be used in assessing the relationship between the AE and the study treatment:

Table 12 Attribution Categories

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Unrelated to investigational agent/intervention	Unrelated	The AE *is clearly **NOT** related* to the intervention
	Unlikely	The AE *is **doubtfully related*** to the intervention
Related to investigational agent/intervention	Possible	The AE ***may be related*** to the intervention
	Probable	The AE ***is likely related*** to the intervention
	Definite	The AE ***is clearly related*** to the intervention

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All AEs will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

8 STATISTICAL CONSIDERATION

8.1 General Consideration

Descriptive statistics will be employed to evaluate the endpoint and analyze the data. Summary statistics for continuous variables will include mean, standard deviation, median and range. Categorical variables will be presented as frequency counts and percentages; and time-to-event variables will be summarized by Kaplan-Meier (KM) medians and survival plots. Data listings will be created to support tables and present data. The preliminary efficacy analysis will be conducted on the efficacy evaluable population and safety analysis will be performed on the safety population. SAS 9.2 or higher will be used for data analysis. The details of statistical analysis will be described in the Statistical Analysis Plan (SAP). The data will be tabulated and analyzed with respect to patient enrollment and disposition, demographic, and baseline characteristics.

8.2 Sample Size and the Design

This is a multi-center, open-label, 2 stage monotherapy study of ADXS11-001 in subjects with persistent/recurrent, loco-regional or metastatic SCCA of the anorectal canal that was previously treated in the metastatic setting.

Primary Efficacy Measures are:

1. The overall response
2. Progression-Free Survival (PFS)

We employed a 2-stage design for testing these 2 primary efficacy measures. Simon's 2-stage method is not directly applicable because it is for single proportion type endpoint. However, we used Simon's method with null and alternative response rates of 10% in Stage 1 and 20% in Stage 2 to obtain the total sample sizes for both stages and use the Multinomial Two-Stage approach proposed by Benny Zee, *et al* (1999) [24] to obtain the stopping probabilities.

By Simon's method, we need to enroll 31 subjects at Stage 1 and an additional 24 subjects in Stage 2 if 3 or more responses are observed in Stage 1. Based on this sample size plan, we formed the following 2 endpoints, 2-stage framework:

In Stage 1 of the study, we will enroll 31 subjects. The safety and efficacy data of the subjects will be evaluated. After 31 evaluable subjects have been enrolled, further accrual will be temporarily stopped in Stage 1 for an efficacy interim analysis evaluation. If the efficacy from Stage 1 demonstrates a response rate $\geq$10% or 6-month PFS $\geq$20%,

the enrollment will re-open to Stage 2. The enrollment will be complete in Stage 2 when an additional 24 evaluable have been accrued (total from Stages 1 and 2 = 55).

The hypothesis testing in Stage 1 is given in the following:

- Stage 1:
  - Null Hypothesis (H_0): Response rates (r_1) <10% and 6-month PFS rate (p_1) <20%;
  - Alternative Hypothesis (H_a): Response rates (r_1) ≥10% or 6-month PFS rate (p_1) ≥20%
- Stage 2:
  - Null Hypothesis (H_0): Response rates (r_2) ≤ 25% and 6-month PFS rate (p_2) ≤ 50%;
  - Alternative Hypothesis (H_a): Response rates (r_2) ≧ 25% or 6-month PFS rate (p_2) ≥ 50%

Using the Multinomial Two-Stage approach proposed by Benny Zee, *et al* (1999),[24] we simulated 50,000 trials to examine the Type I and II errors under this design assumption. The following estimates, including Type I and II errors, from these simulations are summarized in the following table.

Type I	Type II
Type I Error = 0.03236 ASN for H0 = 32.20192 P(stop early | H0) = 0.94992	Power = 0.924

8.3 Analysis of Study Endpoints

8.3.1 Analysis of Primary Endpoints for Efficacy

The following are the primary efficacy endpoints for both phases;

1. Overall Tumor Response (measured by RECIST 1.1);
2. Progression-Free Survival (PFS)

These endpoints are well established and commonly used to evaluate signs of clinical activity and efficacy.

