ADVAXIS
IMMUNOTHERAPIES™

PROTOCOL ADXS001-07

A PHASE 1 STUDY EVALUATING HIGH DOSE ADXS11-001 TREATMENT IN WOMEN WITH CARCINOMA OF THE CERVIX

SPONSOR: ADVAXIS, INC.
305 COLLEGE ROAD EAST
PRINCETON, NJ 08540
609-452-9813 (OFFICE)
609-452-9818 (FAX)

Original Version 1.0: March 26, 2014

Amendment 1.0/Version 2.0: December 19, 2014

Amendment 2.0/Version 3.0: March 13, 2015

Amendment 3.0/Version 4.0: June 12, 2015

Amendment 4.0/Version 5.0: August 10, 2015

Amendment 5.0/Version 6.0: December 1, 2015

Amendment 6.0/Version 7.0: January 4, 2016

PROTOCOL APPROVAL

Protocol Number: ADXS001-07

Title of Protocol: A Phase 1 Study Evaluating High Dose ADXS11-001 Treatment in Women with Carcinoma of the Cervix

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Prepared by:

_____ _____

[redacted] Advaxis Inc. Date

Approved by:

_____ _____

[redacted] Advaxis Inc. Date

SUMMARY OF CHANGES

FOR PROTOCOL AMENDMENT 6.0

#	Section	Page	Revision	Rationale
1	Synopsis	11-13	Updated length of subject trial duration from 2 to 5 years, included the 6 month oral antibiotic course and *Lm* Surveillance Monitoring requirements, updated the Main Criteria for Eligibility and updated language for ADXS11-001 [redacted] Updated adverse event tracking to extend until completion of the *Lm* Surveillance Monitoring phase.	Administrative update in support of the FDA recommendations.
2	List of Abbreviations	14-15	Updated to include CMP, CRP, ESR, TNFα and PI3K.	Administrative update.
3	3.2 ADXS11-001 Immunotherapy	18	Section header and content were revised with AXDS11-001 information.	Administrative update
4	3.3 ADXS11-001 Mechanism Action	18-19	Section header and content were revised with AXDS11-001 mechanism of action.	Administrative update
5	3.4.1 Summary of Safety of ADXS11-001	19-21	Section was updated with safety data information.	Safety administrative update
6	3.4.1.1 Delayed/Late Listeria Infection	21-22	Safety Section revised to include 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.
7	5.2 Exclusion Criteria (#14)	28	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
8	5.2 Exclusion Criteria(#15)	28	New exclusion criterion was added to exclude subjects who are receiving or are expected to receive treatment with PI3K or TNFα inhibitors during study participation or in future.	Exclusion criteria added to mitigate risk of listeria infection.

#	Section	Page	Revision	Rationale
9	5.2 Exclusion Criteria #16	28	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.	Exclusion criterion added based on FDA recommendation of prophylaxis and 6-month antibiotic treatment.
10	5.2 Exclusion Criteria (#21)	29	New exclusion criterion added 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.
11	6 Study Design and Treatment Plan	29	Updated antibiotic regimen added.	Inclusion added based on FDA recommendation of antibiotic regimen for prophylaxis during study treatment and 6 month course post-treatment.
12	7.3 Patient Study Participation	33	New section added to detail patient study participation duration.	Updated to include the 3 year *Lm* Surveillance Monitoring Phase
13	Table 5: Schedule of Events	34-35	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 footnotes for consistency with the revised corresponding study procedure.	Safety updates and administrative clarifications per FDA recommendation.
14	8.1 Study Procedures	36-38	Prior/Concomitant Therapies and Procedures and Adverse Events updated to require 6 month post-study treatment antibiotics as well as recording of adverse/serious events from the time informed consent is signed through the completion of *Lm* Surveillance period. Updated to require antibiotic usage to be documented on the respective eCRFs.	Safety updates and administrative clarifications per FDA recommendation.

#	Section	Page	Revision	Rationale
			Surgical History – surgical history will be obtained for all subjects. Surgical procedures that occur after study enrollment will be documented separately. Prophylactic Medications – NSAIDS doses and antiemetic administration will be done per label or package insert. Coagulation Profile – will be assessed at Screening only. Dispense/Prescribe Oral Prophylactic Antibiotics section updated with details for on study and post study antibiotic regimen.	
15	8.5 Safety Follow-Up/Post-Treatment Visit	39-40	New paragraphs added regarding the updated *Lm* Surveillance Monitoring.	Safety update based on FDA recommendation.
16	9.1.1 Baseline Tumor Assessments	40	Section was updated by providing imaging areas to be included.	Safety administrative change
17	10.2.1 Safety Precautions	49	Section was updated to provide further clarification	Safety administrative change
18	11.1 ADXS11-001 Pretreatment Prophylaxis Regimen	51	Section was updated for revisions to the IV fluids volume and premedication regimen clarification	Safety administrative change
19	11.3 Administration of ADXS11-001	52	New paragraph added to note that [redacted]	Safety update to mitigate potential listeria events.
20	11.5.1 and 11.5.2 Listeria Infection Identification and Management	57-59	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.
21	11.7 Major and Minor Surgery and ADXS11-001 Treatment	61	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.

#	Section	Page	Revision	Rationale
22	12 Concurrent Therapies and Procedures	62-63	Added PI3K and TNFα to the list of prohibited therapies.	Safety update to include FDA recommendations.
23	13.2 Collection of Safety Information	64	Updated to include tracking of adverse events and serious adverse events during the 3 year *Lm* Surveillance Monitoring period.	Safety update to align with FDA recommendations.
24	13.8 Laboratory Test Abnormalities, Table 13, Laboratory Tests	71-72	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.
25	Throughout protocol		[redacted]	Safety administrative change
26	Throughout protocol		ADXS11-001 250 mL will be infused intravenously over [redacted]	Safety administrative change

INVESTIGATOR SIGNATURE PAGE

Protocol No.:	ADXS001-07
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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 #

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 SYNOPSIS

Sponsor: **Advaxis, Inc.**	**Name of Finished Product:** **ADXS11-001**	**Type of Treatment:** ***Lm*-LLO Immunotherapy**

Study Title:

Phase 1 Study Evaluating High Dose ADXS11-001 Treatment In Women With Carcinoma of the Cervix

Type of Study:

Open-label, Phase 1

Study Centers: Multi-center

Objectives:

The primary objective of the study is:

a) To evaluate the tolerability and safety of ADXS11-001 in subjects with persistent, metastatic, or recurrent squamous and non-squamous carcinoma, adenosquamous, or adenocarcinoma of the cervix

Secondary objectives:

a) To evaluate tumor response and progression-free survival (PFS) by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and immune-related RECIST (irRECIST) criteria

b) To evaluate and describe the data from correlative immunologic studies of ADXS11-001 treatment

Methodology:

In this Phase 1, dose-escalation, open-label, multi-center study, subjects with persistent, metastatic, or recurrent carcinoma of the cervix who have failed conventional therapy will receive ADXS11-001 every 3 weeks during a 12- week treatment cycle. Subjects will receive a prophylactic regimen to be completed at least [redacted] prior to each ADXS11-001 infusion to mitigate and manage potential immune response seen with immunotherapy administration. 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 72 hours at the completion of the last dose of ADXS11-001 or immediately following study discontinuation.

Doses will be escalated in the standard 3 + 3 fashion, starting with 5×10^9 colony forming units (CFU) to a maximum dose level of 1×10^{10} CFU. Dose cohorts of 3 subjects each will be treated. In the absence of dose-limiting toxicity (DLT) as defined in Section 6.1 Dose Limiting Toxicity assessed during the first treatment cycle, the dose will be escalated to the next dose level for the next 3 subjects. If DLT is seen in 1 of 3 subjects, another 3 subjects will be treated at that same dose. If DLT is seen in 2 of 6 subjects, then that dose level will be considered maximum tolerated dose (MTD) and the previous dose level will be selected as the recommended Phase 2 dose (RP2D). The RP2D will be selected based on an observed DLT rate of < 33%.

Treatment cycles can be repeated at the RP2D (or less) for an individual subject until a discontinuation criterion is met. Discontinuation criteria include documented disease progression, intolerable side effects not resolved with dose reduction or change in premedications or the subject completes 1 cycle of treatment post observation of complete response (CR) per RECIST 1.1 and immune-related RECIST criteria (irCR).

Sponsor: Advaxis, Inc.	Name of Finished Product: ADXS11-001	Type of Treatment: *Lm*-LLO Immunotherapy

Further assessment of the RP2D level may be explored in an expansion cohort in subjects with persistent, metastatic, or recurrent carcinoma of the cervix who have failed conventional therapy to evaluate the safety and clinical activity of ADXS11-001. Treatment will continue for each subject until a discontinuation criterion is met. The end of treatment will be defined as 1 year after the last subject's first treatment or until that subject has met a discontinuation criterion. All subjects will be followed for adverse events (AEs) and serious adverse events (SAEs) from the time written informed consent is signed through the completion of the *Lm* surveillance period.

Safety will be assessed by comparing treatment-related AEs, changes in physical examinations, vital sign measurements, laboratory abnormalities and *Lm* surveillance monitoring.

Immunologic effects will be measured and evaluated by collection of peripheral blood for preparation of peripheral blood mononuclear cells (PBMCs) and serum in cycle 1 only. PBMCs will be analyzed for the presence and quantitation of HPV-E7 and HPV–E6 specific CD8+ T-cells through ELISpot and other assays as well as T regulatory cells and myeloid-derived suppressor cells. PBMC immunologic gene expression analysis may also be conducted. Serum will be evaluated for serum cytokines, chemokines, and other potential markers.

Number of Subjects Planned:

The dose escalation portion of the study will enroll between 6-12 subjects based on observed AEs and/or DLTs within the dose cohorts. Additional subjects may be enrolled in an expansion cohort at the RP2D level to allow approximately 15 subjects to be treated at that dose level.

Diagnosis and Main Criteria for Eligibility:

- Women at least 18 years of age with histologically-confirmed, measurable and/or evaluable disease as defined by RECIST 1.1
- Subject has persistent, metastatic, or recurrent squamous and non-squamous carcinoma, adenosquamous, or adenocarcinoma of the cervix with documented disease progression that is not amenable to surgery or standard radiotherapy
- Subject may have received ≤2 prior regimens for disease in the metastatic setting. Subjects who have had >2 prior therapies in the metastatic setting MAY be eligible only after consultation with the Investigator and the Sponsor.
- Subjects should have no major existing co-morbidities or medical conditions that will preclude therapy in the view of the principal investigator
- Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and a life expectancy of at least 6 months (to be able to complete 1 study cycle)
- Subjects should not have rapidly progressing disease
- Subjects must be able to tolerate trimethoprim/sulfamethoxazole **and** ampicillin.
- Subjects must not have 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)). More common devices and prosthetics such as: arterial and venous stents, dental and breast implants and venous access devices such as Mediports are permitted. Subjects with any other devices or implants must be approved by Sponsor prior to participation.

Sponsor: Advaxis, Inc.	Name of Finished Product: ADXS11-001	Type of Treatment: *Lm*-LLO Immunotherapy

- Subjects who have undergone a major surgery or who have a new artificial implant and/or medical device which meets eligibility criteria must have a minimum 6-week time period elapsed from the time of surgery to the initiation of study treatment.
- Subjects who are receiving or are expected to receive future treatment with PI3K or TNFα inhibitors.

Test Product, Dose, Mode of Administration:

ADXS11-001 is a live attenuated bioengineered strain of *Listeria monocytogenes (Lm)*-LLO.