The overall tumor response rates will be tabulated for all patients by treatment stage. PFS is defined as the time from treatment start until disease progression or death whichever occurred earlier. Patients who have not progressed or who are still alive at the time of evaluation will be censored for the analysis.

KM method will be used for estimating median times for PFS. The 95% confidence intervals of the medians will be presented.

Subject disposition, demographic and baseline subject characteristics will be summarized separately for Stage 1 and Stage 2. AEs will be classified and summarized by type, incidence, severity, and causality. All AEs will be summarized by subject, treatment, and disease. All subjects who receive at least 1 dose of ADXS11-001 will be included in the safety analyses.

8.4 Safety Monitoring

An external Data Safety Monitoring Committee will not be established for this study. A periodic safety review will be applied by an internal safety review team with medical capabilities to review individual and summary data collected in the safety and clinical databases. Findings having immediate implication for the management of subjects on study will be communicated to all Investigators in the timeframe associated with unexpected and drug-related SAEs.

8.5 Analysis of Safety Data

All AEs will be summarized by patient, treatment, and prior recurrence history (aggressive [recurrence within 2 years]/non-aggressive).

The NCI CTCAE v 4.0 will be used for AE grading (Grades 1 to 4). AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA®) coding system.

The overall incidence of AEs will be summarized and classified by body system and by treatment group. An AE will be summarized if the onset date occurs anytime during study treatment or up to 30 days after the last dose of study treatment; or, if it occurs prior to Day 1 and worsens while on therapy. The type, incidence, severity, and causality of each AE, the duration of the event, and any required treatment interventions will be tabulated.

Physical examination results will be presented in the patient data listings. Vital sign measurements will be summarized at each infusion using descriptive statistics. The incidence of clinically significant laboratory abnormalities will be presented, and laboratory data will be summarized at each infusion by the NCI CTCAE v 4.0 toxicity grades. Laboratory data will be presented for patients having Grade 3 or 4 changes from baseline.

9 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

[redacted]

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Safety Precautions

ADXS11-001 is a live strain of *Listeria monocytogenes* (*Lm*) that has been attenuated such that it is cleared by severe combined immunodeficiency (SCID) mice lacking cellular immunity and gamma interferon knock-out mice lacking adaptive immunity. It has also been altered such that it is impossible for it to recombine with wild-type *Lm*. [redacted]

Wild-type Listeria is Gram-positive, non-spore-forming, facultative bacilli that are hemolytic and catalase-positive. Although healthy adults and children can contract a

wild-type Listeria infection, they do not usually become seriously ill. People at risk of severe illness from wild-type Listeria are pregnant women, newborns, and persons with impaired immune function.[25]

Even though ADXS11-001 is non-pathogenic, all *Lm* species are classified as [redacted] according to the BMBL 5th Edition. In the US there currently is no method to reclassify Advaxis attenuated *Lm* strains in a manner that differentiates them from the more virulent wild type parent strain 10403S. Universal precautions and institutional guidelines should be used when handling investigational drugs and human specimens.

Precautions as stated in the BMBL 5th Edition include:[25]

> ***Wild-type L. monocytogenes poses a potential hazard to laboratory personnel. The Gram-positive, non-spore-forming, aerobic bacilli are hemolytic and catalase-positive. Bacteria have been isolated from soil, dust, human food, animals, and asymptomatic humans. Most cases of listeriosis have arisen from eating contaminated food products, most notably soft cheeses, raw meat, and unwashed raw vegetables. Although healthy adults and children can contract a Listeria infection, they do not usually become seriously ill. At risk of severe illness are pregnant women, newborns, and persons with impaired immune function.***
>
> ***Laboratory Hazards:*** *Wild-type Listeria monocytogenes may be ubiquitous in the environment and may be found in feces, cerebrospinal fluid (CSF), and blood, as well as food and environmental materials. Ingestion is the most common mode of exposure, but wild-type Listeria can also cause eye and skin infections following a direct exposure. Wild-type Lm infections in pregnant women occur most often in the third trimester and may precipitate labor. Transplacental transmission of Lm poses a grave risk to the fetus and may result in disseminated abscesses contributing to a mortality rate of nearly 100%.*
>
> ***Recommended Precautions:*** [redacted] *practices, containment equipment, and facilities are recommended for activities with clinical specimens and cultures known or suspected to contain the agent. Gloves and eye protection should be worn while handling the agent. Pregnant women who work with Listeria monocytogenes in the clinical or research laboratory setting should be fully informed of the potential hazards associated with the organism, including potential risks to the fetus.*

[redacted]

9.6 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Advaxis or designee, the amount dispensed for each subject and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy.

9.7 Destruction of ADXS11-001

It will be the investigator's responsibility to ensure that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures and that:

- Written authorization for disposal/destruction has been granted by Advaxis
- Arrangements have been made for the disposal
- Appropriate records of the disposal have been documented

Refer to the Pharmacy Manual for ADXS11-001 for drug destruction details.

10 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

The confidentiality of records and information that could identify subjects must be protected, respecting privacy and confidentiality rules in accordance with applicable regulatory requirements.

The Investigator will agree to maintain in confidence all information furnished by the Sponsor and all data generated in the study, except as provided or required by law, and will divulge such information to the IRB/IEC with the understanding that confidentiality will be maintained by the committee.

The identity of all subjects in this study must remain confidential, and only the initials of said subjects will appear on the eCRF. Qualified representatives from the relevant regulatory agencies, the Sponsor, or its agents may inspect the subject/study records. Subject data obtained during the study may be presented in scientific publications, but at no time will subject names be used.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US FDA Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure

information is required. It is the Investigator's/sub Investigator's responsibility to comply with any such request. The Investigator/sub Investigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements.

The Investigator/sub Investigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The Investigator/sub Investigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes.

10.3 Compliance with Law, Audit and Debarment

International Conference on Harmonisation (ICH) Guidance on Good Clinical Practice ([GCP] CPMP/ICH/135/95) and the Sponsor require the Investigator to be aware of his/her obligations in the conduct of this study.

Representatives of the Sponsor must be allowed to visit all study site locations periodically to assess data quality and study integrity. On site, they will review study records and directly compare them with the original source documents, discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by auditors designated by the Sponsor and by government inspectors who must be allowed access to CRFs, source documents, and all other study files. Sponsor audit reports will be kept confidential.

THE INVESTIGATOR MUST NOTIFY THE SPONSOR PROMPTLY OF ANY INSPECTIONS SCHEDULED BY REGULATORY AUTHORITIES AND PROMPTLY FORWARD COPIES OF INSPECTION REPORTS TO THE SPONSOR.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and

functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The Investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the Investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the Investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

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12 APPENDICES

12.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

12.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. (http://ctep.cancer.gov/reporting/ctc.html).

12.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study .

In addition, volumetric analysis will be explored by central review for response assessment.

13 SUMMARY OF CHANGES

#	Section	Page	Revision	Rationale
1	List of Abbreviations	8-9	Updated to include CMP, CRP, ESR, TNFα and PI3K. Deleted GGT, LEEP.	Administrative update.
2	Synopsis	10-11	Updated length of subject trial duration from 4 to 6 years, included the 6 month oral antibiotic course and *Lm* Surveillance Monitoring requirements. Updated adverse event tracking to extend until completion of the *Lm* Surveillance Monitoring phase. Added Lm Surveillance Monitoring as a safety evaluation criterion.	Administrative update in support of the FDA recommendations.
3	2 TRIAL DESIGN and throughout protocol, where applicable	12	Updated the Stage 1 primary objective of 6-month PFS rate from 25% to 20% as a requirement for initiation of Stage 2 in order to align more closely with the rates achieved in similar patient populations with later stage HPV-related cancer. Added paragraph detailing safety follow-up and Survival follow-up frequency. Clarified that patients still deriving clinical benefit from ADXS11-001 therapy at the end of their 2-year treatment period or at the end of the study may be enrolled into a separate extension study, as available.	Sponsor decision based on discussions with key opinion leaders involved in the treatment of patients with persistent/recurrent, loco-regional or metastatic squamous cell carcinoma of the anorectal canal. Administrative update in support of the FDA recommendations. Administrative update.
4	2 TRIAL DESIGN and throughout protocol, where applicable	12	Revised ADXS11-001 dose level from $1x10^9$ CFU to $5x10^9$ CFU.	Sponsor decision based on clinical rationale and potential for higher doses to result in better clinical response
5	4.2.1.1 Summary of Safety of ADXS11-001	16	Section was updated with safety data information.	Safety administrative update
6	4.2.2 Delayed/Late Listeria Infection	18-19	Safety section added describing the clinical experience to-date with *Lm* clearance and the description of the index case of delayed/late listeria infection.	Per FDA Safety Section, revised to inform investigators/patients on the recent delayed/late listeria event.