[redacted]

Reference Therapy:

None

Study Duration:

Each subject will participate in the trial for up to 5 years from the time the subject signs informed consent through the final study contact. The study duration includes an active study treatment phase (~24 months) and a 3-year *Lm* surveillance monitoring period, which includes 6 months of oral antibiotic administration to commence upon completion of the active study treatment phase or upon study discontinuation.

Criteria for Evaluation:

Safety: Recorded AEs; physical examinations, including vital sign measurements; clinical laboratory evaluations; *Lm* surveillance blood cultures

Efficacy: Tumor response and progression free survival (PFS)

Immunologic effects: Collection and analysis of peripheral blood

Statistical Methods:

Descriptive statistics will be used to summarize and evaluate the outcomes.

Demographic and baseline subject characteristics will be summarized. AEs will be classified and summarized by type, incidence, severity, and causality. All AEs will be summarized by subject, dose level, and prior recurrence history (aggressive/non-aggressive). All subjects who received at least 1 dose of ADXS11-001 will be included in the safety analyses.

Disease response will be tabulated for all subjects who receive ADXS11-001. PFS is defined as the time from first dose of study treatment until objective tumor progression or death. Subjects who have not progressed or who are still alive at the time of evaluation will be censored for the analysis. Kaplan-Meier curves and descriptive statistics will be used to summarize PFS.

2 LIST OF ABBREVIATIONS

ALT	alanine transaminase
APC	anaphase-promoting complex
AST	aspartate transaminase
BMBL	Biosafety in Microbiological and Biomedical Laboratories
BOR	best overall response
[redacted]	[redacted]
BUN	blood urea nitrogen
CBC	Complete blood count
CFU	colony forming unit(s)
CIN	cervical intraepithelial neoplasia
CMP	Comprehensive metabolic panel
CR	complete response
CRF	case report form
CRP	C-reactive Protein
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose limiting toxicity
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
GCP	Good Clinical Practice
GGT	gamma-glutamyl-transferase
GMP	Good Manufacturing Practice
GOG	Gynecologic Oncology Group
HPV	human papillomavirus
ICC	invasive cervical cancer
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
irBOR	immune-related best overall response
irCR	immune-related complete response
irPD	immune-related progressive disease
irPR	immune-related partial response
irRC	immune-related response criteria
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
irSD	immune-related stable disease
IV	intravenous
LDH	lactic dehydrogenase

LLO	listeriolysin O
Lm	*Listeria monocytogenes*
MDSCs	myeloid-derived suppressor cells
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug(s)
PBMCs	peripheral blood mononuclear cells
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PI3K	Phosphoinositide 3-kinase
PR	partial response
pRB	retinoblastoma protein
PT	prothrombin time
PTT	partial thromboplastin time
QID	four times a day
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAER	Serious Adverse Event Report
SCID	severe combined immunodeficiency
SD	stable disease
SOP	Standard Operating Procedure
SumD	sum of the longest diameters
TAAs	tumor associated antigens
tLLO	truncated listeriolysin O
TMTB	total measurable tumor burden
TNFα	Tumor necrosis factor alpha
Treg	T regulatory cells
ULN	upper limit of normal
US, USA	United Stated of America
WBC	white blood cell

3 BACKGROUND AND RATIONALE

3.1 Cervical Cancer and Its Relationship to the Human Papillomavirus

Cervical cancer is the second most common cancer in women worldwide and the most common cancer in developing countries.[1] . Worldwide, over half a million women are diagnosed with cervical cancer each year, predominantly in under-developed countries, where most cases present at an advanced stage due to lack of effective cervical cancer screening systems.[1] In the United States (US), it is estimated that 12,340 women were diagnosed with cancer of the cervix, and 4,030 women died of the disease in 2013.[2]

The human papilloma virus (HPV) is now recognized to be the primary etiologic agent for cervical carcinogenesis, and cervical cancer is the first cancer recognized by the World Health Organization to be 100% attributable to an infection with high-risk HPV genotypes.[1] However, the majority of HPV-infected individuals have an asymptomatic course, with clearance of the virus occurring within 1 or 2 years in 90% of cases. Ten percent of individuals experience persistent HPV infection, which increases their risk of developing invasive cancers. Ultimately, approximately one-half of the 10% of individuals with persistent HPV infection will develop malignant disease, a process that may take up to 30 years.[3]

Although many HPV types have been associated with cervical neoplasia, types 16, 18, 31, 35, 39, 45, 51, 52, 56, and 58 cause most invasive cancers and are considered "high-risk" HPV-genotypes. HPV-16 accounts for approximately 53% of invasive cervical cancer (ICC) cases in most countries, followed by HPV-18, which accounts for approximately 13%.[4] The high-risk HPV genotypes produce 2 oncoproteins, designated E6 and E7, which bind and inactivate the tumor suppressor's p53 and retinoblastoma protein (pRB), respectively. The E6 mediated inhibition of p53 blocks apoptosis, whereas E7 inhibition of pRB abrogates cell cycle arrest leading to deregulated cellular proliferation and ultimately malignancy.[5]

Persistent HPV infection may lead initially to abnormal changes in cervical cells, termed cervical dysplasia or cervical intraepithelial neoplasia (CIN). However, CIN is a distinct clinic pathological entity from ICC and defines premalignant lesions (namely CIN 2/3) that, if left untreated, may eventually progress to ICC. However, these lesions have a high rate of spontaneous remission and can be curatively treated with a minor gynecologic surgical procedure such as loop electrical electrosurgical procedure or a cone biopsy.

In the US, most cases of ICC are detected at early stages because of the implementation of cervical cancer screening programs. Staging of ICC is usually based on the American Joint Committee on Cancer or the International Federation of Gynecology and Obstetrics system, which are similar. Approximately 60% of ICC cases are diagnosed at stage I, 25% at stage II, 10% at stage III, and 5% at stage IV.[6] Standard treatments for ICC include surgery, radiation alone, chemotherapy alone, or combination radiation/chemotherapy. Surgery and radiation therapy are considered to be equally

effective for early-stage, small-volume disease. For more advanced disease, that is not reliably curable by surgery, additional treatments including radiation and potentially systemic chemotherapy are required. Several clinical trials have shown an overall survival advantage with cisplatin concurrent with radiation therapy (chemoradiation), and chemoradiation with cisplatin is the currently recommended treatment for locally advanced cervical cancer.[7] Platinum doublet chemotherapy is currently recommended as standard of care for patients with recurrent cervical cancer that is not amenable to surgery or radiation.[7] In general, survival correlates with stage, with a 5-year survival for stage IA of almost 100%, stage IB2 and IIB 50%–75%, stage III 30%-50%, and stage IV 15%. For locally recurrent disease, pelvic exenteration can lead to a 5-year survival rate of 32%-62% in selected patients.[7]

Although most cases of early-stage cervical cancer can be cured, treatments are associated with significant long-term morbidity [7] and most have an impact on fertility. Cisplatin, the most commonly used and most active therapy, has produced response rates ranging from 20%-30% and overall survival of less than 10 months.[8] In addition, patients with recurrent disease will typically have already received cisplatin concurrent with radiotherapy as a first-line therapy, and may no longer be sensitive to cisplatin.[9] In view of the low level of success with cytotoxic therapies, and the poor prognosis of patients with advanced cervical cancer, there is certainly an unmet medical need for novel, more efficacious, less toxic therapeutic approaches for ICC.

For over 3 decades, the Gynecologic Oncology Group (GOG) has studied a number of cytotoxic agents and combinations for the treatment of women with recurrent/metastatic cervical cancer. After the identification of cisplatin as a drug with significant activity, GOG Phase 3 trials focused on the development of cisplatin-containing regimens that might yield superior results compared to single-agent therapy. Unfortunately, the higher response rates associated with combination therapy often did not result in improved survival. Median survival in this patient population remains less than 1 year and combination therapy leads to more adverse effects, particularly myelosuppression. Most patients with recurrent and/or metastatic cervical cancer may no longer be sensitive to cisplatin-based chemotherapy as they most likely have already received cisplatin concurrent with radiotherapy as a first line therapy and, thus, experience treatment-related toxicity with no derived benefit from further cisplatin treatment.[9] When tumor responses do occur, they typically are of short duration. Furthermore, the widespread acceptance of adding cisplatin to radiation treatment as a radiation sensitizer in first-line chemoradiation treatment of ICC means that most patients with recurrent cervical cancer have already been treated with cisplatin. This prior exposure significantly reduces the effectiveness of cisplatin or carboplatin for recurrent cervical cancer. Recently, the results of the GOG 240 Phase 3 study were published where the addition of bevacizumab to combination chemotherapy was associated with a 3.7 month improvement in median overall survival in patients with advanced cervical cancer.[9, 10] However, cisplatin containing chemotherapy regimens continue to be the standard of care in this patient population worldwide.[8] Despite this, there continues to be a large unmet medical need for agents with different mechanisms of action (such as antiangiogenics, checkpoint

inhibitors, or therapeutic HPV immunotherapies) that when used alone or in combination can improve the survival of patients with recurrent cervical cancer.

3.2 ADXS11-001 Immunotherapy

ADXS11-001 is a live attenuated *Listeria monocytogenes* (*Lm*) immunotherapy, developed for the treatment of 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 (truncated LLO, tLLO) fused to the full length E7 peptide of HPV-16.

3.3 ADXS11-001 Mechanism of Action

ADXS11-001 is rapidly taken up by antigen presenting cells (APC) within the subject. This causes activation of the APC and results in a multi-factorial stimulation of innate immunity. To the subject, this activation can manifest as flu-like symptoms or symptoms associated with cytokine release that occur during or in the hours immediately following administration. Once inside the APC, ADXS11-001 can escape the phagolysosome into the cytoplasm where it secretes the HPV-E7-tLLO fusion protein. This peptide, along with other *Lm* peptides, is very rapidly ubiquitinated and transported to the proteasome where the peptides are broken down and cross-presented through major histocompatibility complex (MHC) Class 1 and Class 2 pathways. This cross-presentation, in immunologic context of responding to a "perceived" acute infection, stimulates the development of adaptive immunity culminating in HPV-specific effector T-cells that can infiltrate into the tumor microenvironment (TME) and destroy tumor cells immunologically.

Advaxis *Lm*-LLO immunotherapies have broad effects on the immune system and the ability to neutralize mechanisms of immune tolerance. These *Lm*-LLO immunotherapies take advantage of the ability of *Lm* to present target antigens in the cytoplasm of APCs that generate a target-specific T-cell immunity. High avidity T-cells are generated where possible, but when they are not, *Lm* stimulates an up-regulation of T-cell responses to sub-dominant epitopes. Advaxis *Lm*-LLO immunotherapies secrete tumor peptides fused to LLO from multiple copies of plasmids. This increased LLO secretion triggers endocrine and exocrine signaling of the immune system that results in a relative reduction in the number and function of regulatory T-cells and myeloid-derived suppressor cells (MDSC) in the TME, which enables tumor cell killing, even when the T-cells are lower avidity. Tumor antigen specific T-cell immunity generated in the context of *Lm*-LLO immunotherapies can be effective even when targeting self-antigens or viral targets that are partially cross-reactive.

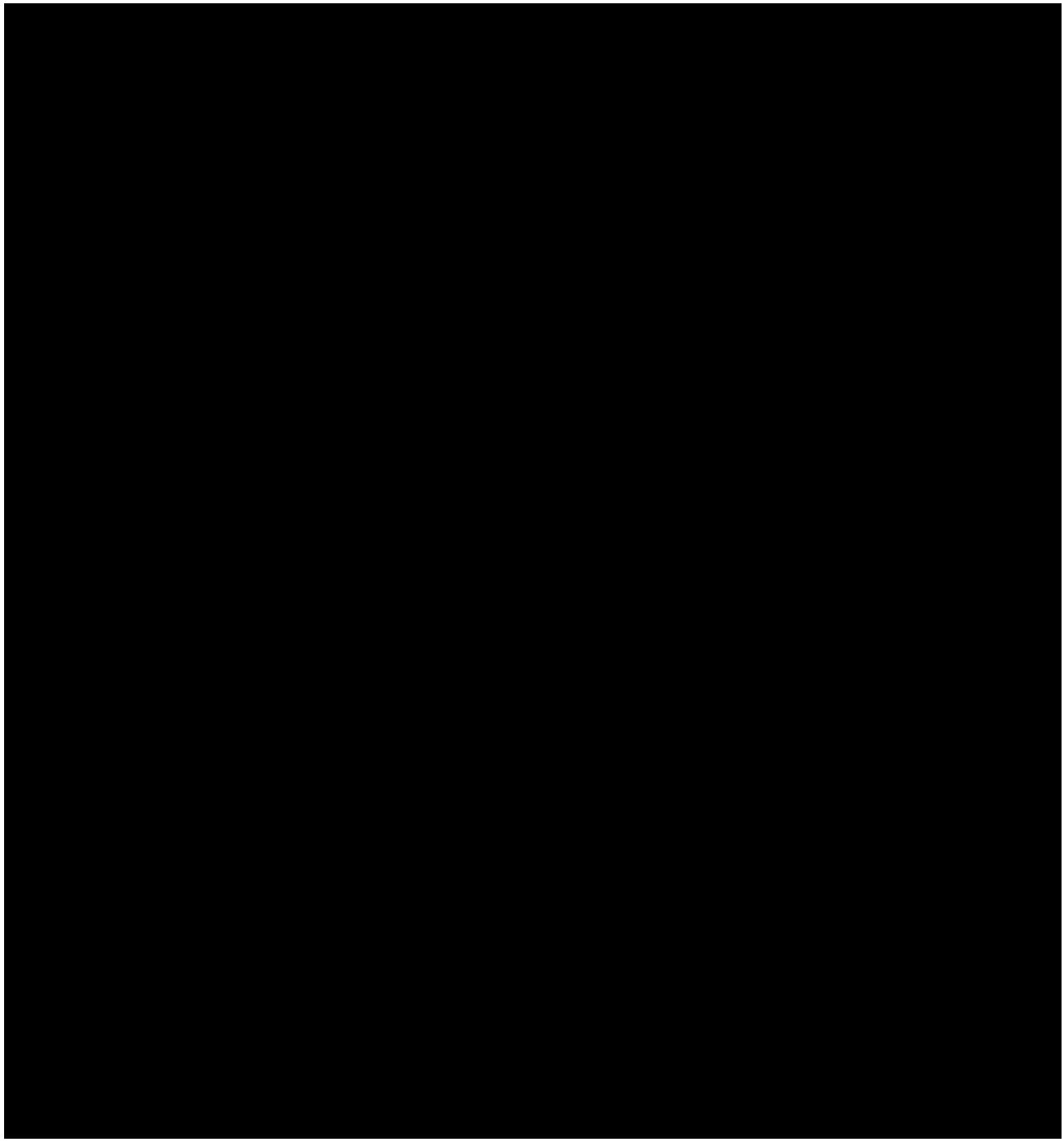
Studies have shown that ADXS11-001 has anti-tumor activity against multiple types of high-risk HPV, including cross-reactive activity where there are minor differences in HPV E7 T-cell epitopes. As an investigational drug product, ADXS11-001 has no direct effect on the tumor tissue, but is designed to stimulate the subject's own immune system

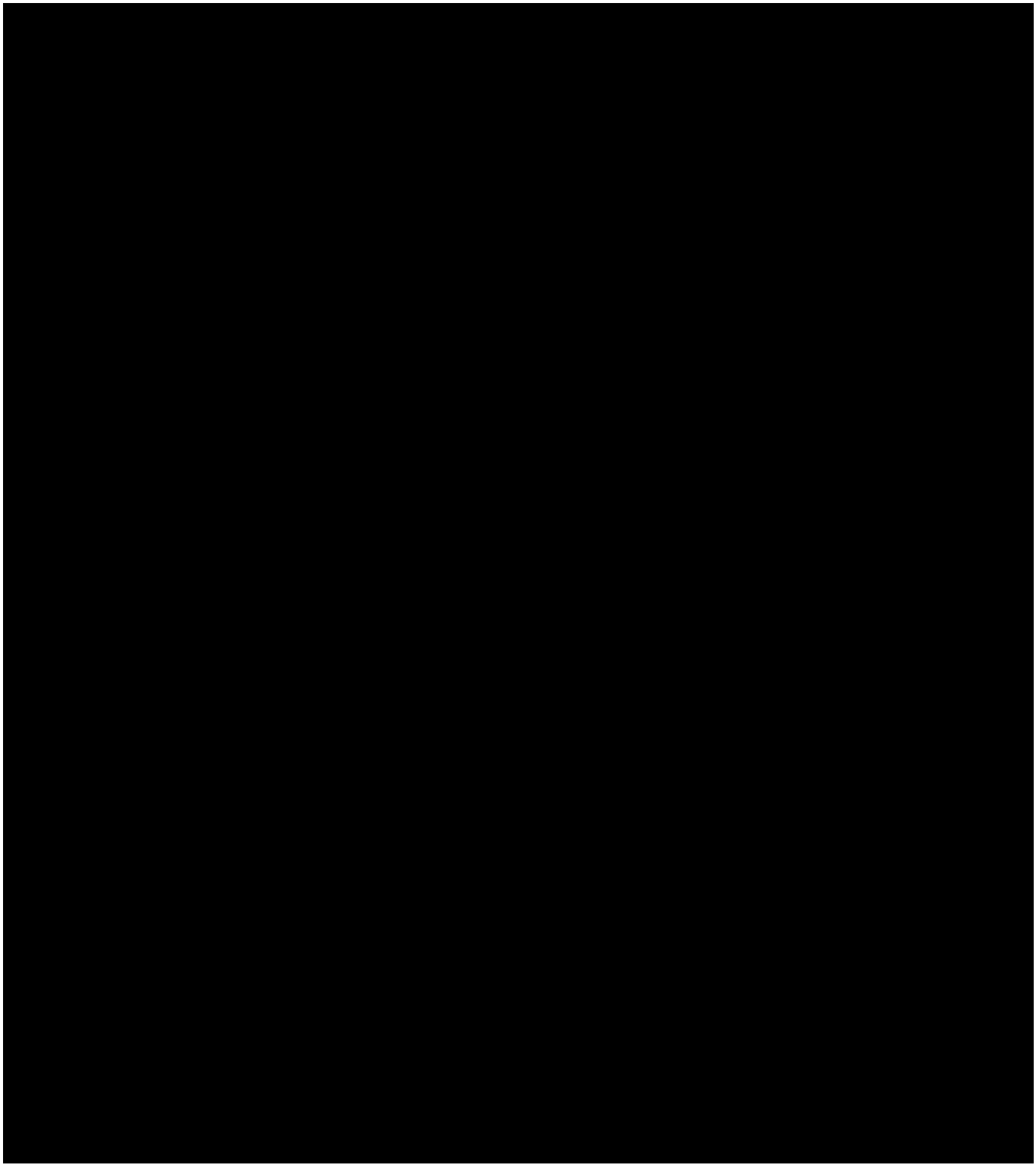
to generate an effective immune response targeting the tumor-associated antigen like HPV-E7.

3.4 Previous Clinical Experience with ADXS11-001

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

3.4.1 Summary of Safety of ADXS11-001





[redacted]

3.4.1.1 Delayed/Late Listeria Infection

ADXS11-001 has been attenuated over [redacted] more in comparison to wild-type (wt)-*Lm*. [redacted]

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 of any subject beyond 48 hours post-dosing and no *Lm* was detected in the urine and feces in any subject at the highest dose of ADXS11-001 tested (1 x 10^{10} CFU) [11].

wt-*Lm* is known to form and persist within biofilms, especially on medical devices despite antibiotic treatment [12]. Although rare, medical device–related infections such as ventriculo-peritoneal shunt infection, peritoneovenous shunt infection, and prosthetic joint infection have been reported [13-16]. ADXS11-001is highly sensitive to antibiotics such as ampicillin and sulfamethoxazole/trimethoprim, 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]

3.4.2 Summary of Efficacy for ADXS11-001 Studies in Cervical Cancer

[redacted]

[redacted]

[redacted]

3.5 Study Rationale

Since treatment with ADXS11-001 immunotherapy has shown prolonged survival, stable disease and objective tumor responses including CRs, and PRs, it may be able to improve survival in second-line treatment of recurrent cervical cancer in a clinically meaningful way. This trial proposes to evaluate a high dose of ADXS11-001 (1×10^{10} CFU). Depending on the level of toxicity seen in the study, 2 dose levels are possible: 1×10^{10} CFU and 5×10^{9} CFU. A standard 3 + 3 design will be used to evaluate and

determine the maximum tolerated dose (MTD) and subsequent recommended Phase 2 dose (RP2D). The standard dose of 1 x 10^9 CFU is not included as a dose level in this study [redacted]

4 OBJECTIVES

4.1 Primary Objectives

The primary objectives of the study are:

a) To evaluate the tolerability and safety of ADXS11-001 in subjects with persistent, metastatic or recurrent squamous and non-squamous cell carcinoma, adenosquamous, or adenocarcinoma of the cervix

4.2 Secondary Objectives

a) To evaluate tumor response and progression-free survival (PFS) by RECIST 1.1 and immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)

b) To evaluate and describe the data from correlative immunologic studies of ADXS11-001 treatment

5 SUBJECT SELECTION

5.1 Inclusion Criteria

1. Subject is at least 18 years of age or older on day of signing informed consent

2. Subject has histologically-confirmed, persistent, metastatic or recurrent squamous or non-squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix with documented disease progression (disease not amenable to surgery or standard radiotherapy).

3. Subject may have received ≤2 regimens for disease in the metastatic setting. Subjects who have had >2 prior treatment regimens in the metastatic setting MAY be eligible only after consultation with the investigator and the sponsor, and providing all other inclusion/exclusion criteria have been met. Subjects must have either documented disease progression OR become intolerant to prior therapy, in the metastatic setting.

4. Subject has measurable and/or evaluable disease for response assessment per RECIST 1.1. Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

5. Subject is able to provide written informed consent.

6. Subject demonstrates adequate organ function as defined in Table 3. All screening laboratory testing should be performed within 3 days of treatment initiation.

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematologic	
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 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.

7. Subject has resolved acute effects of any prior therapy to baseline severity of Grade <2 per CTCAE except for AEs not constituting a safety risk by investigator judgment.

8. Subject must have an ECOG performance status of 0 or 1.

9. Women of childbearing potential with a negative urine pregnancy test at Screening.

10. Female subjects of childbearing potential must agree to ongoing use 2 methods of study doctor approved birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study from Screening through 120 days after the last dose of study medication (see Section 13.10). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for >1 year.

5.2 Exclusion Criteria

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

2. Subject has received chemotherapy and/or radiation therapy (except palliative radiation therapy for disease-related pain) within ≤2 weeks of first ADXS11-001 infusion.

3. Subject has not recovered (i.e., Grade ≤1 at baseline) from AEs, with the exception of alopecia due to previously administered agent(s).

4. Subject has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or *in situ* cervical cancer that has undergone potentially curative therapy.

5. 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. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.

6. Has neuropathy (sensory and motor) ≥Grade 3 per CTCAE v 4.03.

7. Subject has diagnosis of immunodeficiency, is dependent on or has received systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment with the exception of topical corticosteroids and occasional inhaled corticosteroids, as indicated.