#	Section	Page	Revision	Rationale
7	ADXS11-001 Rationale for Dose Selection and Regimen	19-21	Section was revised for clarity and details of the rationale for increasing ADXS11-001 dose.	Based on previous clinical experience with ADXS11-001, patients with advanced HPV disease may receive added benefit to treating with higher doses and repeating treatments until progression or complete response with ADXS11-001.
8	4.2.4 Study Stopping Rules	21-22	New section added as a safety precaution for the increased ADXS11-001 dose.	Administrative update in support of the FDA recommendations.
9	5.1.2 Exclusion Criteria (6.b)	25	Revised to allow intermittent use of inhaled steroids in addition to the bronchodilators or local steroid injections, with sponsor approval.	Administrative update
10	5.1.2 Exclusion Criteria (#10)	26	New exclusion criterion was added to exclude subjects with implanted devices that pose high risks for colonization or inability of removal.	Exclusion criteria added to mitigate risk of colonization of foreign bodies and medical devices
11	5.1.2 Exclusion Criteria (#11)	26	New exclusion criterion was added to exclude subjects who are receiving or are expected to receive treatment with TNF blocking agent(s) during study participation or in future.	Exclusion criteria added to mitigate risk of listeria infection.
12	5.1.2 Exclusion Criteria (#12)	26	New exclusion criterion was added to exclude subjects who are receiving or are expected to receive treatment with PI3K inhibitor(s) during study participation or in future.	Exclusion criteria added to mitigate risk of listeria infection.
13	5.1.2 Exclusion Criteria (#13)	26	New exclusion criterion was added to exclude subjects with a known contraindication (e.g. allergies/sensitivities) to the administration of trimethoprim sulfamethoxazole and/or ampicillin. Deleted Exclusion Criterion: Has contraindication to administration of amoxicillin, ampicillin, ciprofloxacin, erythromycin, gentamycin, penicillin, and trimethoprim/sulfamethoxazole.	Exclusion criterion added based on FDA recommendation of prophylaxis and 6-month antibiotic treatment.

#	Section	Page	Revision	Rationale
14	5.1.2 Exclusion Criteria (#18)	26	Revised exclusion criterion regarding major surgeries to exclude subjects who have undergone a major surgery or had a newly implanted artificial (prosthetic) joint(s), implants and/or devices where a minimum of 6 weeks has not elapsed from the time of surgery. Additional requirements for the resolution of all toxicities and/or complications was included.	Exclusion criteria added as a required safety update to mitigate potential listeria events.
15	Table 5 Treatment Delay/Discontinuation Guidelines for Drug-Related Adverse Events	28	Timing clarified for restarting (added 'or baseline' for non-heme grade 2-3 toxicities) and corrected for discontinuing subjects (changed within 12 weeks to within 3 weeks).	Administrative update
16	5.2.2 Administration of ADXS11-001	28	New paragraph added to note that ADXS11-001 must not be administered via central venous catheter or infusion port and that the central venous catheter or infusion port must not be used for 72 hours following the ADXS11-001 infusion until the subject receives the first dose of oral antibiotics.	Safety update to mitigate potential listeria events.
17	5.2.4 Pretreatment Prophylaxis Regimen	29	Section updated to include IV fluid hydration and revised for consistent formatting. Additional NSAID and antiemetic administrations were revised to be given per label or package insert.	Administrative update
18	5.2.5 ADXS11-001 Dosing	29	All subjects will now receive a 7 day course of oral antibiotics (instead of 3 day course) following each ADXS11-001 treatment.	Administrative update in support of the FDA recommendations.
19	5.5.1 Acceptable Concomitant Therapies and Procedures	30	'Study subjects should be reminded that acetaminophen or other NSAIDs (other than naproxen or ibuprofen) should not be used for pretreatment prophylaxis since these medications can interfere with treatment' was deleted from the first paragraph.	Administrative update.
20	5.5.2 Prohibited Concomitant Therapies	31	Added PI3K inhibitors and TNFα blocking agents to the list of prohibited therapies and restricted chronic use of systemic glucocorticoids, as they have the potential to reduce immune response.	Safety update to include FDA recommendations.