8. Subject has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of trial 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 trial treatment.

9. Subject 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 subject or the study.

10. Subject is pregnant or breastfeeding, or expecting to conceive a child/children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

11. Subject is currently participating in or has participated in a study of an investigational agent(s) or using an investigational device within 4 weeks of the first dose of trial treatment.

12. Subject has active infection requiring systemic therapy or is dependent on or currently receiving antibiotics that cannot be discontinued before dosing. (Note: Subjects who discontinue an antibiotic prior to dosing must wait at least 5 half-lives after the last dose of antibiotic before receiving any ADXS11-001 infusion).

13. Subject has a known psychiatric or substance abuse disorder(s) that would interfere with cooperation with the requirements of the trial.

14. 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)). 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. Sponsor must be contacted prior to consenting any subject who has any other device and/or implant.

15. Subjects who are receiving or may receive future treatment with PI3K or TNFα inhibitors.

16. Subject with a contraindication (e.g., sensitivity/allergy) to trimethoprim/ sulfamethoxazole **and** ampicillin.

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

18. Subject has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).

19. Subject has a known active hepatitis B (e.g., HBsAg reactive) or hepatitis C (e.g., HCV RNA [qualitative] is detected).

20. Subject has received a live vaccine within 30 days prior to the first dose of trial treatment.

21. Has undergone a major surgery, including surgery for a new artificial implant and/or device, within 6 weeks prior to the initiation of ADXS11-001 treatment. NOTE: All toxicities and/or complications must have recovered to baseline or Grade 1 prior to the initiation of ADXS11-001 study therapy. Sponsor must be consulted prior to enrolling subjects on the study who recently had a major surgery or have new artificial implant, and/or devices.

22. Subject has a known allergy to any component of the study treatment formulations.

23. Subject has a history of listeriosis or prior ADXS11-001 therapy.

6 STUDY DESIGN AND TREATMENT PLAN

In this Phase 1, open-label, multi-center study, subjects with persistent, metastatic or recurrent squamous cell or non-squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix who have failed conventional therapy will receive the highest dose tolerated of ADXS11-001 infused intravenously (IV) [redacted] (± 10 minutes) with overall infusion volume of 250 mL on Day 1 of Weeks 1, 4, 7, and 10 of each 12-week cycle. Subjects must complete the prophylactic regimen at least [redacted] prior to each ADXS11-001 infusion (as noted in Section 11.1) to mitigate and manage the potential immune response seen with immunotherapy administration.

Subjects who experience a DLT during the dose escalation portion of the study or experience events described as a DLT in any subsequent treatment cycle will be discontinued from study treatment. However, if the subject who experienced a DLT shows significant response to ADXS11-001, they may be eligible to receive ADXS11-001 at a lower dose level for subsequent doses and cycles following discussion and agreement between the Investigator and Sponsor. See Section 6.1 Dose Limiting Toxicity Criteria for definition of DLT.

The treatment to be used in this trial is outlined below in Table 4. Trial treatment should begin on the day of randomization or as close as possible to the date on which the treatment level is allocated/assigned.

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

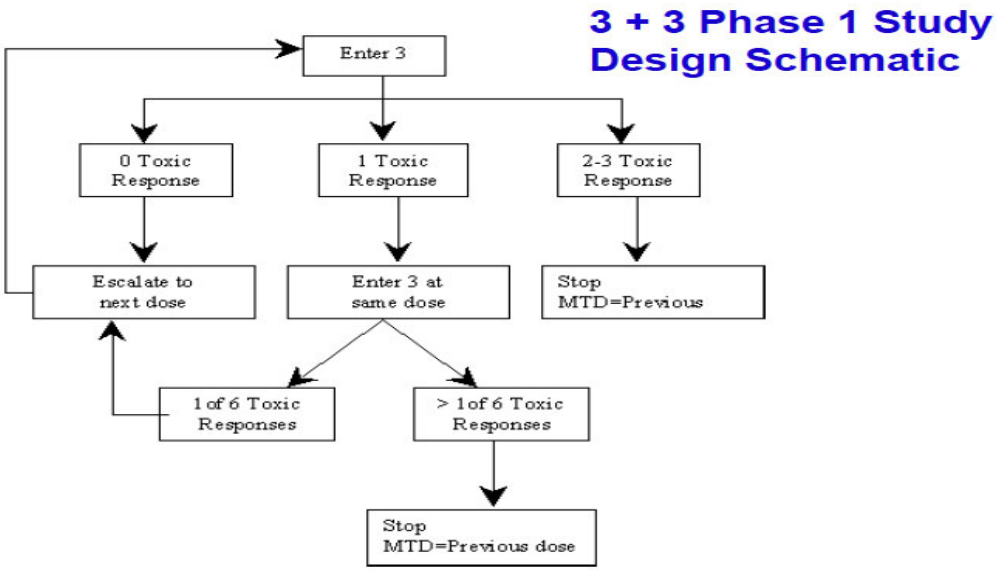
Table 4 Trial Treatment

Dose Level	ADX11-001	Schedule
1	5 x 10^9 CFU	Q3wks
2	1 x 10^{10} CFU	Q3wks
-1	1 x 10^9 CFU	Q3wks

ADXS11-001 will be given as a [redacted] 250 mL IV infusion every 3 weeks in repeating 12-week cycles

A standard 3 + 3 design will be used in the dose escalation portion of the study. ADXS11-001 will be administered in sequential cohorts of 3-6 subjects, with a minimum of 48 hours between initial dosing for each of the first 3 subjects treated at each dose level. The first cohort will enroll a minimum of 3 subjects, according to a standard 3 + 3 design shown schematically in Figure 1.

Figure 1 3+3 Design Schematic



- Subjects in the first cohort will receive a dose of ADXS11-001 5 x 10^9 CFU (Dose Level 1).

- If no DLTs are experienced in the 28 day DLT observation period at Dose Level 1, the next dose level of ADXS11-001 1 x 10^{10} CFU (Dose Level 2) will be explored.

- If 1 DLT is experienced at Dose Level 2 (ADXS1-001 1 x 10^{10} CFU), then 3 additional subjects will be enrolled at that same dose level. If there is 1 DLT among the 6 subjects, then the Dose Level 2 may be identified as the RP2D and will be expanded to further define safety and efficacy.

- If ≥2 DLTs are observed within 28 days of dosing for subjects in the first dose cohort, the starting dose of ADXS11-001 will be de-escalated to 1 x 10^9 CFU and a dose de-escalation cohort may be enrolled (Dose Level -1).

All decisions regarding dose level escalation or de-escalation will be guided by the 3 + 3 study design and will be made by the Sponsor in consultation with the Investigator(s).

The RP2D will be selected based on an observed DLT rate of <33%. The Sponsor reserves the right to expand the number of subjects in each of the cohorts to better evaluate safety and tolerability. Cohorts will be expanded in groups of 3 subjects.

Following identification of the RP2D, additional subjects may be enrolled into the expansion cohort to allow approximately 15 subjects to be treated at that dose level. All subjects in the Dose Expansion Cohort may be enrolled simultaneously.

DLTs will only be assessed during the first 28 days in cycle 1 (See Section 6.1, Dose Limiting Toxicity Criteria, for DLT definition). Transient hypotension which may require IV fluids for management is an expected event that subjects may experience with ADXS11-001 infusions. Subjects with signs of cytokine release symptoms ≥Grade 3 (per CTCAE v 4.03) that persist for more than 24 hours despite symptomatic treatment, will be judged to have a DLT. Blood cultures will not be obtained on a routine basis but will be collected in subjects who have persistent fever 24 hours after the end of ADXS11-001 infusion. Subjects will receive a 7-day course of either oral 80 mg trimethoprim / 400 mg sulfamethoxazole once daily or 160 mg trimethoprim / 800 mg sulfamethoxazole (DS) 3 times over the course of the 7 days. Subjects with known allergy to sulfa drugs may receive ampicillin 500 mg 4 times daily for 7 days beginning on Day 4 (approximately 72 hours) after each study treatment infusion. 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. Study cycles can be repeated at the RP2D (or less) for each subject until a discontinuation criterion is met. Criteria include documented disease progression, intolerable side effects not resolved with dose reduction or change in pre-medications, or the completion of 1 cycle of treatment post observation of complete response per RECIST 1.1 and immune-related RECIST criteria (irCR).

Safety will be assessed by comparing treatment-related AEs, changes in physical examinations, vital sign measurements, and laboratory abnormalities.

Immunologic effects will be measured and evaluated by collection of peripheral blood for preparation of peripheral blood mononuclear cells (PBMCs) and serum immediately prior to each ADXS11-001 infusion and 2 weeks after every ADXS11-001 infusion in Cycle 1 only (Day 1 of Weeks 3, 6, 9, and 12). PBMCs will be analyzed for the presence and quantitation of HPV-E7 and HPV–E6 specific CD8+ T-cells through ELISpot and other assays as well as Treg cells and MDSCs. PBMC immunologic gene expression analysis may also be conducted. Serum will be evaluated for serum cytokines, chemokines, and other potential markers. Blood will be collected in Cycle 1 only at 3 time points immediately prior to each ADXS11-001 infusion and 2 hours and 4 hours post infusion (±15 minutes- Day 1 of Weeks 1, 4, 7, and 10).

Subjects should arrive at the study center on the days of their scheduled ADXS11-001 administration in order to be evaluated, have laboratory specimens collected before treatment commences, and complete the study prophylactic regimen at least [redacted] pre-infusion before receiving the ADXS11-001 infusion.

Subjects will remain at the study site for a minimum of 4 hours after the infusion for safety observations, and if necessary treatment of side effects resulting from the study treatment administration. Treatment and observation of side effects may take up to an additional 4 hours, so subject arrival at the study center should be early enough to accommodate a possible 9-hour visit day. Vital signs will be taken pre-dose then every [redacted] after the infusion as a safety measure.

After the initial study cycle, subjects who respond or have immune-related SD at or after tumor assessments may receive additional treatment at the same dose and schedule, until either evidence of disease progression, intolerable side effects not resolved with dose reduction or change in premedications, or for 1 completed study cycle post achievement of CR per RECIST 1.1 and immune-related RECIST criteria (irCR). These subjects may continue to be evaluated for response every 12 weeks.

Study treatment will be modified as per Table 11 in Section 11.6.1 Treatment Modification Guidelines.

6.1 Dose Limiting Toxicity Criteria

DLT will be evaluated during the first 28 days of the first cycle during the dose escalation portion of the trial. All toxicities will be graded using CTCAE v 4.03. The occurrence of any of the following toxicities will be considered a DLT, if judged by the Investigator to be possibly, probably or definitely related to therapy. Treatment modifications for DLT are shown in Table 11.

Hematologic:

1. Grade 4 hematologic toxicity.

2. Febrile Neutropenia, defined as absolute neutrophil count (ANC) < 1000/mm^3 with a single temperature of >38.3° C (101° F) or a sustained temperature of >38° C (100.4° F) for more than 1 hour.

3. Grade 3 thrombocytopenia lasting >72 hours.

4. Grade 4 thrombocytopenia.

Non-Hematologic:

1. ≥Grade 3 non-hematologic toxicity, (excluding nausea, vomiting and/or diarrhea lasting <3 days and reversible with medical intervention).

2. Grade 3 non hematologic laboratory values, (excluding transient Grade 3 laboratory value abnormalities, hematologic and non-hematologic, reversible within 5 days and without necessity for medical intervention).

3. Listeremia: positive blood cultures(s) along with persistent (for 72 hours post dose) symptoms consistent with listeremia (e.g., fever and muscle aches, often preceded by diarrhea or other gastrointestinal symptoms).

4. ≥Grade 3 flu-like symptoms or cytokine release symptoms that persist for >24 hours after study treatment administration despite symptomatic treatment.

7 INVESTIGATIONAL CENTERS

This is a multi-center study.

7.1 Subject Accrual

Subjects will be recruited from a population of patients with recurrent, metastatic, or persistent squamous and non-squamous cell carcinoma, adenosquamous or adenocarcinoma of the cervix. The subject's medical record, including the most recent treatment, will be reviewed by the Investigator to determine the suitability of the subject for the study.

7.2 Subject Enrollment

Each subject who gave signed informed consent and was screened for admission into the study will be assigned a unique sequential number that also includes their study site. The identification number and the subject's initials should be recorded on all case report forms (CRFs) and correspondence regarding the subject following study registration.

7.3 Subject Study Participation

Each subject may participate in the study for up to 5 years from the time informed consent is signed through the final study contact. This includes a study treatment phase (~24 months), a 3-year post-ADXS11-001 treatment *Lm* surveillance period which includes a prophylactic oral antibiotic administration period (6 months) and *Lm* surveillance monitoring approximately every 3 months for 3 years. It is expected that a subject will participate in the study until the completion of the full 3-year *Lm* surveillance period. However, following the completion of the 6 month oral antibiotic treatment, a subject will be eligible to participate in other investigational clinical studies.

8 STUDY EVALUATION

The key study procedures and the frequency of their occurrences are outlined in Table 5.

Table 5 Schedule of Events

Study Procedure	Screening[1]	12 Week Treatment Cycle[2]												End of Therapy[6]	Follow-Up
	Days -28 to 0	Wk 1[4] Pre	I	Post	Wk 2	Wk 3[5]	Wk 4	Wk 5	Wk 6[5]	Wk 7	Wk 8	Wk 9[5]	Wk 10	Wk 11	Wk 12		
Administrative Procedures																	
Informed consent[7]	X																
Eligibility Criteria	X	X															
Demographics/Medical History	X																
Surgical History[8]	X																
Prior Cancer History	X																
Prior/Concomitant Medications	X	X	X				X			X			X			X	
Non Drug Treatment/Procedures[9]	X	X	X				X			X			X			X	
Prophylactic Medication[10]		X					X			X			X				
ADXS11-001 Administration[11]			X				X			X			X				
Dispense/Prescribe Oral Prophylactic Antibiotics[12]			X				X			X			X			X	X
Phone Call[3]																	X
Clinical Procedures/Assessments																	
Review Adverse Events (AE)[13]	X	X	X				X			X			X			X	X
Physical exam[14]	X	X					X			X			X			X	
Vital Signs[15]	X	X	X				X			X			X			X	
ECOG Performance Status	X	X					X			X			X			X	
Laboratory Procedures/Assessments[16]																	
CBC with Differential	X	X					X			X			X			X	
Serum Chemistry Panel	X	X					X			X			X			X	
Coagulation Profile[17]	X																
Urine Dipstick	X	X					X			X			X			X	
Pregnancy Test[18]	X	X					X			X			X			X	
Lm Surveillance Monitoring[19]																	X
Efficacy Measurements/Correlative Studies																	
Tumor Imaging[20]	X														X	X	
Immune monitoring/T Cell[21]		X				X	X		X	X		X	X		X		
Cytokines[22]		X	X				X			X			X				

[1] Screening procedures, including tumor evaluations will be performed within 28 days prior to first dose of study treatment to determine study eligibility.

[2] Repeating 12-week treatment cycles.

[3] 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 AEs or SAEs.

[4] At every ADXS11-001 infusion, the indicated pre and post procedures will be performed.

[5] Week 3, Week 6 and Week 9 visits will be performed during Cycle 1 only. After cycle 1, these visits are not required.

[6] End of Therapy is not a visit. Assessments noted here must be completed upon the decision to discontinue a subject from study treatment.

[7] Informed Consent must be obtained prior to conducting screening evaluations.

[8] Documentation of non-cancer surgeries, including, but not limited to artificial (prosthetic) joints, implants and/or devices, such as port/stent implant placed prior to study enrollment.

[9] Documentation of any on-study non-drug treatment and surgical procedures, including but not limited to artificial (prosthetic) joints, implants and/or devices.

[10] The pretreatment prophylactic regimen will be administered prior to and completed at least [redacted] before each ADXS11-001 infusion.

[11] ADXS11-001 may be administered ± 7 days within Day 1 of each scheduled infusion. ADXS11-001 should not be administered less than 2 weeks apart without Sponsor approval.

[12] All subjects will receive a 7-day course of oral antibiotic therapy starting 72 hours after administration of ADXS11-001. All subjects will also receive an additional 6-month oral antibiotic course to be initiated 72 hours following the last dose of study treatment or upon discontinuation of study treatment.

[13] AEs and SAEs will be assessed from the time Informed Consent is obtained through the completion of the *Lm* surveillance period. . All AE/SAEs will be followed through resolution. All AEs/SAEs experienced during this period must be recorded on the eCRF.

[14] Physical Examinations are to be completed prior to the ADXS11-001 administration to confirm safety criteria for study drug administration are met. PEs may be performed more frequently, as clinically indicated. Height will be measured at screening only. Weight will be collected prior to each ADXS11-001 infusion.

[15] Monitor vital signs every [redacted] following the completion of every ADXS11-001 infusion.

[16] All laboratory procedures are to be completed and assessed by the investigator within 3 days prior to the administration of study treatment to confirm safety criteria for study treatment administration are met.

[17] Coagulation profile will be assessed at screening only.

[18] A pregnancy tests must be performed within 72 hours prior to each ADXS11-001 infusion for female subjects of childbearing potential or less than 1 year postmenopausal. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

[19] *Lm* surveillance will include routine monitoring of CBC, CMP (including CRP, ESR) and blood cultures. Following completion of study treatment all assessments will be performed every 3 months (±2 weeks) for 3 years beginning 3 months after the subject's last dose of study treatment.

[20] 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 12 (±1 week) for the duration of study participation. Apparent progression within the first 12 weeks, not accompanied by clinical deterioration, should be confirmed ≥4 weeks later.

[21] Immune monitoring/T-cell samples will be collected immediately prior to each ADXS11-001 infusion (Day 1 of Weeks 1, 4, 7, and 10) and between 11-14 days **after every ADXS11-001 infusion in Cycle 1 only.**

[22] Cytokine samples will be collected **in Cycle 1 only** at 3 time points immediately prior to each ADXS11-001 infusion and 2 hours and 4 hours post infusion (±15 minutes- Day 1 of Weeks 1, 4, 7, and 10).

8.1 Study Procedures

A series of clinical tests and procedures will be performed to assess toxicity and response throughout the study. The evaluations for this study will include:

1. Informed Consent - each subject must sign a copy of the most current Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved informed consent document. A copy of the signed document will be maintained with the subject's records.

2. Medical History - past or current medical conditions, current medications, and medications taken within 30 days of study entry.

3. Surgical History - A surgical history will be obtained by the Investigator or qualified designee. Surgical history will include all clinically relevant surgeries including, but not limited to artificial (prosthetic) joints, implants and/or devices, such as ports or stents. Surgical procedures that occur after study enrollment will be documented separately.

4. Prior Cancer History - A prior cancer history will be obtained by the Investigator or qualified designee. The prior cancer history will include histological confirmation of cancer, tumor staging (refer to the most current American Joint Committee on Cancer Staging Manual, the fifth edition or higher), and prior cancer therapies and best response(s), if applicable.

5. Prior/Concomitant Therapies and Procedures- All prescription and nonprescription medication (excluding vitamins and nutritional supplements) taken by the subject from 28 days prior to signing informed consent and up to and including the completion of the 3-year *Lm* surveillance period will be recorded in the medical record and on the eCRF.

6. AEs/SAEs- The Investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs/SAEs from the time written informed consent is obtained through the completion of the 3-year *Lm* surveillance period of the study. AEs/SAEs experienced during this period will be reported and recorded in the eCRF. AEs will be graded and recorded throughout the study according to CTCAE v 4.03 (see Section 13.6). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to study treatment.

7. Physical Examination - evaluation by body system.

8. Vital Sign Measurements - temperature, pulse, respiration rate, and blood pressure and weight will be taken pre-dose then every [redacted] after each infusion of ADXS11-001. Weight will be taken pre-dose only. Height will be measured at screening only.

9. Prophylactic Medications - The pretreatment prophylactic regimen will be administered prior to and be completed at least [redacted] before each ADXS11-001 infusion as outlined in Section 11.1. Subjects may continue to receive NSAIDs doses and antiemetic administration per label or package insert, as needed following ADXS11-001 infusions

10. ECOG Performance Status Score - according to the ECOG performance status criteria.

11. Hematology Profile - a complete blood count (CBC) with differential, and platelet count.

12. Chemistry Profile - glucose, total protein, albumin, uric acid, blood urea nitrogen (BUN), creatinine, lactic dehydrogenase (LDH), AST, ALT, alkaline phosphatase, total bilirubin, sodium, potassium, bicarbonate, chloride, and calcium.

13. Coagulation Profile – international normalized ratio (INR) or prothrombin time (PT) and activated partial thromboplastin time (aPTT) will be assessed at screening only.

14. Urinalysis – routine dipstick measurements and, if clinically indicated, microscopic analysis.

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

16. Dispense/Prescribe Oral Prophylactic Antibiotics – **(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 3 times during the 7 consecutive days or 80 mg trimethoprim/400 mg sulfamethoxazole administered daily for 7 consecutive days or for subjects with sulfa allergy ampicillin 500 mg 4 times daily for 7 consecutive days may be administered. **(2) Post Study Treatment** - All subjects will receive a 6-month course of oral trimethoprim/sulfamethoxazole or ampicillin for subjects with sulfa allergy to be initiated approximately 72 hours following the last dose of study treatment or at the time of study discontinuation. The dose of trimethoprim/sulfamethoxazole consists of either 160 mg trimethoprim/800 mg sulfamethoxazole (DS) tablet administered 3 times a week or 80 mg trimethoprim/400 mg sulfamethoxazole administered daily. The dose of ampicillin consists of 500 mg 4 times daily for 6 months. Review the approved product labeling for Bactrim and ampicillin, and monitor antibiotic tolerance as dosing adjustments may be necessary.

17. Tumor Imaging– Computed tomography (CT) and magnetic resonance imaging (MRI) will be considered the best currently available and reproducible methods to measure target lesions (as defined in Section 9.1.4, Definition of Target/Non-target Lesions) selected for response assessment. Baseline tumor imaging/disease

assessment must be performed within 28 days prior to the first dose of study drug. Then imaging studies and tumor assessments will be performed every 12 weeks (± 1 week) after the initial ADXS11-001 infusion. Apparent progression within the first 12 weeks, not accompanied by clinical deterioration, should be confirmed ≥4 weeks later. (See Section 9.1.12, Tumor Response).

18. Immune Monitoring - The generation of E6 and E7 specific immune responses in the peripheral blood will be assessed by ELISpot or enzyme-linked immunosorbent assay (ELISA) based assays. Blood for immune monitoring will be collected immediately prior to every ADXS11-001 infusion and 2 weeks after each ADXS11-001 infusion in cycle 1 only (Day 1 of Weeks 1, 3, 4, 6, 7, 9, 10, and 12).

    - T cell ELISpot - For blood collection, peripheral blood samples (around 50 mL total) will be withdrawn at the time points specified above. Whole blood will be processed over a Ficoll gradient to obtain PBMC, and PBMC will be washed, counted, aliquotted and frozen in dimethyl sulfoxide-containing freezing medium prior to long-term storage in liquid nitrogen. Sterile technique will be maintained throughout so that viable cells may be cultured and assayed after thawing. The peptide pools of E6 and E7 antigens for determination of immune responses will be provided by Advaxis.