#	Section	Page	Revision	Rationale
21	5.6.3.1 Listeriosis and Listeria Infection - Identification and Management	37	New sections provide information on the identification process and management of potential/confirmed listeria infection.	Safety administrative change added to provide information on the identification and management of listeria.
22	5.6.4 Management and Surveillance of Listeria During Study Participation	37-38	New sections provide information on the mitigation of and management of listeria infection.	Safety administrative change added to provide information on the identification and management of listeria.
23	5.7.5 Major and Minor Surgeries and ADXS11-001 Treatment	40	New section added to describe the minimum time period required between major surgery and treatment administration for patients prior to and during study treatment.	Safety update to mitigate potential listeria events.
24	6.1 Schedule of Events	43-44	Added *Lm* Surveillance Monitoring schedule which includes a 6 month post ADXS11-001 antibiotic (Trimethoprim/Sulfamethoxazole) treatment to mitigate the risk of delayed listeria infection. Text clarified in the table and footnotes for consistency with the revised corresponding study procedure.	Safety updates and administrative clarifications per FDA recommendation.
25	7.1.2.1 Adverse/Serious Adverse Event Monitoring	46	In addition to administrative corrections, the section revised to include adverse and serious adverse events to be collected from the time written informed consent is obtained through 30 days after the last ADXS11-001 dose is administered.	Administrative update
26	7.1.3 Laboratory Procedures/Assessments	47	Text revised to note the total amount of blood to be drawn over the course of the trial will be based on local laboratory requirements (previously noted that they can be found in the Laboratory Manual).	Administrative update
27	Table 8 Laboratory Tests	48	Additional lab tests including *Lm* Blood cultures, ESR and CRP was added to the table. Table footnotes updated to detail *Lm* Surveillance Monitoring requirements.	Safety update to include FDA recommendations for the identification of listeria infection.
28	7.1.6.2 Treatment Period	56	Administrative clarifications made to section including NSAID and antiemetic administration post ADXS11-001 infusion to be given per label or package insert on Day 1 and Day 2, as needed.	Safety update based on FDA recommendation.

#	Section	Page	Revision	Rationale
			New paragraph added detailing the prophylactic antibiotic instructions during the Study Treatment Phase and Post Study Treatment.	
29	7.1.6.3 Safety Follow-up/Post-Treatment Visits	58	New paragraphs added regarding the updated *Lm* Surveillance Monitoring.	Safety update based on FDA recommendation.
30	7.1.6.4 Survival Follow-up	58	Section revised to show survival follow-up to be conducted at each visit during the Lm Surveillance Period and via telephone every 3 months (± 2 weeks) after the Lm Surveillance period to determine survival status for all subjects.	Administrative update
31	7.2.3.1 Serious Adverse Events	60	Deleted ”or the initiation of new anti-cancer therapy, whichever is earlier, ” from the timing of SAE collection.	Administrative update
32	8.2 Sample Size and the Design	62-63	PFS percentage changed from 25% to 20% throughout the section. Reference corrected ‘Benny Zee, *et al* (1999)’	Administrative update
33	9.4 Storage and Handling Requirements	65	Storage temperature for ADXS11-001 was changed to -80°C (±10°C) based on stability data.	Safety administrative change