19. Cytokines/Chemokines – Blood for cytokine and chemokine analysis will be collected in Cycle 1 only at 3 time points immediately prior to each ADXS11-001 infusion and 2 hours and 4 hours post infusion (± 15 minutes) Day 1 of Weeks 1, 4, 7, and 10.

8.2 Screening Evaluations

All subjects must undergo Screening evaluations prior to the first ADXS11-001 infusion. Screening evaluations used to determine the subject's study eligibility must be completed within 28 days prior to the first ADXS11-001 infusion and include the following: histological confirmation of persistent, metastatic or recurrent squamous or non-squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix, tumor evaluations, medical history, prior and concomitant therapies; physical examination; vital sign measurements including weight, height (at Screening only); and ECOG Performance Status. Laboratory tests for Screening including hematology, coagulation, and chemistry profile; urinalysis; and a pregnancy test for women of childbearing potential must be performed within 28 days prior to the first dose of study treatment but maybe used as Cycle 1 Day 1 safety labs if done within 3 days of the first dose of study treatment. Screening/Baseline tumor evaluations must be performed 28 days prior to the first dose of study treatment.

Results of all screening evaluations must be reviewed by the principal Investigator or his/her designee to ensure that all eligibility criteria have been satisfied prior to subject

enrollment. Written informed consent must be obtained prior to the performance of any study specific Screening evaluations.

8.3 Study Cycle Evaluation

Baseline imaging studies and tumor assessments must be performed within 28 days prior to the first ADXS11-001 infusion in the first Treatment Period. Subsequent assessments will be conducted at Week 12 in Cycle 1, followed by assessment every 12 weeks (± 1 week) thereafter. Apparent progression within the first 12 weeks not accompanied by clinical deterioration, should be confirmed 3 to 4 weeks later.

Blood samples for immune monitoring and cytokine/chemokine analysis should be collected per schedule in Cycle 1 only (See Section 8.1 Study Procedures).

A physical examination, an ECOG Performance Status, vital sign measurements, hematology and chemistry profiles, and urinalysis will be performed prior to each study treatment infusion and at the end of therapy. Subjects will also be asked about the occurrence of any AEs and changes to concomitant medications.

Vital signs (including blood pressure, pulse rate, respiratory rate, and temperature) will be checked and recorded prior to administration of ADXS11-001 and [redacted] following the infusion. Weight will be collected prior to each ADXS11-001 infusion.

A urine pregnancy test will be performed within 72 hours prior to each ADXS11-001 infusion and at the end of therapy for all women of childbearing potential.

8.4 End of Therapy Evaluations

End of therapy is not a visit. It is a list of assessments that must be completed upon the decision to discontinue a subject from study treatment. These evaluations include: a physical examination, ECOG Performance Status, vital sign measurements, weight, hematology, coagulation, and chemistry profiles, urinalysis, and imaging studies, if indicated. AEs and changes to concomitant medications will also be assessed and documented.

8.5 Safety Follow-Up/Post-Treatment Visits

Safety follow-up will be conducted via a telephone call at 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. Safety follow-up will also continue to be monitored for AEs and SAEs during the 3-year *Lm* surveillance period of the study (see below).

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 period 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 1 dose of ADXS11-001. It will occur every 3 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, subjects must continue to be monitored closely, including additional testing and a blood culture, for possible signs/symptoms of listeriosis. This testing may be performed at the investigational site or at another acceptable location following consultation with the Sponsor.

9 EVALUATION CRITERIA

9.1 Safety

The safety of ADXS11-001 administration will be assessed according to the NCI CTCAE v 4.03 criteria which will be used to define the grades and levels of toxicity. These criteria will be applied to:

- Observation of the infusion site for swelling, irritation, immune reaction or other abnormalities
- Changes from baseline in physical examination findings and vital signs
- Changes from baseline in laboratory parameters (hematology, coagulation, and serum chemistry)
- Evidence of allergic and constitutional symptoms
- Reported AEs

Safety evaluations will be performed throughout the duration of the study. All subjects who received at least 1 dose of ADXS11-001 will be evaluated for safety. See Section 13.2, Collection of Safety Information, for the definition of an AE.

9.1.1 Baseline Tumor Assessments

The baseline tumor burden (unidimensionally-measured or evaluable disease) will be assessed during the pretreatment evaluations. The Investigator will identify prospectively, the lesions to be followed in order to evaluate the subject's response to therapy (see Section 9.1.4, Definition of Target/Non-target Lesions). Imaging areas will include the chest, abdomen, pelvis and other areas as indicated by clinical presentation.

9.1.2 Tumor Imaging and Assessment of Disease

Computed tomography (CT) and magnetic resonance imaging (MRI) will be considered the best currently available and reproducible methods to measure target lesions (as

defined in Section 9.1.4, Definition of Target/Non-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 12-week cycle of ADXS11-001 treatment will be considered evaluable for response.

9.1.3 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, ≥ 1.0 cm). Measurable disease will be present if the subject has one 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, inflammatory breast disease, 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.

9.1.4 Target/Non-Target Lesions

All measurable lesions, up to a maximum of 2 lesions per organ and 5 lesions 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 assessment time points as target lesions.

9.1.5 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 5 lesions total) 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.

9.1.6 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 (up to 2 lesions per organ, up to total 5 lesions) is measured. At each subsequent tumor assessment (TA), 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

9.1.7 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 subject 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 subject 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 (i.e., an increase in tumor burden representing an additional 73% increase in 'volume' which is equivalent to a 20% increase diameter in a measurable lesion).

9.1.8 Immune-Related Response in Non-Measurable Lesions

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 (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 scheduled assessment.

9.1.9 Overall Response

Overall response will be determined based on RECIST 1.1 criteria and by irRECIST criteria (Table 6). 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 6 Tumor Response Evaluation: Comparison of RECIST 1.1 and irRECIST

Criteria	RECIST 1.1	irRECIST
New measurable lesions (≥ 10 mm)	Always represents PD	Incorporated into tumor burden
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

Criteria	RECIST 1.1	irRECIST
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 Subjects with an initial finding of progressive disease (irPD) before or at the 12-week imaging assessment, but without rapid clinical deterioration, require confirmation of irPD with a second, consecutive scan obtained ≥ 4 weeks from the initiation documentation. Subjects 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 12 weeks of the study).

9.1.10 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 subject'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 7).

Table 7 Best Overall Response (RECIST 1.1)

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

Target Lesions	Non-Target Lesions		
Baseline (Index) and New Measurable Lesions	**Baseline Lesions**	**Unequivocal New Lesions**	**Overall Response**
Any	Any	Yes	PD

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

9.1.11 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 8). As with the primary definitions of tumor response, early progression (i.e., irPD occurring prior to Week 12) will not preclude an irBOR of irCR, irPR or irSD resulting from the Week 12 assessment. An assessment of irPD at or after Week 12 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 8 Immune-Related Best Overall Response (irBOR)

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

9.1.12 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 on tumor burden or even the appearance of new lesions. If radiological imaging shows 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 a reduction of in the tumor burden demonstrating CR, PR or SD compared to the initial 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. If the repeat imaging confirms initially documented PD but shows no evidence of further tumor progression, subjects should be discontinued from the study treatment.

10 INVESTIGATIONAL DRUG 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.

ADXS11-001 will be supplied free of charge by Advaxis, Inc.

10.1 Packaging and Labeling

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

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.

10.1.1 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.

10.1.2 Returns and Reconciliation

The Investigator is responsible for keeping accurate records of the clinical supplies received from Advaxis or designee, the amount dispensed to subjects 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.

10.1.3 Destruction of ADXS11-001

It will be the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, and local regulations and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

[redacted]

If ADXS11-001 is destroyed at the site, 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

10.2 ADXS11-001 Records at Investigational Site

It will be the responsibility of the Investigator to ensure that a current record of ADXS11-001 disposition is maintained at each study site where ADXS11-001 is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should minimally include:

- The amount received and placed in storage area
- The amount currently in storage area
- The label identification, lot, or batch number
- Dates and initials of person responsible for each ADXS11-001 inventory entry/movement
- The amount dispensed to and returned by each subject, including unique subject identifiers
- The amount transferred to another area for dispensing or storage
- Non-study disposition (e.g., lost, wasted, broken)
- The amount destroyed at study site, if applicable

10.2.1 Safety Precautions

ADXS11-001 is a live attenuated 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. It is a naturally occurring bacterium that is present in the environment and is known to cause illness in some people when they eat foods contaminated with *Lm*. 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.

Even though ADXS11-001 is non-pathogenic, all *Lm* species are classified as [redacted] according to the BMBL 5th Edition. Universal precautions and institutional guidelines should be used when handling investigational drugs and human specimens. Except for the transmission of mother to fetus, human-to-human transmission

of *Lm* is not known to occur.[19] Shedding studies completed in Phase 1 demonstrated that, in the absence of antibiotics, ADXS11-001 was rapidly cleared from the blood with no *Lm* detected in the blood of any subject beyond 48 hours post-dosing, and no *Lm* was detected in the urine and feces in any subject at the highest dose of ADXS11-001 tested (1×10^{10} CFU) [11].

Based on the mechanism of action of ADXS11-001 and the inability of *Lm* to be transferred from human-to-human, there is no need for subjects who receive ADXS11-001 to avoid contact with people who are elderly, pregnant, newborns, or have weakened immune systems.

Precautions as stated in the BMBL 5th Edition include:

> ***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 Lm 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. Biopsy specimens must be fixed immediately by dropping the specimen in formaldehyde solution. 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]

11 CLINICAL SAFETY MANAGEMENT

11.1 ADXS11-001 Pretreatment Prophylaxis Regimen

Mild to moderate flu-like symptoms and cytokine release symptoms (e.g., constitutional symptoms such as fever, chills, rigors, fatigue, 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., 500 mL 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 [redacted] 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.

11.2 Step-Up Regimen for ADXS11-001 Pre-Dose Treatment Prophylaxis

Antiemetics such as promethazine or ondansetron will continue to be given as described above in Section 11.1. Thus, subjects will leave the study site with doses of the NSAID and antiemetic to take later in the day, as appropriate.

11.3 Administration of ADXS11-001

[redacted]

11.4 Supportive Care Guidelines

[redacted]

11.4.1 Cytokine Release Symptoms

Cytokine release symptoms are 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, fatigue, headache, nausea, vomiting, rash, tachycardia, hypotension and shortness of breath which usually presents several hours after the infusion and lasts 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 to 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-6have 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, have demonstrated good results in treating cytokine-induced hypotension [20-23] and are 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 subjects who have experienced these AEs are shown in Table 9.

Table 9 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)
All other cytokine release symptoms (e.g. chills, rigors, fever, nausea, vomiting)	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 subject'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 subjects 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 subjects 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**.[20-23]**

11.4.2 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.

11.5 Management of Infusion Reactions

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 10 below shows the management guidelines for subjects who experience an infusion reaction associated with administration of ADXS11-001.

Table 10 Recommended Management Guidelines for Infusion Reactions

NCI CTCAE Grade	Management
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. 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	3. Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine 4. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. 5. Hospitalization may be indicated. 6. 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

11.5.1 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.[24] 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 subjects, 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. *Lm* 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 [24].

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]

11.5.2 Management and Surveillance of Listeria during Study Participation

In the event a subject experiences a persistent fever lasting 72 hours after receiving study treatment then the oral antibiotic regimen will be replaced by broad spectrum IV antibiotic treatment. If symptoms consistent with sepsis occur close to ADXS11-001 administration or at any time after ADXS11-001 administration, immediate medical attention must be sought. A microbial culture will be taken to identify the agent of sepsis and antibiotic sensitivity testing should be performed to confirm susceptibility. An infectious disease consult should be obtained for further management of these subjects.

All subjects will receive a 6-month course of an oral antibiotic regimen as a prophylactic measure 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, comprehensive metabolic panel (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 1 dose of ADXS11-001 and occur every 3 months (±2 weeks) for 3 years.

Should a diagnosis of listeriosis be made at any point after treatment with ADXS11-001 and the 6-month course of oral antibiotics are completed, immediate and intensive IV antibiotic treatment (ampicillin +/- gentamycin 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 subjects will be prepared and educational training performed.

11.6 ADXS11-001 Toxicities and Treatment

Please refer to Section 3.4.1 for summary information on the ADXS11-001 AE profile.

ADXS11-001 is a live attenuated bioengineered nonpathogenic strain of *Lm*, and one that is known to stimulate a strong innate immune response characterized by high levels of cytokine release from immune cells into the general circulation. This pattern of side effects is consistent with other immunotherapy agents.

The most likely AEs associated with ADXS11-001 are comprised primarily of individual flu-like symptoms (e.g., fever, chills, body ache, and fatigue) or cytokine release symptoms (e.g., headache, nausea, vomiting, tachycardia, shortness of breath, hypotension and rash). The symptoms usually present within 2-4 hours after the completion of infusions 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 and 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, subjects with significant liver disease are excluded, and particular attention is to be paid to hepatic abnormalities.

Please reference the ADXS11-001 IB for complete information regarding AEs.

During the time the subjects are at the study site, the infusion line will be left in place to administer parenteral drugs, should that be necessary. As described in Section 11, subjects will be pretreated to minimize side effects of the study agent. The Investigator should observe the subjects for signs of inflammation and/or infection, including unremitting fever or vomiting, that require more intense therapy, and to treat them appropriately. All such treatments are to be listed on the eCRF.

11.6.1 Treatment Modification Guidelines

The dose of ADXS11-001 will not be modified (e.g., reduced or increased). However, treatment may be delayed or discontinued for drug related severe and life-threating toxicities, as shown below in Table 11.

Table 11 Treatment Delay/Discontinuation Guidelines for Drug-Related Adverse Events

Toxicity	Grade	Hold treatment	Timing for restarting treatment	Discontinue Treatment
Hematologic	1,2,3	No	N/A	N/A
	4	Yes	Toxicity resolves to ≤Grade 1 or baseline	Toxicity does not resolve to ≤Grade 1 or baseline within 12 weeks
Non-hematologic, excluding cytokine release symptoms and DLTs	1	No	N/A	N/A
	2-3	Yes	Toxicity resolves to ≤Grade 1	Toxicity not resolved to ≤Grade 1 within 12 weeks of last infusion[a]
	4	N/A	Permanent treatment discontinuation	Permanent Discontinuation from Treatment

[a] With investigator and sponsor agreement, subjects with a non-hematologic AE (e.g. alopecia, neuropathy) still at grade 2 after 12 weeks, may continue treatment if only asymptomatic and controlled.

11.6.2 ADXS11-001 Treatment Alterations

Subjects who experience a DLT during the dose escalation portion of the study or experience events described as a DLT in any subsequent treatment cycle will be discontinued from study treatment. However, if the subject who experienced a DLT shows significant response to ADXS11-001, they may be eligible to receive ADXS11-001 at a lower dose level for subsequent doses and cycles following discussion and agreement between the Investigator and Sponsor. See Section 6.1 Dose Limiting Toxicity Criteria for definition of DLT.

11.7 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 subject; 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 new implants and/or devices (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.

11.8 Discontinuation of Study Subjects

11.8.1 Subject Study Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be discontinued 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.

A subject may be discontinued from the trial for any of the following reasons:

- Screen Failure
- AE/SAE
- Lost to Follow-Up
- Disease Progression
- Death
- Withdrawal of Consent by Subject
- Investigator Decision/Study Non-Compliance by Subject
- Achieved Complete Remission
- Completed Study (at least 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 subject's medical records. The subject 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 study 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 13.2 Collection of Safety Information.

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 subject's records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter).

11.8.2 Suspension or Discontinuation of the Study

The occurrence of any Grade 4 (life threatening) toxicity may result in the temporary suspension of the study to evaluate available safety information to justify continued enrollment of subjects into the study.

The study may be stopped at the study center at any time by the investigator. Advaxis may stop the study (and/or the study center) for any reason.

12 CONCURRENT THERAPIES AND PROCEDURES

All prescription and nonprescription medication (excluding vitamins, nutritional supplements and hormone replacement therapy) taken by the subject from 30 days prior to screening and up to and including completion of the 3-year *Lm* surveillance period 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, antibiotics and procedures administered/performed following the completion of study treatment, including during the 3-year *Lm* surveillance period, should also be captured in the eCRF.

Study subjects should be reminded that acetaminophen should not be used for pretreatment prophylaxis associated with the foreseeable AEs related to the study treatment since this medication can interfere with treatment.

Medications 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 specifically prohibited during the trial, discontinuation from trial therapy may be required. The Investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy rests with the Investigator and/or the subject's primary physician. However, the decision to continue the subject's on-trial therapy requires the mutual agreement of the Investigator, the Sponsor, and the subject.

Subjects are prohibited from receiving the following therapies during the screening and treatment phases (including retreatment for post-complete response relapse) of this trial:

- Anti-cancer systemic chemotherapy or biological therapy
- Surgical treatment as per consultation with the sponsor
- PI3K and TNFα inhibitors
- Immunotherapy not specified in this protocol
- Investigational agents other than ADXS11-001
- Radiation therapy (except palliative radiation therapy for disease-related pain with a consult with the sponsor's medical monitor)
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed.
- Acetaminophen is not to be used for premedication but may be used for supportive care measures. NSAIDs, such as naproxen and ibuprofen have been evaluated and are confirmed not to interfere with efficacy.

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

13 ADVERSE EVENT REPORTING IN CLINICAL TRIALS

13.1 Importance of Adverse Event Reporting

Timely and complete reporting of safety information assists Advaxis in identifying any untoward medical occurrence, thereby allowing: (1) the protection of the safety of study subjects, (2) a greater understanding of the overall safety profile of ADXS11-001, (3) recognition of dose-related ADXS11-001 toxicities, (4) appropriate modification of study protocols, (5) improvements in study design or procedures, and (6) adherence to worldwide regulatory requirements.

AEs will be reported to FDA according to 21 CFR 312.32.

13.2 Collection of Safety Information

An AE is defined as any untoward medical occurrence in a subject 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.

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.

During clinical trials, AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of 1 or more AEs.

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 during the study treatment period of the study. AEs and SAEs will be recorded during the 3-year *Lm* surveillance period of the study and at each examination on the AE eCRF. The reporting timeframe for AEs meeting any serious criteria is described in Section 13.7.1.

Disease progression associated with the underlying malignancy need not be reported as an "adverse event", per se. Naturally, it is captured as a part of the intended endpoints.

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset and end dates, severity (grade of the event), Investigator's opinion of the relationship to ADXS11-001 (see definitions below), treatment/action required for the AE, and information regarding resolution/outcome.

AEs and other symptoms will be graded according to the expanded NCI CTCAE v 4.03. For AEs not contained within the toxicity criteria, the principal Investigator will be responsible for assessing the severity of an AE on the basis of the jeopardy to the

subject's health and well-being and the ability of the subject to function during the event. These AEs will be graded as mild, moderate, or severe.

The following categories and definitions of causal relationship to ADXS11-001 should be used for all Advaxis clinical trial AEs:

- Definite: there is a reasonable causal relationship between ADXS11-001 and the AE; the event responds to withdrawal of ADXS11-001 (dechallenge) and recurs with rechallenge when clinically feasible

- Probable: there is a reasonable causal relationship between study treatment and the AE; the event responds to dechallenge; rechallenge is not required

- Possible: there is a reasonable causal relationship between ADXS11-001 and the AE; the event responds to dechallenge or dechallenge information is lacking or unclear; rechallenge is not required

- Unlikely: There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the AE

- Unrelated: there is not a temporal relationship to ADXS11-001 administration (too early, late, or ADXS11-001 not taken) or there is a reasonable causal relationship between another drug, concurrent disease, or circumstance and the AE

13.3 Adverse Event Follow-Up

AEs and SAEs related to ADXS11-001 (definitely or possibly) should be followed to resolution or stabilization and reported as SAEs if they become serious. This also applies to subjects experiencing AEs that cause interruption or discontinuation of ADXS11-001 or those experiencing AEs that are present at the end of their participation in the study; such subjects should receive post treatment follow-up as appropriate. If an ongoing AE changes in its severity or in its perceived relationship to ADXS11-001, a new AE entry in the eCRF for the event should be completed.

13.4 Adverse Events Related to Study Conditions

If the Investigator believes that an AE is not related to ADXS11-001, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or complication of a diagnostic procedure), the relationship should be specified in the comment section of the AE page of the eCRF and on the Serious Adverse Event Report (SAER) form.

13.5 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 the Sponsor and within 2 working days hours to inVentiv Health Clinical Pharmacovigilance (Attn: iHC SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@inventivhealth.com).

13.6 Evaluating Adverse Events

An Investigator who is a qualified physician will evaluate all AEs according to the CTCAE v 4.03 (See Table 12). Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE case report forms/worksheets. All AEs regardless of CTCAE grade must also be evaluated for seriousness.

Table 12 Evaluating Adverse Events

V4.03 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	**A serious adverse event is any adverse event occurring at any dose or during any use of Advaxis product that:**	
	†Results in death; or	
	†Is life threatening; or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or	
	†Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new cancer; (that is not a condition of the study) or	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	**Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units**	
Action taken	**Did the adverse event cause the Advaxis product to be discontinued?**	

Relationship to test drug	**Did the Advaxis product cause the adverse event? The determination of the likelihood that the Advaxis product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. The following components are to be used to assess the relationship between the Advaxis product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Advaxis product caused the adverse event (AE):**	
	Exposure	Is there evidence that the subject was actually exposed to the Advaxis product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Advaxis product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
Relationship	**The following components are to be used to assess the relationship between the test drug and the AE:**	
to Advaxis product	**Dechallenge**	**Was the Advaxis product discontinued or dose/exposure/frequency reduced?** **If yes, did the AE resolve or improve?** **If yes, this is a positive dechallenge. If no, this is a negative dechallenge.** **(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Advaxis product; or (3) the trial is a single-dose drug trial); or (4) Advaxis product(s) is/are only used one time.)**
	Rechallenge	**Was the subject re-exposed to the Advaxis product in this study?** **If yes, did the AE recur or worsen?** **If yes, this is a positive rechallenge. If no, this is a negative rechallenge.** **(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Advaxis product(s) is/are used only one time).** **NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE ADVAXIS PRODUCT, OR IF REEXPOSURE TO THE ADVAXIS PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.**

	Consistency with Trial Treatment Profile	**Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Advaxis product or drug class pharmacology or toxicology?**
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of an Advaxis product relationship).**
Definite:		**The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug**
Probable:		**The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug AND the event cannot have been reasonably explained by an intercurrent medical condition or the event cannot be the effect of a concomitant medication**
Possible		**The event follows a reasonable temporal sequence from administration of the study drug or the event follows a known response pattern to the study drug BUT the event could have been produced by an intercurrent medical condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug or the event could be the effect of a concomitant medication**
Unlikely		**The event is clearly due to causes distinct from the use of the study drug, such as a documented pre-existing condition, the effect of a concomitant medication, a new condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug**
Unrelated		**The event does not follow a temporal relationship to the study treatment administration (too early, late, or study treatment(s) not taken) or there is a reasonable causal relationship between another drug, concurrent disease, or circumstance and the AE**

13.7 Handling and Reporting of Adverse Events to the Sponsor

13.7.1 Serious Adverse Events

A SAE 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, that occurs to any subject from the time the consent is signed through the completion of the 3-year *Lm* surveillance period 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 in the previous paragraph also must be reported immediately to inVentiv Health Clinical Pharmacovigilance (Attn: iHC SAE Reporting; FAX 866-880-9343 or email: i3drugsafetyPV@inventivhealth.com).

Collection of complete information concerning SAEs is extremely important. Thus, follow-up information that becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.

Periodically, according to Advaxis SOPs, the IB will be updated to include new and relevant safety information. Once the appropriate regulatory authorities have been

notified of a serious, unexpected, and related event, further reporting of the same event will be considered expected.

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).

AE reports meeting the requirements of a 7 Day Reports, 15 Day Reports, or the requirements for inclusion in the Annual Periodic Reports will be submitted as required to FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will be provided a copy of the submission and will utilize this for submission to local IRB/EC as required. The submission will cross reference the Sponsor's Investigational Compound Number (IND, CSA, etc.).

All subjects with SAEs must be followed up for outcome.

13.8 Laboratory Test Abnormalities

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 13.

Laboratory tests should be performed within 3 days prior to dosing. Subjects must meet all lab criteria prior to initial dosing. For subsequent dosing, hepatic and renal function eligibility criteria must be met. Results must be reviewed by the Investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

All laboratory test values captured as part of the study should be recorded on the appropriate laboratory test results pages of the eCRF. In addition, in order for Advaxis to collect additional information about clinically important laboratory abnormalities, the following laboratory abnormalities should be captured on the AE pages of the eCRF:

- Any laboratory test result that meets the criteria for a SAE; laboratory test results that meet the criteria for a SAE should also be reported to Advaxis using the SAER form (see Section 13.7, Handling of Serious Adverse Events)
- Any laboratory abnormality that requires the subject to have ADXS11-001 discontinued or interrupted
- Any laboratory abnormality that requires the subject to receive specific corrective therapy

It is expected that wherever possible the clinical, rather than the laboratory term, would be used by the reporting Investigator (e.g., anemia versus low hemoglobin value).

Table 13 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin ((β-hCG)
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Blood for correlative studies
Red blood cell count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	*Lm* Surveillance blood cultures*
Absolute neutrophil count	C-Reactive Protein (CRP)*	Urine pregnancy test †	
	Carbon dioxide ‡ *(CO_2 or bicarbonate)*		
	Creatinine		
	Calcium		
	Chloride		
	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 (BUN)		

† 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.

13.9 Other Safety Considerations

Any clinically significant changes noted during interim or final physical examinations, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should be recorded on the AE page of the eCRF. All required *Lm* surveillance labs should be recorded on the lab and AE page of the eCRF, as appropriate.

13.10 Pregnancy

An Investigator approved method of birth control must be used during the course of the study. Prior to enrollment, study candidates who are women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. 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 subject must not receive ADXS11-001 and may not be enrolled in the study.

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 (e.g., vasectomy) should be considered of childbearing potential.

All study participants should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

In the case of pregnancy, ADXS11-001 will be discontinued and protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., X-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

Although pregnancy and lactation are not considered AEs, it is the responsibility of the investigator or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), that occurs during the trial or 120 days of completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All 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).

14 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

14.1 Introduction

This is an open-label, single agent clinical trial. Descriptive statistics will be employed to evaluate the safety and tolerance of ADXS11-001. 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 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 data will be tabulated and analyzed with respect to subject enrollment and disposition, demographic, and baseline characteristics.

14.2 Statistical Analysis Plan

This is a Phase 1 open-label, multi-center clinical trial. Descriptive statistics will be employed to evaluate the safety and tolerance of ADXS11-001. 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 medians and survival plots. Data listings will be created to support tables and present data. The safety analysis will be performed on the safety population. The efficacy analysis will be performed on the efficacy population. SAS 9.2 or higher will be used for data analysis.

The data will be tabulated and analyzed with respect to subject enrollment and disposition, demographic, and baseline characteristics.

14.3 Sample Size

- The dose escalation portion of the study will enroll between 6-12 subjects based on observed AEs and/or DLTs within the dose cohorts.

- Additional subjects may be enrolled in an expansion cohort of the highest dose level to allow approximately 15 subjects to be treated at that dose level.

14.4 Treatment Randomization and Blinding

This is an open-label, multi-center trial. No placebo or active control is used and therefore no randomization is involved.

14.5 Study Populations

All subjects who receive at least 1 dose of study treatment will be included in the safety analyses. All subjects who complete at least 1 cycle of ADXS11-001 treatment will be included in the efficacy population.

14.5.1 Subject Disposition

The number and percentage of subjects entering and completing the clinical study will be presented overall and by dose cohort.

14.5.2 Demographic Information and Baseline Characteristics

Demographic and baseline characteristic will be descriptively summarized by study phase and dose.

14.5.3 Protocol Deviation

Protocol deviations will be listed by subject.

14.5.4 Analysis of Safety

All subjects who receive at least 1 dose of study treatment will be included in the safety analyses.

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

The CTCAE v 4.03 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 ADXS11-001 dose. An AE will be summarized if the onset date occurs any time 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 subject 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 CTCAE v 4.03 toxicity

grades. Laboratory data will be presented for subjects having Grade 3 or 4 changes from baseline.

14.5.5 Analysis of Efficacy

All subjects who complete at least one cycle of ADXS11-001 treatment will be included in the efficacy analyses. The following are efficacy parameters for the study:

1. Objective Response Rate (ORR)

2. Duration of tumor response

3. Stable Disease Rate (proportion of CR, PR, SD)

4. Duration of Stable Disease (SD)

5. Progression free survival (PFS)

Tumor response will be evaluated by RECIST 1.1 and irRECIST criteria. The ORR will be calculated as the proportion of subjects who achieved CR/irCR or PR/irPR. The duration of response is defined as the time interval from CR/irCR or PR/irPR to disease progression or death. If the subject's disease remains responsive by the time of discontinuation or completion of the study, the duration will be censored at that time point. The stable disease rate will be calculated as the proportion of subjects who achieved CR/irCR, PR/irPR or SD/irSD. The duration of SD is defined as the time interval from CR/irCR or PR/irPR or SD/irSD to disease progression or death. If the subject's disease remains stable by the time of discontinuation or completion of the study, the duration will be censored at that time point.

PFS is defined as the time interval from first infusion of study treatment to disease progression or death. If the subject's disease has not progressed by the time of discontinuation or completion of the study, the PFS will be censored at that time point.

Efficacy parameters will be descriptively summarized by dose cohorts as well as for all cohorts combined. Tumor response will be summarized according to response category. Response rate and stable disease rate will be summarized by frequency table. For durations of response and SD/irSD as well as PFS, the Kaplan-Meier method will be used to estimate the median times. Descriptive statistics and Kaplan-Meier curves will be presented.

14.6 Interim Analysis

No formal interim analysis is planned for the study. However, AEs and toxicity reports will be monitored.

15 INVESTIGATOR OBLIGATIONS

15.1 Compliance with the Protocol and Protocol Revision

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

When a situation occurs that requires a temporary departure from the protocol, the Investigator or other physician in attendance should contact the medical monitor as soon as possible in order to discuss the situation and agree on an appropriate course of action. The investigator will describe the departure from the protocol and the circumstances requiring it on the eCRF.

The Investigator may not modify this protocol. Amendments initiated by Advaxis or its agents will be confirmed in writing in the form of a protocol amendment. All such amendments must be approved by the IRB/IEC; however, amendments that reduce risks to the subjects may be implemented prior to obtaining IRB/IEC approval. No additional subjects can be enrolled until the amendment is approved by the IRB/IEC.

Documentation of approval signed by the chairperson or designee of the IRB/IEC must be sent to Advaxis. If the revision is an administrative letter, investigators must inform and obtain approval from their IRB/IEC.

15.2 Informed Consent

The Investigator must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical trials in which they volunteer to participate.

15.2.1 Informed Consent Procedures

Preparation of the consent form is the responsibility of the investigator and must include all elements required by the ICH, GCP, and applicable regulatory requirements and must adhere to GCP. The consent form also must include a statement that Advaxis, its agents, and the regulatory authorities have direct access to subject records. Prior to beginning the study, the Investigator must have written IRB/IEC approval of the informed consent form and any other information to be provided to the subjects.

The Investigator must provide the subject or legally acceptable representative with a copy of the consent form and written information about the study in the language in which the subject is most proficient. The language must be nontechnical and easily understood. The investigator should allow time necessary for the subject or legally acceptable representative to inquire about the details of the study. Informed consent must be signed and personally dated by the subject or legally acceptable representative and by the person

who conducted the informed consent discussion. The subject or legally acceptable representative should receive a copy of the signed informed consent form and any other written information provided to study subjects prior to the subject's participation in the trial.

15.2.2 Update of Informed Consent

The informed consent and any other information provided to subjects or legally acceptable representative should be revised whenever important new information becomes available that is relevant to the subject's consent and should receive IRB/IEC approval prior to use. The Investigator, or a person designated by the investigator, should fully inform the subject or legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented. During a subject's participation in the trial, any updates to the consent form and any updates to the written information will be provided to the patient.

If a protocol amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB/IEC for review and approval, (2) the revised consent form must be used to obtain consent from subjects currently enrolled in the study, and (3) the new consent form must be used to obtain consent from new subjects prior to enrollment.

15.3 Monitoring for Protocol Compliance

Representatives of Advaxis 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 Advaxis and by government inspectors who must be allowed access to eCRFs, source documents, and all other study files. Advaxis audit reports will be kept confidential.

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

15.4 Records and Reports

The Investigator will be required to prepare and maintain adequate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with ADXS11-001 or entered as a control in the investigation. Data reported on the eCRF that are derived from source documents must be consistent with the source documents, or the discrepancies must be explained.

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 Advaxis 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 subjects' initials will appear on the eCRF. Qualified representatives from the relevant regulatory agencies, Advaxis, 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.

Subjects will be identified by initials and identification number, if applicable. All requested information must be entered on the eCRF in the spaces provided. If an item is not available or is not applicable, it must be documented as such. Do not leave a space blank.

The Investigator will maintain a Signature Sheet (Delegation of Authority Page) to document signatures and initials of all persons authorized to make entries and/or corrections on the eCRFs, as applicable.

The completed eCRF must be promptly reviewed and electronically signed and dated by a qualified physician who is an Investigator or sub-investigator. If any changes are made or additional data are added to an eCRF after the investigator has signed and dated the form, the investigator must initial and date the change or addition. The Investigator must retain a copy of the eCRF, including records of changes and corrections.

All baseline and reassessment radiographs used to assess response must be available for independent review.

15.5 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have specified written and dated approval from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The investigator also should provide the IRB/IEC with a copy of the IB or product labeling, information to be provided to subjects, and any updates.

The Investigator should provide the IRB/IEC with reports, updates, and other information (e.g., safety updates, amendments, and administrative letters) according to regulatory requirements or institution procedures.

15.6 Records Retention

The Investigator must retain ADXS11-001 disposition records, copies of eCRFs (or electronic files), and source documents for the maximum period required by applicable regulations and guidelines, institution procedures, or the period specified by Advaxis, whichever is longer. The Investigator must contact Advaxis prior to destroying any records associated with the study. Advaxis will notify the investigator when the trial records are no longer needed. If the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IEC). Notice of such transfer will be given in writing to Advaxis.

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